GENERAL PHARMACOLOGY

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UNIT -1

GENERAL PHARMACOLOGY

a. Introduction to Pharmacology- Definition, historical landmarks and scope of pharmacology, nature and source of drugs, essential drugs concept and routes of drug administration, Agonists, antagonists(competitive and non competitive), spare receptors, addiction, tolerance, dependence, tachyphylaxis, idiosyncrasy, allergy.

b. Pharmacokinetics- Membrane transport, absorption, distribution, metabolism and excretion of drugs .Enzyme induction, enzyme inhibition, kinetics of elimination

CHAPTER-1

GENERAL PHARMACOLOGY

DEFINITIONS

Pharmacology is the science that deals with the study of drugs and their interaction with the living systems. The word pharmacology is derived from the Greek word—***Pharmacon*** meaning an active principle and ***logos*** meaning a discourse.

Pharmacokinetics is the study of the absorption, distribution, metabolism and excretion of drugs, i.e. what the body does to the drug (in Greek *Kinesis = movement*).
Pharmacodynamics is the study of the effects of the drugs on the body and their mechanisms of action, i.e. what the drug does to the body.

Drug (*Drogue*—a dry herb in French) is a substance used in the diagnosis, prevention or treatment of a disease. **WHO definition**, "A drug is any substance or product that is used or intended to be used to modify or explore physiological systems or pathological states for the benefit of the recipient."

Therapeutics deals with the use of drugs in the prevention and treatment of disease.

Pharmacoeconomics deals with the cost, i.e. economic aspects of drugs used therapeutically.
Pharmacogenetics ***(and pharmacogenomics)*** is the science that deals with the study of genetic basis for variation in drug responses
Pharmacoepidemiology is the study of both the useful and adverse effects of drugs on large number of people.
Pharmacovigilance is related to the detection, assessment, understanding and prevention of adverse effects of drugs
Toxicology deals with the adverse effects of drugs and also the study of poisons, i.e. detection, prevention and treatment of poisoning *(Toxicon = poison in Greek)*.
Chemotherapy is the use of drugs and chemicals for the treatment of infections. The term now also includes the use of chemical compounds to treat malignancies.

Orphan drugs are drugs to be used for prevention and treatment of rare diseases.

HISTORICAL LANDMARKS

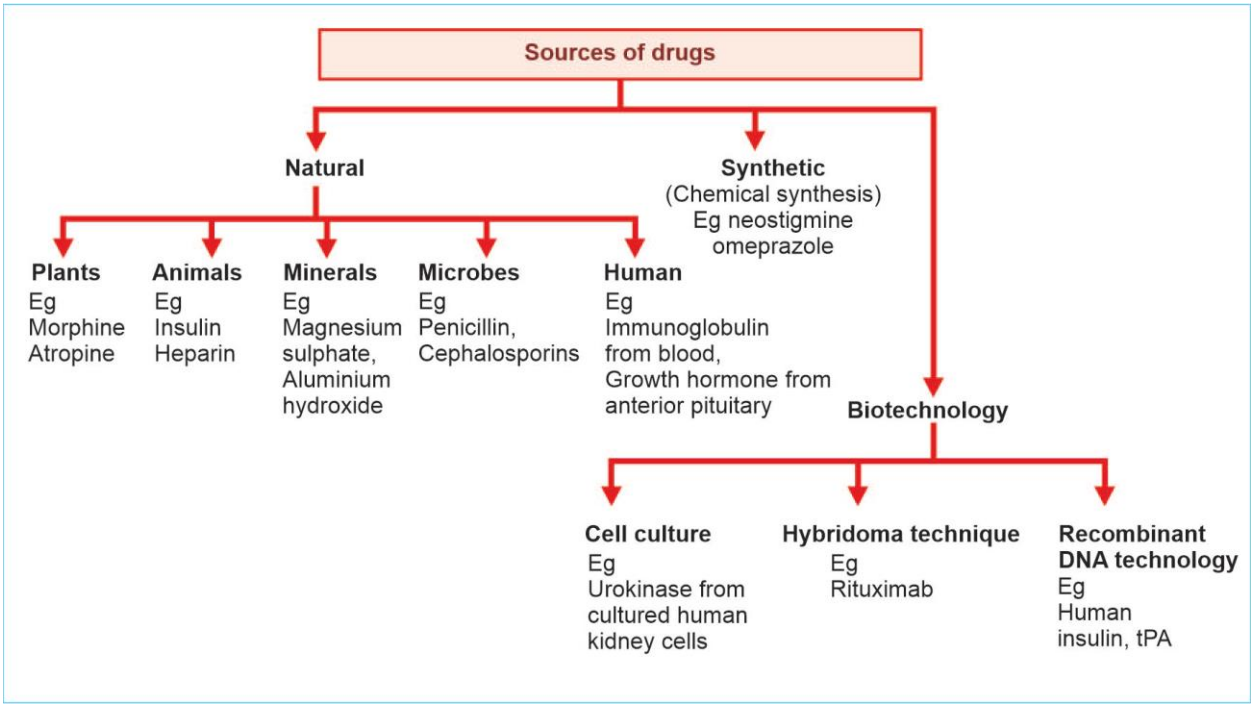
- The useful and toxic effects of many plant and animal products were known to man since ancient times. In fact, there has been a quest for drugs and remedies since the existence of mankind itself. In early days, there was a close relationship between religion and the treatment of diseases. The knowledge of the use of drugs often rested with the priest or holyman. Drugs were thought to be magical in their actions. Several cultures like the Chinese, Greek, Indian, Roman, Persian, European and many others contributed a great deal to the development of medicine in early times. The drug prescriptions included preparations from herbs, plants, animals and minerals. However, written information on remedies used in early times is lacking. The Indian and the Chinese writings are amongst the oldest written material in medicine. India's earliest pharmacological writings are from the 'Vedas'. Rigveda (3000 BC) has description of some medicines.
- An ancient Indian physician Charaka, and then, Sushruta and Vagbhata, described many herbal preparations included in '**Ayurveda**' (meaning the science of life). Indians practiced vaccination as early as 550 BC. '**Pen Tsao**' the Chinese materia medica was written as early as 1700 BC and it contained classification of medicinal plants and some preparations of plants, metals and animals. The Egyptian medical papyri (1600 BC) described several preparations.
- The largest of them, Ebers Papyrus lists some 800 preparations. The Greeks studied the toxic effects of various plant extracts. Their contribution to the growth of modern medicine is significant. **Hippocrates** (460–377 BC), a Greek physician, studied the cause of disease and wrote on the ethics of medicine and recommended judicious use of drugs. Galen (130–201 BC), also a Greek physician, practiced in Rome and put forth a doctrine that diseases are due to an imbalance of fluids—blood, phlegm, black bile and yellow bile. He believed that drugs had some properties like warmth, coldness, dryness or humidity and also thought that it is beneficial to use a combination of drugs to obtain these effects.
- In the Middle Ages, many herbal gardens were cultivated by the monasteries. **Paracelsus** the '**Grandfather of Pharmacology**' born in Switzerland was the son of a physician. He opined that complicated mixture of drugs should not be used and also wrote, "all drugs are poisons—it is only the dose which makes a thing a poison." This statement holds good even today.Though medicine developed simultaneously in several countries, the spread of knowledge was limited because of poorly developed communication across the world. By the beginning of the first century, it was realized that there was a need to standardize the method of obtaining uniform medical preparations.
- James Gregory (1735–1821 AD) recommended certain dangerous measures like blood letting use of emetics and purgatives in the treatment of diseases—such measures were often fatal. He meant to induce other suffering to relieve pain/suffering and this was probably the basis of the word '**allopathy**' meaning 'the

other suffering'. This word, still being used for the modern system of medicine, is a misnomer. **Homeopathy** meaning 'similar suffering' was introduced by **Samuel Hahnemann.** The principles of this system include 'like cures like' and 'dilution enhances the potency of drugs'. Various traditional systems of medicine were practiced in different parts of the world like Homeopathy, Ayurveda, Unani, Siddha system and Allopathy.

- Thus several systems of medicine were introduced, of which only a few survived. The basic reason for the failure of these systems is that man's concepts about diseases were incorrect and baseless in those days. By the end of the 17th century, the importance of experimentation, observation and scientific methods of study became clear.
- **Francois Magendie** and **Claude Bernard** popularized the use of animal experiments to understand the effects of drugs. Simultaneous development of other branches of science, viz. botany, zoology, chemistry and physiology helped in the better understanding of pharmacology. By the nineteenth century, methods for isolation of drugs were developed. **Rudolph Bucheim** (1820–1879) set up the first laboratory in his home at Dorpat Estonia in 1847 exclusively meant for research on drugs.
- **Oswald Schmiedeberg** (1838–1921), a student of Bucheim, conducted extensive research on drugs, trained 120 students and wrote a medical textbook. He has been called '**Father of Pharmacology**' for his contribution and was the most prominent pharmacologist of the 19th century.

NATURE & SOURCES OF DRUGS

The sources of drugs could be natural, or synthetic and biotechnology.



A. Natural Sources

Drugs can be obtained from:

1. Plants, e.g. atropine, morphine, quinine, digoxin, pilocarpine, and physostigmine.
2. Animals, e.g. insulin, heparin, gonadotrophins and antitoxic sera.
3. Minerals, e.g. magnesium sulphate, aluminium hydroxide, iron, gold, sulphur and radioactive isotopes.
4. Microorganisms—antibacterial agents are obtained from some bacteria and fungi, e.g. penicillin, cephalosporins, tetracyclines.
5. Human—some drugs are obtained from human source, e.g. immunoglobulins from blood, growth hormone from anterior pituitary and chorionic gonadotrophins from the urine of pregnant women.

B. Synthetic

Most drugs used now are synthetic. They may be manufactured in large quantities and therefore can be less expensive, e.g. quinolones, omeprazole, sulfonamides, pancuronium and neostigmine.

C. Biotechnology

Use of biotechnology in the production of drugs and biologicals has helped to treat many ailments which were once incurable. It has been possible to synthesize many congeners with minor modifications.

For example:

• By **cell cultures,** e.g. urokinase from cultured human kidney cells.

• By **recombinant DNA technology,** e.g. human insulin, tissue plasminogen activator, haematopoietic growth factors like erythropoietin, filgrastim and sargramostim.

• By **hybridoma technique,** e.g. monoclonal antibodies like rituximab.

ESSENTIAL MEDICINES (DRUGS) CONCEPT

- The WHO has defined Essential Medicines (drugs) as "those that satisfy the priority healthcare needs of the population." They are selected with due regard to public health relevance, evidence on efficacy and safety, and comparative cost effectiveness. Essential medicines are intended to be available within the context of functioning health systems at all times and in adequate amounts, in appropriate dosage forms, with assured quality and adequate information, and at a price the individual and the community can afford.
- It has been realized that only a handful of medicines out of the multitude available can meet the health care needs of majority of the people in any country, and that many well tested and cheaper medicines are equally (or more) efficacious and safe as their newer more expensive congeners. For optimum utilization of resources, governments (especially in developing countries) should concentrate on these medicines by identifying them as Essential medicines. The WHO has laid down criteria to guide selection of an essential medicine.
- To guide the member countries, the WHO brought out its first Model List of Essential Drugs along with their dosage forms and strengths in 1977 which could be adopted after suitable modifications according to local needs. This has been revised from time to time and the current is the 20th list (2017)$ which has 433 medicines, including 25 fixed dose drug combinations (FDCs). India produced its National Essential Drugs List in 1996, and has revised it in 2011, and now in 2015 with the title "National List of Essential Medicines". The latest list includes 376 medicines, of which 20 are FDCs. These medicines have been marked into 3 categories for being available at primary, secondary and tertiary levels of health care facility.
- Adoption of the essential medicines list for procurement and supply of medicines, especially in the public sector healthcare system, has resulted in improved availability of medicines, cost saving and more rational use of drugs.

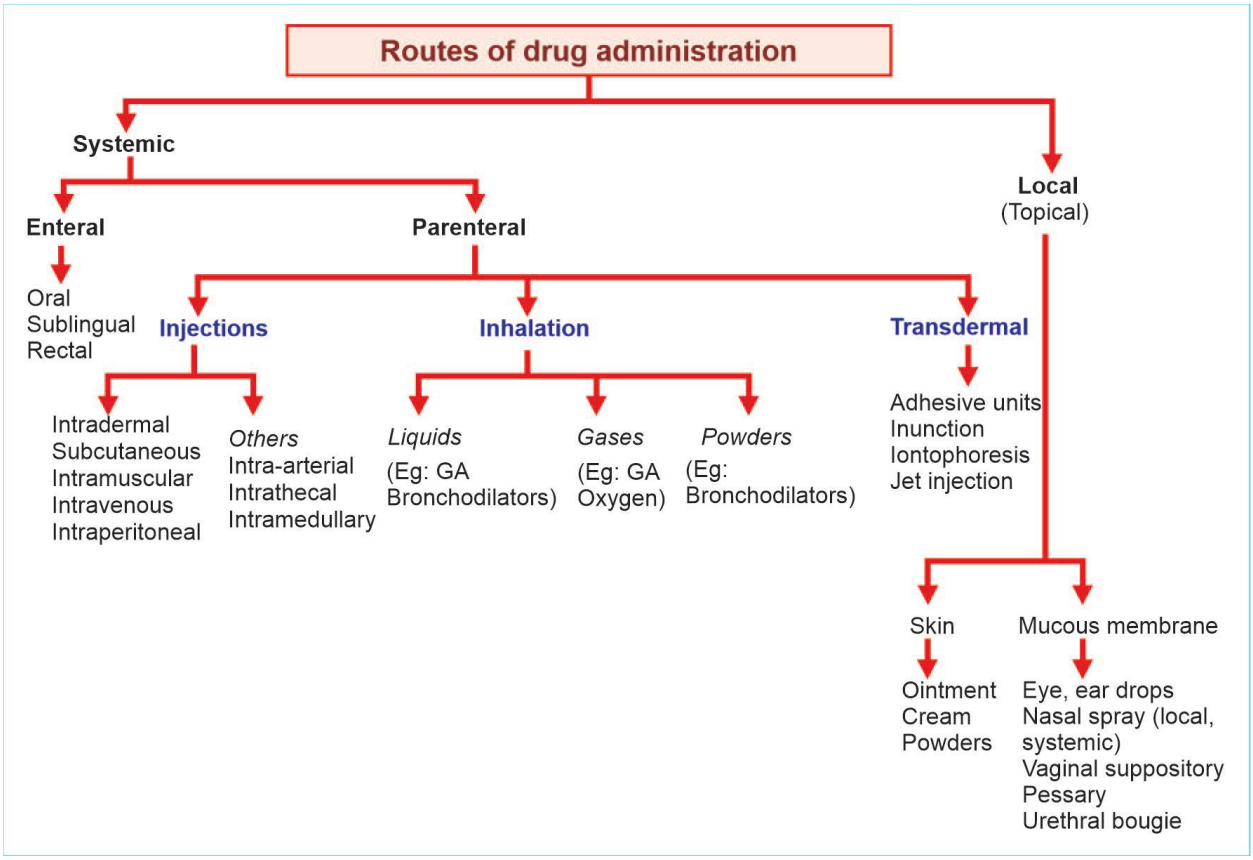
Prescription and non-prescription drugs

As per drug rules, majority of drugs including all antibiotics must be sold in retail only against a prescription issued to a patient by a registered medical practitioner. These are called ‘prescription drugs’, and in India they have been placed in the schedule H of the Drugs and Cosmetic Rules (1945) as amended from time to time. However, few drugs like simple analgesics (paracetamol aspirin), antacids, laxatives (senna, lactulose), vitamins, ferrous salts, etc. are considered relatively harmless, and can be procured without a prescription. These are ‘non-prescription’ or ‘over-the-counter’ (OTC) drugs; can be sold even by grocery stores.

Orphan Drugs

These are drugs or biological products for diagnosis/treatment/ prevention of a rare disease or condition, or a more common disease (endemic only in resource poor countries or areas) for which there is no reasonable expectation that the cost of developing and marketing it will be recovered from the sales of that drug. As per Orphan Drug Amendment (1983) Act of USA, a rare disease/condition is one that affects less than 0.2 million people in the USA. Though these drugs may be life saving for some patients, they are commercially difficult to obtain as a medicinal product. Governments in developed countries offer tax benefits and other incentives to pharmaceutical companies for developing and marketing orphan drugs. Orphan drug status has been awarded to many drugs in the USA, Europe and some other countries. Few examples of drugs granted ‘Orphan Drug’ status are listed in the box.

ROUTES OF DRUG ADMINISTRATION



SYSTEMIC ROUTES

Enteral Routes

Enteral routes include oral, sublingual and rectal routes.

1. **Oral route** is the most commonly used, oldest and safest route of drug administration. The large surface area of the gastrointestinal tract, the mixing of its contents and the differences in pH at different parts of the gut facilitate effective absorption of the drugs given orally. However, the acid and enzymes secreted in the gut and the biochemical activity of the bacterial flora of the gut can destroy some drugs before they are absorbed.

Advantages

- Safest route
- Most convenient
- Most economical
- Drugs can be self-administered
- Non-invasive route.

Disadvantages

- **Slow action:** Onset of action is slower as absorption needs time—hence particularly not suitable for emergencies.

• **Drug properties:** Irritant and unpalatable drugs cannot be administered.
• **Poor absorption:** Some drugs may not be absorbed due to certain physical and chemical characteristics, e.g. streptomycin is not absorbed orally.
• **GI irritation:** Irritation to the gastrointestinal tract may lead to vomiting.
• **Unpredictable absorption:** There may be irregularities in absorption.
• **Metabolism:** Some drugs may be destroyed by gastric juices, e.g. insulin.

2. Sublingual

Here, the tablet or pellet containing the drug is placed under the tongue. As the drug dissolves, it is absorbed across the sublingual mucosa, e.g. nitroglycerin, nifedipine, buprenorphine.

Advantages

• Absorption is rapid—within minutes the drug reaches the circulation.
• First pass metabolism is avoided becausethe drug directly reaches the systemic circulation.
• After the desired effect is obtained, the drug can be spat out to avoid the unwanted effects.

Disadvantages

• Buccal ulceration can occur.
• Lipid-insoluble drugs, drugs of higher molecular weight, irritant and unpalatable drugs cannot be given by this route.

3. Rectal

Rectum has a rich blood supply and drugs can cross the rectal mucosa to be absorbed for systemic effects. Drugs absorbed from the upper part of the rectum are carried by the superior haemorrhoidal vein to the portal circulation (can undergo first pass metabolism), while that absorbed from the lower part of the rectum is carried by the middle and inferior haemorrhoidal veins to the systemic circulation.

Eg: Drugs like indomethacin, chlorpromazine, diazepam and paraldehyde can be given rectally. Some irritant drugs are given rectally as suppositories.

Advantages

• Gastric irritation is avoided.
• Can be administered by unskilled persons.
• Useful in geriatric patients; patients with vomiting, those unable to swallow and after gastrointestinal surgery.
• Also useful in unconscious patients.

Disadvantages

• Irritation of the rectum can occur.
• Absorption may be irregular and unpredictable. Drugs may also be given by rectal route as enema.

Parenteral Routes

Routes of administration other than the enteral (intestinal) route are known as parenteral routes. Here the drugs are directly delivered into the tissue fluids or blood.

Advantages

• Action is more rapid and predictable than oral administration.
• These routes can be employed in an unconscious or uncooperative patient.
• Gastric irritants can be given parenterally and, therefore, irritation to the gastrointestinal tract can be avoided.
• It can be used in patients with vomiting or those unable to swallow.
• Digestion by the gastric and intestinal juices and the first pass metabolism are avoided.

Therefore, in emergencies, parenteral routes are very useful for drug administration as the action is rapid and predictable and are useful even in unconscious patients.

Disadvantages

• Asepsis must be maintained
• Injections may be painful
• More expensive, less safe and inconvenient
• Injury to nerves and other tissues may occur.

Parenteral routes include:

1. Injections
2. Inhalation
3. Transdermal route

1. Injections

Injections are given with the help of syringe and needle.

Intradermal

The drug is injected:

• Into the layers of the skin raising a bleb, e.g. BCG vaccine, tests for allergy.
• By multiple punctures of the epidermis through a drop of the drug.

Eg. Smallpox vaccine. Only a small quantity can be administered by this route and it may be painful.

Subcutaneous (SC) Injection

Here the drug is deposited in the SC tissue, e.g. insulin, heparin. As this tissue is less vascular, absorption is slow and largely uniform, making the drug long-acting. It is reliable and patients can

be trained for self-administration. Absorption can be enhanced by the addition of the enzyme hyaluronidase.

Disadvantages

- As SC tissue is richly supplied by nerves, irritant drugs cannot be injected because they can cause severe pain.
- In shock, absorption is not dependable because of vasoconstriction.
- Repeated injections at the same site can cause lipoatrophy resulting in erratic absorption.

Intramuscular (IM)

Aqueous solution of the drug is injected into one of the large skeletal muscles — deltoid, triceps, gluteus or rectus femoris. Absorption into the plasma occurs by simple diffusion.

Drugs are absorbed faster from the deltoid region than gluteal region especially in women. The volume of injection should not exceed 10 ml. For infants, rectus femoris is used instead of gluteus because gluteus is not well-developed till the child starts walking. If the drug is injected as oily solution or suspension, absorption is slow and steady and can have prolonged effect. Soluble substances, mild irritants, depot preparations, suspensions and colloids can be injected by this route.

Advantages

- Intramuscular route is reliable.
- Absorption is rapid.

Disadvantages

- Intramuscular injection may be painful
- May even result in an abscess. Local infection and tissue necrosis are possible.
- Nerve injury should be avoided—irritant solutions can damage the nerve, if injected near a nerve.
- In case of some drugs, absorption by IM route is slower than oral, e.g. diazepam, phenytoin.
- For some drugs, IM route should be avoided, e.g. heparin, calcium gluconate, diazepam, and tetracycline.

Intravenous (IV)

Here, the drug is injected into one of the superficial veins so that it directly reaches the circulation and is immediately available for action. Drugs can be given IV as:

1. A bolus: Where an initial large dose (loading dose) is given, e.g. heparin. The drug is dissolved in a suitable amount of the vehicle and injected slowly.
2. Slow injection—over 15–20 minutes, e.g. aminophylline.
3. Slow infusion—when constant plasma concentrations are required, e.g. oxytocin in labour or when large volumes have to be given, e.g. dextrose, saline. Generally, about one litre of solution

is infused over 3 to 4 hours. However, the patient's condition and the drug factors like the onset and duration of action of the drug dictate the rate of infusion.

Advantages

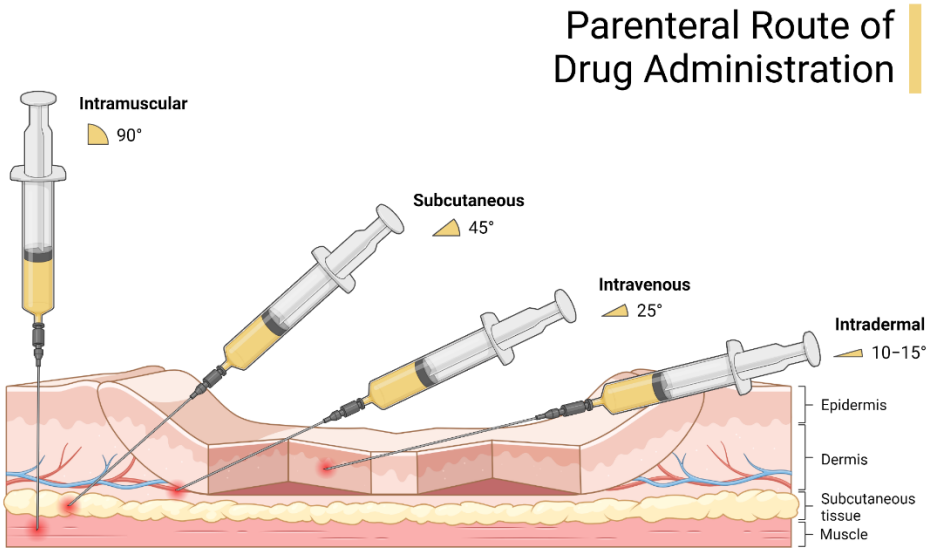
• Most useful route in emergencies as the drug is immediately available for action.
• Provides predictable blood concentrations with 100% bioavailability.
Large volumes of solutions can be given.
• Irritants can be given by this route as they get quickly diluted in blood.
• Rapid dose adjustments are possible—if unwanted effects occur, infusion can be stopped; if higher levels are required, infusion rate can be increased—specially for short-acting drugs.

Disadvantages

• Once injected, the drug cannot be withdrawn.
• Irritation of the veins may cause thrombophlebitis.
• Extravasation of some drugs may cause severe irritation and sloughing.
• Only aqueous solutions can be given IV but not suspensions, oily solutions and depot preparations.
• Self-medication is difficult.
• Risk of embolism—though rare.

Intraperitoneal

Peritoneum offers a large surface area for absorption. Fluids are injected intraperitoneally in infants. This route is also used for peritoneal dialysis.



Other Injections

Intrathecal: Drugs can be injected into the subarachnoid space for action on the CNS e.g. spinal anaesthetics.

Intra-articular: Drugs are injected directly into a joint for the treatment of arthritis and other diseases of the joints.
e.g. In rheumatoid arthritis, hydrocortisone is injected into the affected joint.

Intra-arterial: Intravenous and intra-arterial are intravascular routes. In intra-arterial route, the drug is injected directly into the arteries.
It is used only in the treatment of:
1. Peripheral vascular diseases
2. Local malignancies
3. Diagnostic studies like angiograms.

Intramedullary: Injection into a bone marrow—now rarely used.

2. Inhalation

Lungs offer a large surface area for absorption of drugs. Volatile liquids and gases are given by inhalation.
e.g. General anaesthetics.
In addition, drugs can be administered as solid particles, i.e. solutions of drugs can be atomised and the fine droplets are inhaled as aerosol.
e.g. salbutamol.

Advantages

• Almost instantaneous absorption of the drug is achieved because of:
– The large surface area of the lungs
– Thin alveolar membrane
– High vascularity

Disadvantages

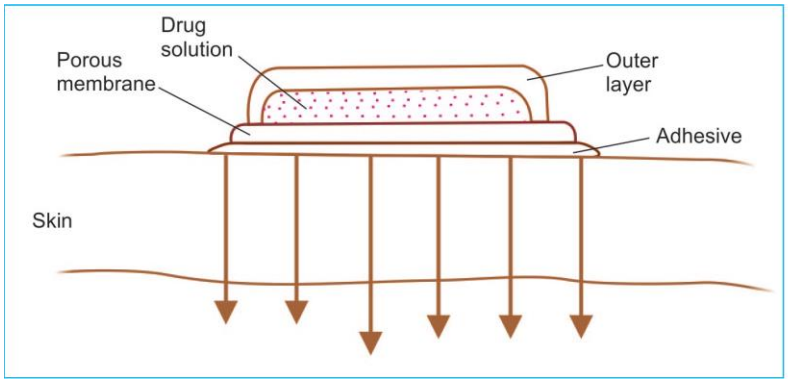
• Irritant gases may enhance pulmonary secretion—should be avoided.
• Drug particles may induce cough, e.g. cromolyn sodium. This is an important route of entry of certain drugs of abuse.

3. Transdermal

Highly lipid-soluble drugs can be applied over the skin for slow and prolonged absorption,
e.g. nitroglycerine ointment in angina pectoris.
Adhesive units, inunction, iontophoresis and jet injection are some forms of transdermal drug delivery.

Adhesive units: Transdermal adhesive units (transdermal therapeutic systems) are adhesive patches of different sizes and shapes made to suit the area of application. The drug is held in a

reservoir between an outer polymer layer and a porous membrane. The under surface of the membrane is smeared with an adhesive to hold on to the area of application. The drug slowly diffuses through the membrane and percutaneous absorption takes place. The rate of absorption is constant and predictable. Highly potent drugs (because small quantity is sufficient) and short-acting drugs (because effect terminates quickly after the system is removed) are suitable for use in such systems. Sites of application depend on the indication—they may be applied over the chest, abdomen, upper arm, back or mastoid region; testosterone patch is applied over the scrotum.
For examples: Hyoscine, nitroglycerin, testosterone, oestrogen, nicotine and fentanyl transdermal patches.



Transdermal adhesive unit

Advantages
- Duration of action is prolonged
- Provides constant plasma drug levels
- Patient compliance is good.

Disadvantages
- Large doses of the drug cannot be loaded into the system
- Can cause irritation to the skin
- Expensive.

Inunction: The route where a drug rubbed into the skin gets absorbed to produce systemic effects is called inunction.

LOCAL/TOPICAL APPLICATION

Drugs may be applied on the skin for local action as ointment, cream, gel, powder, paste, etc. Drugs may also be applied on the mucous membrane as in the eyes, conjunctiva, ears and nose as ointment, drops and sprays.
***Nasal*:** Drugs can be administered through nasal route either for systemic absorption or

for local effects.
For example, for systemic absorption, oxytocin spray is used.
For local effect—decongestant nasal drops,
e.g. oxymetazoline; budesonide nasal spray for allergic rhinitis.
Many drugs are administered as **suppository** for rectum, **bougie** for urethra and **pessary** and douche for vagina. Pessaries are oval-shaped tablets to be placed in the vagina to provide high local concentrations of the drug at the site.
e.g. antifungal pessaries in vaginal candidiasis.

AGONIST

An agonist is a substance that binds to the receptor and produces a response. It has both affinity and intrinsic activity, e.g. adrenaline is an agonist at □ and □ adrenergic receptors; morphine is an agonist at mu(μ) opioid receptors.

ANTAGONIST

An antagonist is a substance that binds to the receptor and prevents the action of agonist on the receptor. It has affinity but no intrinsic activity. An antagonist has a structural similarity to the natural ligand for the receptor because of which the receptor identifies the antagonist as its ligand. Naloxone is an antagonist at μ opioid receptors. It binds to the receptor, has no effect by itself, but blocks the action of the opioid agonists like morphine. Tubocurarine is an antagonist at the nicotinic receptors. It blocks the receptors and prevents the action of acetylcholine on the receptors. It was divided into two types:

1) Competitive
2) Non-Competitive

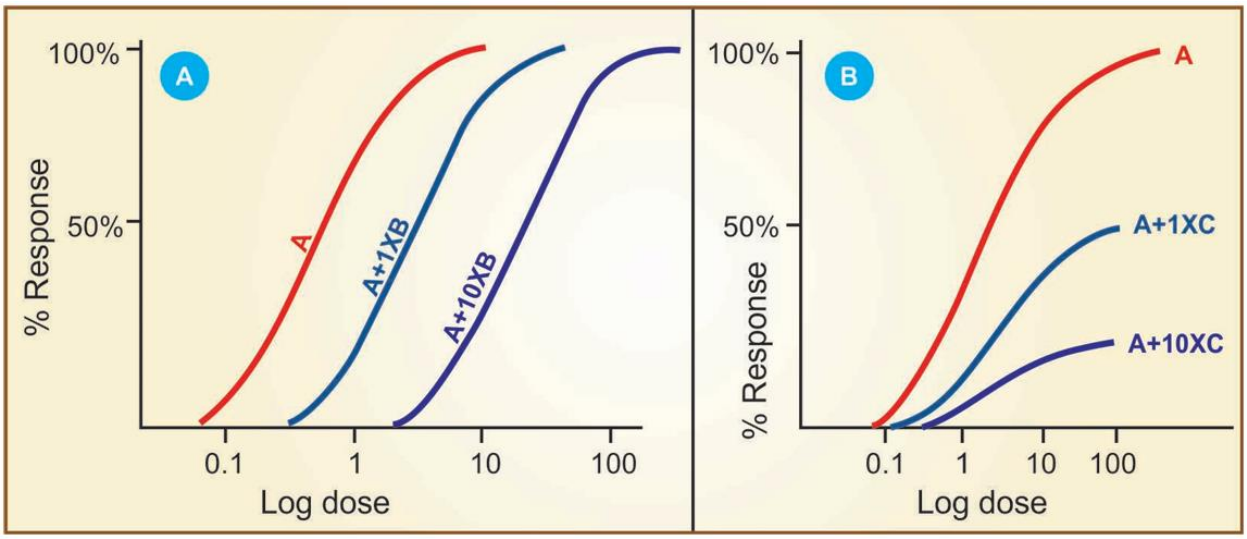
Competitive antagonist:

Competitive antagonism (equilibrium type) The antagonist is chemically similar to the agonist, competes with it and binds to the same site to the exclusion of the agonist molecules. Because the antagonist has affinity but no intrinsic activity , no response is produced and the log DRC of the agonist is shifted to the right. Since antagonist binding is reversible and depends on the relative concentration of the agonist and antagonist molecules, higher concentration of the agonist progressively overcomes the block—a parallel shift of the agonist DRC with no suppression of maximal response is obtained . The extent of shift is dependent on the affinity and concentration of the antagonist. A partial agonist , having affinity for the same receptor, also competes with and antagonizes a full agonist, while producing a submaximal response of its own.

Noncompetitive antagonism :

The antagonist is chemically unrelated to the agonist, binds to a different allosteric site altering the receptor in such a way that it is unable to combine with the agonist , or is unable to transduce the

response, so that the downstream chain of events are uncoupled. This is also called allosteric antagonism. Because the agonist and the antagonist are combining with different sites, there is no competition between them—even high agonist concentration is unable to reverse the block completely. Increasing concentrations of the antagonist progressively flatten the agonist DRC. Noncompetitive antagonists have been produced experimentally, but are not in clinical use.



Dose-response curves showing competitive (a) and noncompetitive (b) antagonism A—agonist, B—competitive antagonist, C—noncompetitive antagonist

SPARE RECEPTORS

In an experiment using adrenaline on rabbit aortic strips, Furchgott showed that the agonist occupied only a small percentage of receptors to produce maximum contraction. Some experiments showed that high concentration of an agonist can still produce maximal response in the presence of an irreversible antagonist and this was because of the presence of **'spare' or reserve receptors.** Thus it is possible to stimulate the myocardium even when 90% of the cardiac β-adrenergic receptors are blocked by an irreversible β-blocker.

ADDICTION

When we take any drug/substance for a long duration, then it show some unusual response in our body. It is a psychological & physical inability to stop consuming drug even drug cause harm. It considered as brain disorder. Drug addiction leads to the development of tolerance which increases the effective dose required for the production of normal therapeutic effect. Discontinuation (or) cessation of the drugs leads to relapse.

Eg: Amphetamines, cocaine, cannibs,alchol etc. These drugs produces addiction without physical dependence.

TOLERANCE

It is diminished effect (response) of any drug, when drug give repeatedly for long duration in same dose. It happens when a person no longer responds to a drug in the way they did it first. So, it takes a higher dose of the drug to achieve the same effect as when the person first used it.

Eg: Excess use of paracetamol

DEPENDENCE

- When a drug is repeatedly administered beyond the dosage prescribed, drug dependence occurs. A condition in which a drug is administered for short intervals & in doses prescribed by the doctor to treat certain condition is not drug dependence; however taking the same drug in doses larger than prescribed, develops drug dependency.
- In case of drug dependence, if the drug administration is stopped or a drug is not taken in large doses, withdrawal syndrome will occur. Although the withdrawal symptoms are drug dependant but anxiety, sweating, shaking, nausea, vomiting and muscle pain are some common symptoms experienced by most of the addicts. With drawl symptoms of some drug dependence are confusion and hallucination.

  Eg: Excess use of Analgesic drug

TACHYPHYLAXIS

An acute development of Tolerance on rapid & repeated administration of a drug is know as Tachyphylaxis. It occurs when the cell receptors undergo transient saturation with the drug.

For example: On administration repeated intravenous doses of ephendrine in an anaesthetized animal (such as dog) at short intervals, smaller hypertensive responses are produced on the blood pressure.

IDIOSYNCRASY

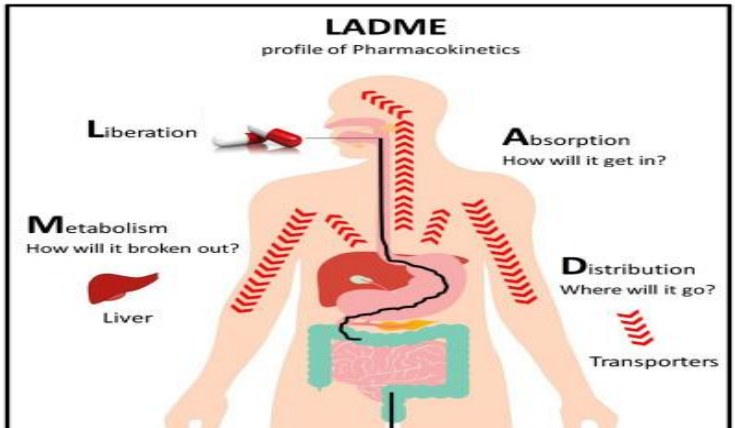
- The abnormal responses or side effect shows upon administration of a drug because of genetic defects in the patient are called as idiosyncrasies.
- These responses don't occur in every patient. The affected individual react in an abnormal way towards the drug. The study of idiosyncrasises is called as pharmacogenetics.

Ex: Chloramphenicol with leads to aplastic anemia.

Barbiturates with produces excitement & mental confusion in some individuals.

ALLERGY

- An inappropriate immune response by the body to a drug is called as drug hypersensitivity or allergy. The allergy is not dose related & is not dependent upon the pharmacological profile of the drug.
- It occurs due to the sensitization of the patient upon first exposure to a drug acting as allergen.
- Upon subsequent administration of the same drug, the immune system gets activated, thereby producing antibodies against the drug. The antigen-antibody reaction results in rashes, oedema, wheezing etc.



PHARMACOKINETICS

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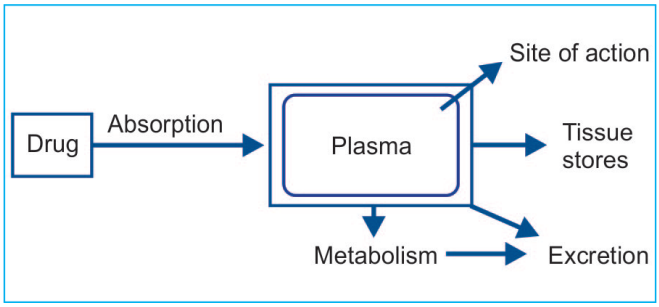
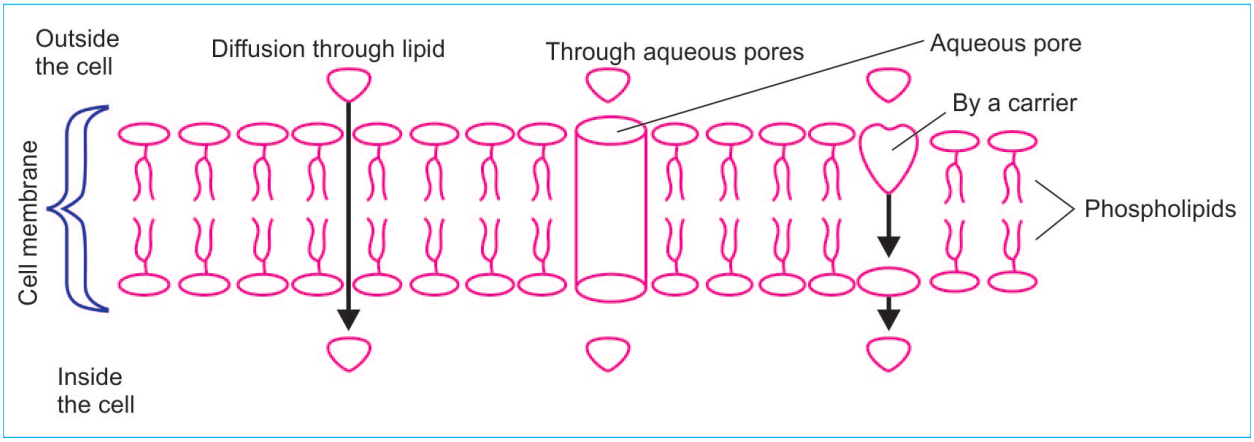
Pharmacokinetics is the study of the absorption, distribution, metabolism and excretion of drugs, i.e. the movement of the drugs into, within and out of the body. For a drug to produce its specific response, it should be present in adequate concentrations at the site of action. This depends on various factors apart from the dose. Once the drug is administered, it is absorbed, i.e. enters the blood, is distributed to different parts of the body, reaches the site of action, is metabolised and excreted.



Schematic representation of movement of drug in the body

All these processes involve passage of the drug molecules across various barriers—like the intestinal epithelium, cell membrane, renal filtering membrane, capillary barrier and so on. To cross these barriers, the drug has to cross the cell membrane or pass in-between the epithelial or endothelial cells. The cell membrane/biological membrane is made up of two layers of phospholipids with intermingled protein molecules.



Movement of drugs across biological membrane

All lipid-soluble substances get dissolved in the cell membrane and readily permeate into the cells. The junctions between adjacent epithelial or endothelial cells have pores through which small water-soluble molecules can pass. Movement of some specific substances is regulated by special carrier proteins. The passage of drugs across biological membranes or drug permeation involves processes like passive (filtration, diffusion) and active transports.

TRANSPORT OF DRUGS ACROSS BIOLOGICAL MEMBRANES

1. Passive transfer
- Simple diffusion
- Filtration

2. Carrier-mediated transport
- Active transport
- Facilitated diffusion

3. Endocytosis and exocytosis

Passive Transfer: The drug moves across a membrane without any need for energy.

Simple Diffusion

Simple diffusion is the transfer of a drug across the membrane in the direction of its concentration gradient. The speed of diffusion depends on the degree of concentration gradient, lipid solubility and ionisation. Higher the concentration gradient, faster is the diffusion across the membrane. Lipid-soluble, unionized drugs are rapidly transferred across membranes by simple diffusion—after dissolving in the lipids of the cell membrane (also called lipid diffusion). Most drugs follow simple diffusion.

Filtration

Filtration is the passage of drugs through aqueous pores in the membrane. Water soluble drugs with molecular size (mol. wt. <100) smaller than the diameter of the pores (7Å) cross the biological membranes by filtration or aqueous diffusion. The movement is along the concentration gradient, e.g. urea.

The capillaries in certain tissues, like the brain and testes, lack the aqueous pores and may also contain efflux pumps. Thus many drugs do not reach them and are called **'sanctuary sites'**.

Carrier-mediated Transport

Transport of certain substances, which cannot move by diffusion, is aided by specific carriers.

Active Transport

Active transport is the transfer of drugs against a concentration gradient and needs energy. It is carried by a specific carrier protein. Only drugs related to natural metabolites are transported by this process, e.g. levodopa, iron, sugars and amino acids. The compound binds to a specific carrier on one side of the membrane and moves across the cell. At the other side of the cell, the complex dissociates and the carrier moves back to transport another molecule. Other substances competing for the same mechanism for transport may interfere with drug movement because this process is saturable, e.g. when penicillin and probenecid are administered together, the duration of action of penicillin is prolonged because both of them compete for renal tubular secretion.

Facilitated Diffusion

Facilitated diffusion is a unique form of carrier transport which differs from active transport in that it is not energy dependent and the movement occurs in the direction of the concentration gradient. The carrier facilitates diffusion and is highly specific for the substance, e.g. uptake of glucose by cells, vitamin B12 from intestines.

Endocytosis and Exocytosis

Endocytosis is the process where small droplets are engulfed by the cell membrane and carried into the cell as a vesicle. The vesicular membrane is then broken down to release the substances. Some proteins and vitamin B12 with the help of intrinsic factor are taken up by this process (like pinocytosis in amoeba). This process is currently being tried for delivery of some anticancer drugs to the tissues. The reverse process—exocytosis is responsible for secretion of many substances from cells, e.g. neurotransmitters stored in nerve endings.

ABSORPTION

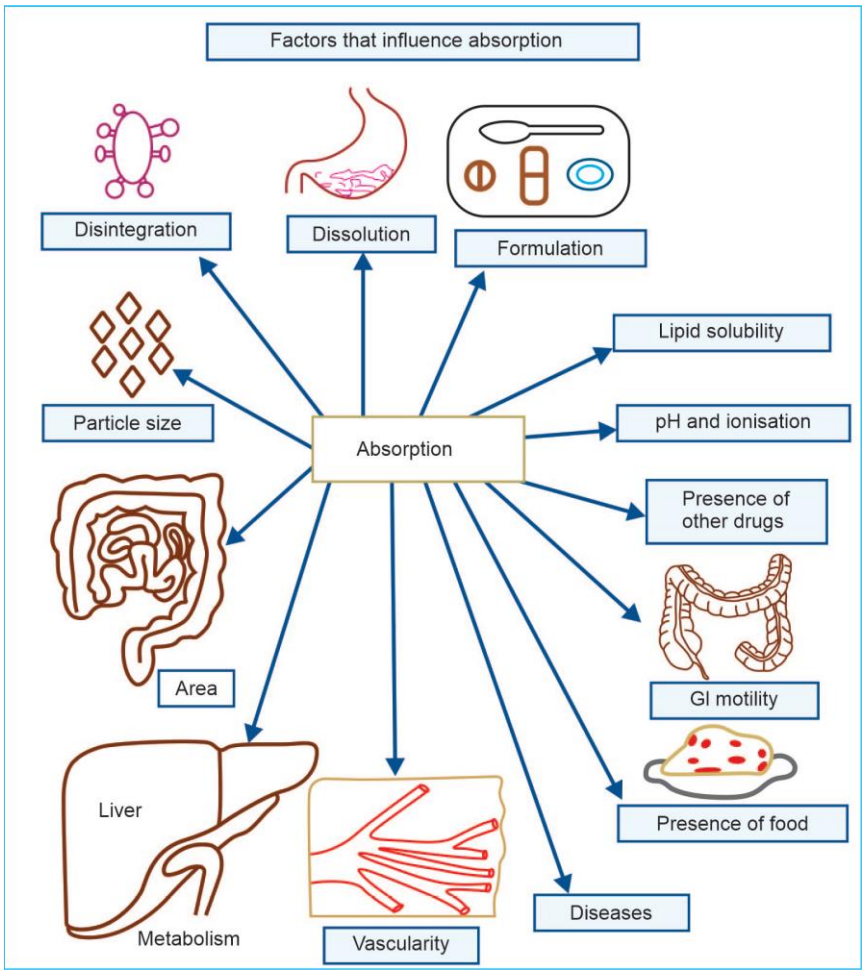
Absorption is defined as the passage of the drug from the site of administration into the circulation. For a drug to reach its site of action, it must pass through various membranes depending on the route of administration.

Absorption occurs by one of the processes described above, i.e. passive diffusion or carrier-mediated transport. Thus except for intravenous route, the drug needs to be absorbed from all other routes of administration. The rate and extent of absorption varies with the route of administration.

Absorption from the Gut

Medication taken orally may be absorbed from any part of the gut. Highly lipid-soluble drugs may be absorbed from the buccal cavity from where it directly enters the systemic circulation. Acidic drugs are absorbed from the stomach, while basic drugs get ionised in the stomach and are not absorbed from the stomach.

Intestines have a large surface area and most drugs are absorbed from the proximal part of the jejunum. Basic drugs are absorbed from the intestines because of the favourable pH. Various factors, like intestinal motility and pH, influence absorption from the gut. Absorption from the large intestine is negligible. It has now been found that certain drugs may be transported out from the cells of the intestinal wall back into the gut lumen. This is done with a reverse transporter or efflux transporter P-glycoprotein.



Factors Influencing Drug Absorption

Several factors influence the rate and extent of absorption of a drug given orally.

A. Pharmaceutical factors

1. **Disintegration and dissolution time:** The drug taken orally should break up into individual particles (disintegrate) to be absorbed. It then has to dissolve in the gastrointestinal fluids and the rate at which it dissolves influences absorption. In case of drugs given subcutaneously or intramuscularly, the drug molecules have to dissolve in the tissue fluids. Liquids are absorbed

faster than solids. Delay in disintegration and dissolution as with poorly water-soluble drugs like aspirin, results in delayed absorption.

2. **Formulation:** Pharmaceutical preparations are formulated to produce desired absorption. Inert substances used with drugs as diluents like starch and lactose may sometimes interfere with absorption.

3. **Particle size:** Small particle size is important for better absorption of drugs. Drugs like corticosteroids, griseofulvin, digoxin, aspirin and tolbutamide are better absorbed when given as small particles. On the other hand, when a drug has to act on the gut and its absorption is not desired, then particle size should be kept large, e.g. anthelmintics like bephenium hydroxynaphthoate.

B. Drug factors

4. **Lipid solubility:** Lipid-soluble drugs are absorbed faster and better by dissolving in the phospholipids of the cell membrane.

5. **pH and ionisation:** Ionised drugs are poorly absorbed while unionised drugs are lipid-soluble and are well absorbed. Strong electrocytes are almost completely ionised at both acidic and alkaline pH. However, most drugs are weak electrolytes and exist in both ionised and unionised forms. The degree of ionization depends on the pH of the medium. Thus acidic drugs remain unionised in acidic as sodium or potassium salts, e.g. phenobarbitone sodium, potassium penicillin-V. Weakly basic drugs form salts with acids and thus we have their hydrochlorides and sulphates, e.g. ephedrine hydrochloride, atropine sulphate. Basic drugs are unionised when they reach the alkaline medium of the intestine from where they are rapidly absorbed, e.g. pethidine, ephedrine. Basic drugs given intravenously may diffuse from blood into the stomach because of acidic pH and may ionise quickly. This is known as ‘ion trapping’. Strong acids and bases are highly ionised and, therefore, poorly absorbed, e.g. heparin, streptomycin.

C. Biological factors

6. **Area and vascularity of the absorbing surface:** The larger the area of the absorbing surface and more the vascularity—better is the absorption. Thus most drugs are absorbed from the small intestine.

7. **Gastrointestinal motility**

• Gastric emptying time—if gastric emptying is faster, the passage of the drug to the intestines is quicker and hence absorption is faster.

• Intestinal motility—when highly increased as in diarrhoeas, drug absorption is reduced.

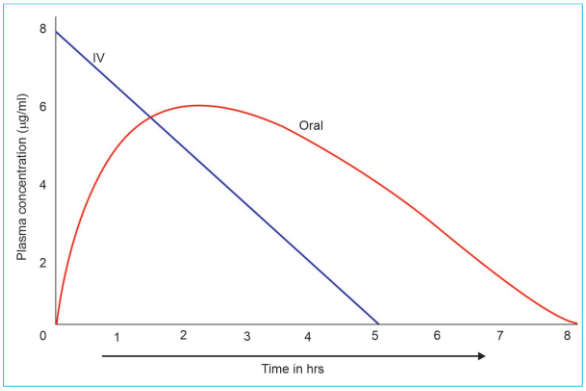
8. **Presence of food** delays gastric emptying, dilutes the drug and delays absorption. Drugs may form complexes with food constituents and such complexes are poorly absorbed, e.g. tetracyclines chelate calcium present in the food—hence their bioavailability is decreased. Moreover, certain drugs like ampicillin, roxithromycin and rifampicin are well absorbed only on empty stomach.

9. **Diseases** of the gut like malabsorption and achlorhydria result in reduced absorption of drugs. Particularly acidic drugs are poorly absorbed in presence of achlorhydria. In the absence of intrinsic factor, vitamin B12 is not absorbed in pernicious anemia.

10. **First pass metabolism:** Some drugs may be degraded in the GI tract, e.g. nitroglycerine, insulin before reaching the circulation. First pass metabolism is the metabolism of a drug during its passage from the site of absorption to the systemic circulation. It is also called **presystemic metabolism** or **first pass effect** and is an important feature of oral route of administration. Such drugs should be given in higher doses or by metabolised in the gut wall and in the liver before reaching the systemic circulation. The extent of first pass metabolism differs from drug to drug and among individuals from partial to total inactivation.

Absorption from Parenteral Routes

On **intravenous administration,** the drug directly reaches the circulation. **intramuscular injection,** the drug is deposited in the muscles and the drug molecules should dissolve in the tissue fluids and then be absorbed. Since muscles have a rich blood supply, absorption is fast. Drug molecules diffuse through the capillary membrane and reach the circulation. Lipid-soluble drugs are absorbed faster.



Plasma concentration–time curve of a drug following a single oral and IV dose

Absorption from **subcutaneous administration** is slower but rate of absorption is somewhat steady. Hyaluronidase increases rate of absorption.

Inhaled drugs are rapidly absorbed from the pulmonary epithelium particularly the lipid-soluble ones. On topical application, highly lipid-soluble drugs are absorbed from the intact skin, e.g.

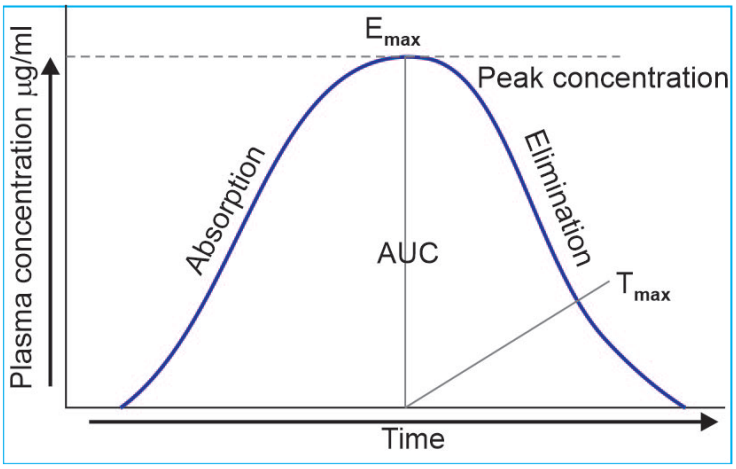
nitroglycerine; but absorption is relatively slow because of the multiple layers of closely packed cells in the epidermis. Most drugs are readily absorbed from the mucous membranes.

BIOAVAILABILITY

Definition: Bioavailability is the fraction (F) of the administered drug that reaches the following administration by any route. Thus, when a drug is given intravenously, the bioavailability is 100%. On IM/SC injection and sublingual administration, drugs are almost completely absorbed (bioavailability >75%) while by oral route, bioavailability may be low due to incomplete absorption and first pass metabolism, e.g. bioavailability of chlortetracycline is 30%, carbamazepine— 70%, chloroquine—80%, minocycline and diazepam almost 100%. Transdermal preparations are absorbed systemically and may have 80–100% bioavailability while for rectal administration it may be 30% to almost 100%. Large bioavailability variations of a drug, particularly when it is unpredictable, can result in toxicity or therapeutic failure as in case of halofantrine.

Bioavailability is calculated by the formula:

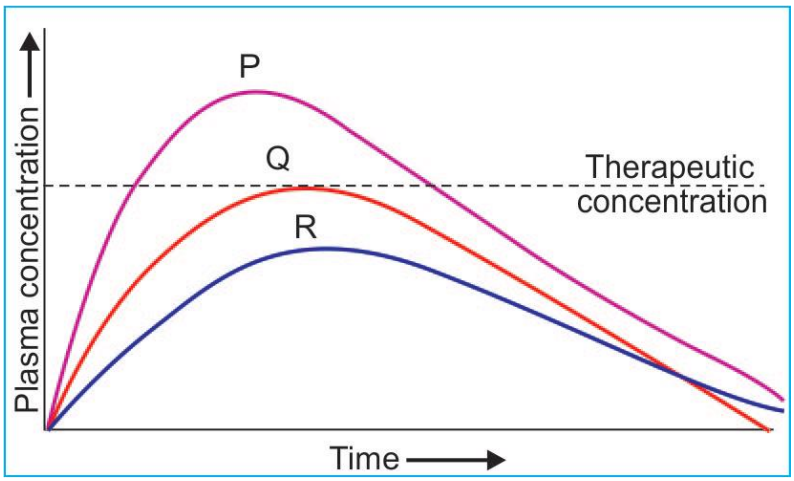
$$\text{Bioavailability (F)} = \frac{\text{AUC (oral)} \times 100}{\text{AUC (IV)}}$$



Graph showing peak plasma concentration (Emax), time to peak plasma concentration (Tmax) and area under the curve (AUC) which are the parameters of bioavailability

BIOEQUIVALENCE

Definition: If two formulations of a drug have the same bioavailability, they are bioequivalent. Comparison of bioavailability of different formulations of the same drug is the study of bioequivalence. If two drug formulations have the same bioavailability and rate of absorption, they are bioequivalent. Often oral formulations containing the same amount of a drug (pharmaceutically equivalent) from different manufacturers may result in different plasma concentrations, or may differ in the rate of absorption, i.e. there is no bioequivalence among them.



Study of bioequivalence—three different oral formulations—P, Q and R of the same drug yield different bioavailability values.

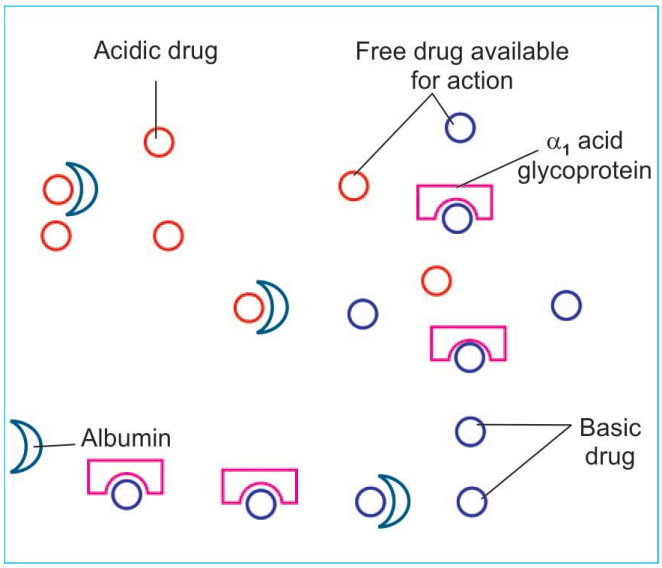
The area under each curve gives the bioavailability of the respective formulation. with poorly soluble, slowly absorbed drugs, mainly due to differences in the rate of disintegration and dissolution. Variation in bioavailability (non-equivalence) can result in toxicity or therapeutic failure of drugs that have low safety margin like digoxin and drugs that need precise dose adjustments like anticoagulants and corticosteroids. For such drugs, in a given patient, the preparations from a single manufacturer should be used.

DISTRIBUTION

After a drug reaches the systemic circulation, it gets distributed to other tissues. It should cross several barriers before reaching the site of action. Like absorption, distribution also involves the same processes, i.e. filtration, diffusion and specialized transport. Various factors determine the rate and extent of distribution, viz. lipid solubility, ionization, blood flow and binding to plasma proteins and cellular proteins. Unionized lipid-soluble drugs are widely distributed throughout the body.

Plasma Protein Binding

On reaching the circulation, most drugs bind to plasma proteins; acidic drugs bind mainly albumin and basic drugs to alpha-acid glycoprotein. The free or unbound fraction of the drug is the only form available for action, metabolism and excretion while the protein bound form serves as a reservoir. The extent of protein binding varies with each drug, e.g. warfarin is 99% and morphine is 35% protein bound while binding of ethosuximide and lithium is 0%, i.e. they are totally free. Some drugs also bind to tissue proteins and specific carrier proteins (e.g. corticosteroids to transcortin, iron to ferritin).



Plasma protein binding

Clinical Significance of Plasma Protein Binding

1. Only free fraction is available for action, metabolism and excretion. When the free drug levels in the plasma fall, bound drug is released. Thus protein binding may delay the drug reaching the site of action.
2. Protein binding serves as a store (reservoir) of the drug and the drug is released when free drug levels fall.
3. Protein binding prolongs the half-life and thereby the duration of action of the drug because the bound form is protected from metabolism and excretion. Bound form is not filtered at the glomerulus and the excretion is therefore delayed. Highly protein bound drugs are generally long-acting.
4. Many drugs may compete for the same binding sites. Thus one drug which has higher affinity for the binding site may displace another from the binding sites and result in displacement interactions, e.g. warfarin is 99% bound to albumin (i.e.free fraction is 1%). If another drug, like indomethacin, reduces its binding to 95%, the free form then becomes 5% which means, there is a

5-fold increase in free warfarin levels which could result in toxicity. Fortunately, the body largely compensates by enhancing metabolism and excretion.
5. Protein binding sites may get saturated with repeated administration of the drug and thereafter more and more drug will remain in the free form.
6. Chronic renal failure and chronic liver disease result in hypoalbuminaemia with reduced protein binding of drugs leading to raised levels of free drug. The normal plasma albumin concentration is 0.6 mm/litre. Highly protein bound drugs should be carefully used in such patients because even therapeutic doses of such drugs can result in toxicity and may require dose reduction.
7. In pregnancy, there is an increase in thyroxine binding protein levels resulting in reduced free thyroxine levels.
8. In acute inflammatory states, alpha 1 acid glycoprotein levels may rise resulting in more extensive binding and thereby lower free drug levels—hence, higher doses may be needed.

Tissue Binding

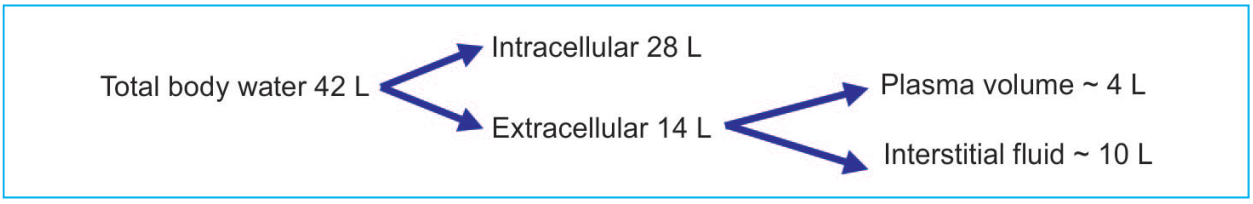
Some drugs get bound to certain tissue constituents because of special affinity for them. Tissue binding delays elimination and thus prolongs duration of action of the drug. For example, lipid-soluble drugs are bound to adipose tissue. Tissue binding also serves as a **reservoir** of the drug.

Redistribution

When some highly lipid-soluble drugs are given intravenously or by inhalation, they get rapidly distributed into highly perfused tissues like the brain, heart and kidney. But soon they get redistributed into less vascular tissues like the muscle and fat resulting in termination of the action of these drugs. The best example is the intravenous anaesthetic thiopental sodium which induces anaesthesia in 10–20 seconds but the effect ceases in 5–15 minutes due to redistribution.

Blood–Brain Barrier (BBB)

The endothelial cells of the brain capillaries lack intercellular pores and instead have tight junctions. Moreover, glial cells envelope the capillaries and together these form the BBB. Drugs have to pass through the cells to cross the barrier. Only lipid-soluble, unionised drugs can cross this BBB. During inflammation of the meninges, the barrier becomes more permeable to drugs, e.g. penicillin readily penetrates during meningitis.
The barrier is weak at some areas like CTZ, posterior pituitary and parts of hypothalamus and allows some compounds to diffuse. Since the pH of CSF is 7.35, weakly basic drugs concentrate in it more than the acidic drugs.



Placental Barrier

Lipid-soluble, unionised drugs readily cross the placenta while lipid-insoluble drugs cross to a much lesser extent. Thus drugs taken by the mother can cause several unwanted effects in the foetus. Lipid-soluble drugs with molecular weight of about 200–500 can easily cross the placenta while those with large molecular size (mol.wt >1000) can hardly cross the placenta. These require transporters for crossing the placenta.

VOLUME OF DISTRIBUTION (V)

For the purpose of pharmacokinetic studies, body can be considered as a single compartment into which drugs are distributed uniformly. Each drug actually follows its own pattern of distribution from plasma to other body fluids and tissues.

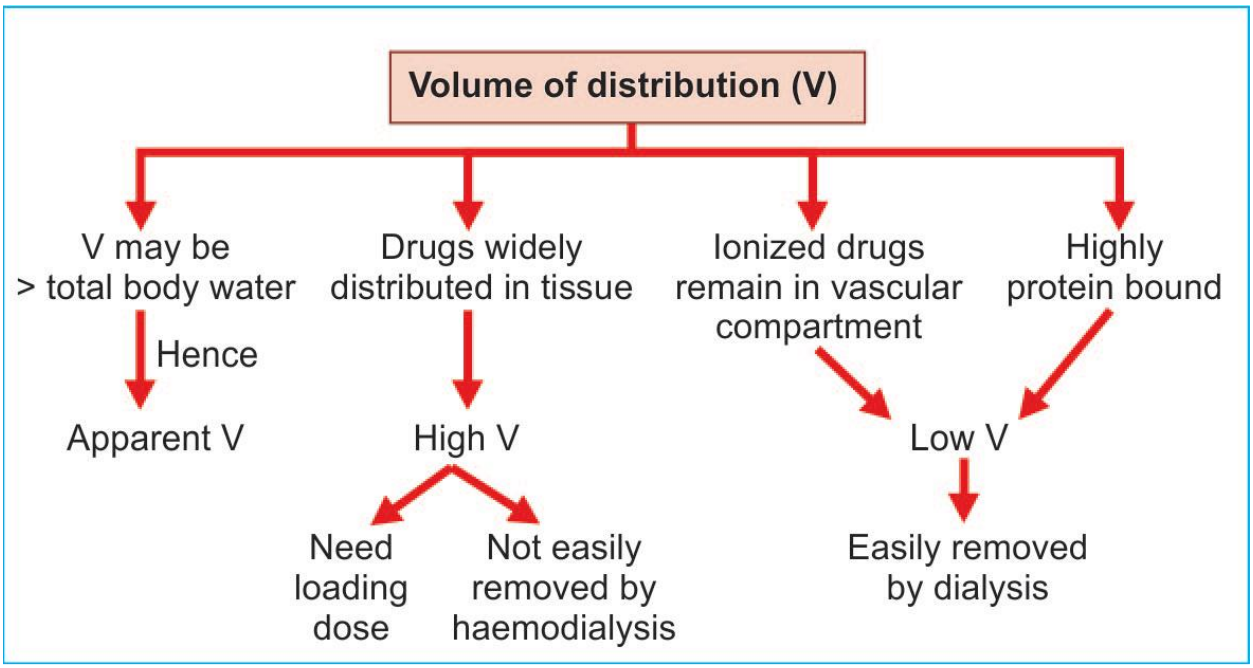
Apparent Volume of Distribution

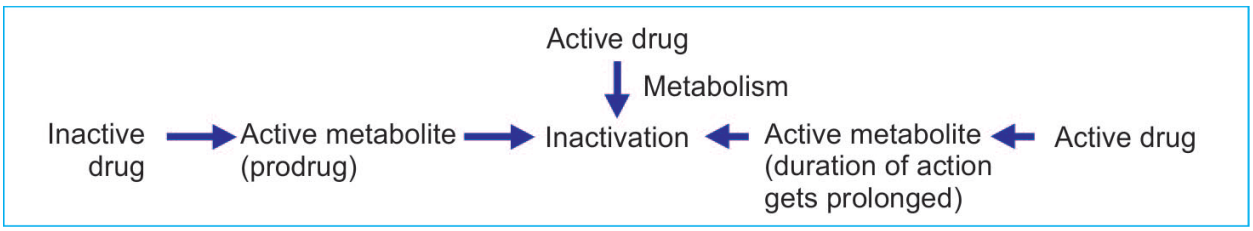
Apparent volume of distribution is a hypothetical concept. This is defined as the volume necessary to accommodate the entire amount of the drug administered, if the concentration throughout the body is equal to that in plasma. It can also be defined as the volume in which the drug can be evenly distributed, if the concentration attained was equal to that in plasma. It is called ‘apparent’ as the volume here is ‘apparently’ needed to hold the drug and the uniform distribution of the drug is presumed. It relates the amount of the drug in the body to the concentration (C) of the drug in plasma. The volume so calculated can be more than the total body water and is therefore called the ‘apparent’ volume of distribution.

It is calculated as:

$$V = \frac{\text{Amount of drug in the body}}{\text{Plasma concentration (C)}}$$

e.g. if the dose of a drug given is 500 mg and it attains a uniform concentration of 10 mg/ litre of plasma in the body, its V = 50 litres.

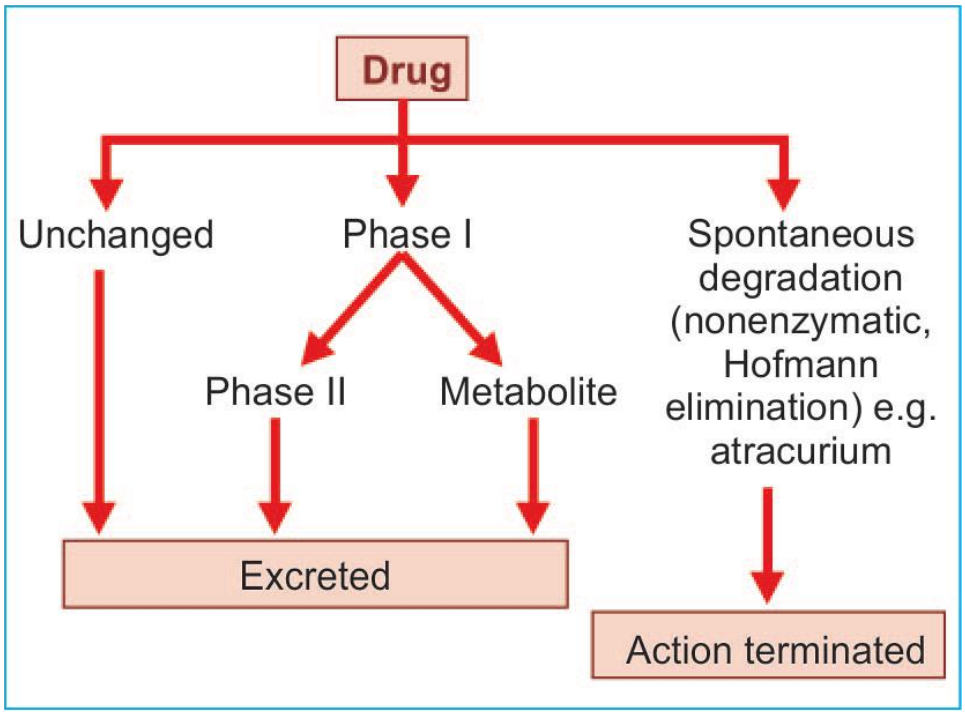




Biotransformation

BIOTRANSFORMATION (METABOLISM)

Biotransformation is the process of biochemical alteration of the drug in the body Body treats most drugs as foreign substances (called xenobiotics) and tries to inactivate and eliminate them by various biochemical reactions. These processes convert the nonpolar, lipid soluble drugs into more polar, water-soluble compounds so that they are easily excreted through the kidneys and not reabsorbed. Some drugs may be excreted largely unchanged in the urine, e.g. frusemide, atenolol.



Phases in metabolism of drugs. A drug may be excreted as phase I metabolite or as phase II metabolite.

Site

The most important organ of biotransformation is the liver. Drugs are also metabolized though to a small extent by the kidney, gut mucosa, lungs, blood and skin.

Consequences of Biotransformation

Though biotransformation generally inactivates the drug, some drugs may be converted to metabolites which are also active or more active than the parent drug.

1. **Inactivation**—Largely biotransformation inactivates the drug and most drugs are converted to inactive metabolites, e.g. phenytoin, paracetamol, phenobarbitone.
2. Formation of active metabolite—(active drug to active metabolite) biotransformation may convert the drug partly to metabolites which are also active or more active than the parent drug, e.g. diazepam to oxazepam; such generation of active metabolites prolongs the duration of action of the drug.
3. Activation of inactive drug—prodrug is an inactive drug which gets converted into an active drug in the body, e.g. Levodopa to dopamine
4. Formation of toxic metabolite—in case of some drugs, the active metabolite may be toxic. For example, paracetamol is converted to N-acetyl-p-benzoquinoneimine (NAPQI) which causes hepatotoxicity; cyclophosphamide is converted to acrolein which causes bladder toxicity.

Some drugs may be converted to epoxides which are short acting but highly reactive molecules. They bind to cells and tissues resulting in toxicity. Epoxide-induced liver damage is countered to a large extent by glutathione conjugation.

Enzymes in Biotransformation

The biotransformation reactions are catalyzed by specific enzymes located either in the liver microsomes (microsomal enzymes) or in the cytoplasm and mitochondria of the liver cells and also in the plasma and other tissues (nonmicrosomal enzymes). Microsomal enzymes are a mixed function oxidase system or mono-oxygenases and require nicotine adenine dinucleotide phosphate (NADPH) and oxygen. Microsomal enzymes cytochrome P450 (CYP) are important in the oxidation reduction reactions. There are several isoforms of the P450 enzymes. Several CYP gene families are known, of which the first three—CYP1, CYP2 and CYP3—are important groups. Some isozymes are CYP1A2, CYP2A6, CYP2B6, CYP2C9, CYP2C19, CYP3A4 and are the most important enzymes involved in biotransformation in the liver. CYP3A4 alone is found to metabolise nearly 50% of the drugs degraded in the liver.

The chemical reactions of biotransformation
can take place in two phases:

1. Phase I (non-synthetic reactions)
2. Phase II (synthetic reactions).

Phase I Reactions

Phase I reactions convert the drug to a more polar metabolite by oxidation, reduction or hydrolysis.

1. Oxidation is the process of addition of oxygen (or a negatively charged radical) to a drug molecule or removal of hydrogen (or a positively charged radical) from a drug molecule. Oxidation reactions are the most important metabolizing reactions, mostly catalyzed by mono-oxygenases present in the liver .They are carried on by a system which includes cytochrome P450, NADPH and molecular oxygen. There are several types of oxidation reactions like:

A. *Microsomal oxidation*

i. S-oxidation (sulfoxidation)
Cimetidine ⟶ cimetidine sulfoxide
ii. N-oxidation
Dapsone ⟶ hydroxylamine dapsone
ii. Dealkylation
Imipramine ⟶ desmethylimipramine
Codeine ⟶ morphine.
iii. Hydroxylation

Salicylic acid ⟶ gentisic acid
Phenytoin ⟶ hydroxy phenytoin
iv. Deamination
Amphetamine ⟶ Benzyl methyl ketone

B. Non-microsomal oxidation

1. Oxidation can also be catalysed by nonmicrosomal enzymes like monoamino oxidase, xanthine oxidase, alcohol dehydrogenase and aldehyde dehydrogenase.
Example: Ethyl alcohol ⟶ CO2 + H2O

2. Reduction may be catalysed by microsomal or non-microsomal enzymes. Microsomal reduction reactions include
i. Nitro reduction
e.g. Chloramphenicol ⟶ Arylamine
ii. Keto reduction
e.g. Cortisone ⟶ hydrocortisone
Disulfiram and nitrites are reduced by **non-microsomal enzymes.**

3. Hydrolysis is the process where a drug molecule is 'split' by the addition of a molecule of water (both microsomal and non- microsomal enzymes may be involved).
Esterases, amidases and peptidases catalyze hydrolytic reactions are non-microsomal enzymes.
For example:
Acetylcholine + H2O ⟶ Choline + Acetic acid
Other drugs like lignocaine, procaine, atropine, pethidine and neostigmine are metabolized by hydrolysis. If the metabolite of phase I reaction is not sufficiently polar to be excreted, it undergoes phase II reactions.

Phase II Reactions

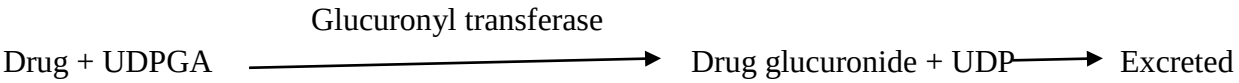
In phase II reactions, endogenous water soluble substances like glucuronic acid, sulfuric acid, glutathione or an amino acid combine with the drug or its phase I metabolite to form a highly polar conjugate which is inactive and gets readily excreted by the kidneys. Large molecules are excreted through the bile.

Conjugation results invariably in inactivation of the drug. Some products of conjugation are glucuronides, ethereal sulphates and amino acid conjugates.

Microsomal conjugation reaction

Glucuronide conjugation is the most common type of metabolic reaction. Endogenous substances like bilirubin and steroid hormones also undergo conjugation. The drug or its phase I metabolite undergoes conjugation with uridine diphosphate glucuronic acid (UDPGA) followed by transfer of glucuronic acid to the drug. The reaction is catalysed by the enzyme UDP glucuronyl transferase

and the drug—glucuronide conjugate formed is polar, inactive and can be readily excreted through the kidneys.



e.g.
Morphine + Glucuronic acid ⟶ Morphine glucuronide.

The enzyme glucuronyl transferase is not adequately formed in the neonate. Hence bilirubin levels increase and result in **neonatal jaundice**. Grey baby syndrome—an adverse effect to high doses of chloramphenicol seen in neonates is also because of the lack of UDP glucuronyl transferase. Several endogenous substances involved in conjugation are supplied by the diet. Hence nutrition is also important for conjugation and thereby detoxification of the drugs.

Non-microsomal conjugation reactions

i. **Acetylation (acetyl conjugation):** Drugs like sulfonamides and isoniazid undergo conjugation with acetylcoenzyme A. This acetylation is catalysed by N-acetyltransferase found in the cytoplasm.
ii. **Methylation (methyl conjugation):** Catecholamines, like adrenaline and dopamine, undergo methyl conjugation or methylation catalyzed by the enzyme transmethylase. The methyl group is donated by methionine and cysteine. The following are other conjugation reactions.
iii. **Glutathione conjugation:** Though a minor pathway of metabolism, glutathione conjugation inactivates highly reactive intermediates formed during the metabolism of drugs like paracetamol. Many epoxides and drugs with nitrate groups undergo glutathione conjugation with the help of the enzyme glutathion- S-transferase.
iv. **Amino acid conjugation** is a minor pathway for metabolism of certain acidic drugs like aspirin, for example: Benzoic acid + glycine ⟶ Hippuric acid
v. **Sulfate conjugation** is catalyzed by sulfotransferases,
e.g steroids, chloramphenicol, methyldopa. Sulfation can also result in the conversion of minoxidil, a prodrug into its active metabolite.
vi. **Glycine conjugation** though also a minor metabolic pathway, drugs like salicylates are conjugated with glycine.

ENZYME INDUCTION

Microsomal enzymes are located in the microsomes that line the smooth endoplasmic reticulum of the liver cells. The **synthesis** of these microsomal enzymes, mainly cytochrome P450, can be enhanced by certain drugs and environmental pollutants. This is called **enzyme induction** and this process speeds up the biotransformation of the inducing drug itself and also other drugs metabolised by the same microsomal enzymes, e.g. phenobarbitone, rifampicin, alcohol, cigarette

smoke, DDT (environmental pollutants), griseofulvin, carbamazepine, phenytoin and many antiretroviral drugs like nevirapine and efavirenz are enzyme inducers.

Enzyme induction may be selective for some particular enzymes (as with DDT) or may be nonselective as with phenobarbitone which could induce most microsomal enzymes. Enzyme induction may be blocked by drugs that inhibit protein synthesis. Enzymes are induced gradually and take about 1–2 weeks for peak effect and induction continues till the drug is administered. However, it is reversible and the enzyme levels return to initial levels in about 1–3 weeks. Enzyme induction can enhance drug metabolism by 2–4 times. However, it can also result in toxicity if the metabolite is toxic.

ENZYME INHIBITION

Some drugs inhibit cytochrome P450 enzyme activity. Drugs like cimetidine bind to cytochrome P450 and competitively inhibit the metabolism of endogenous substances like testosterone and other drugs given concurrently. Enzyme inhibition by drugs is the basis of several drug interactions. Chloramphenicol, erythromycin, ketoconazole, cimetidine, ciprofloxacin and verapamil are some enzyme inhibitors. With some drugs, the binding of enzymes may be irreversible— leading to inactivation of the enzyme. Such substrates are called **suicide inhibitors**, e.g. selegiline, ticlopidine, clopidogrel and prophylthiouracil. Many of the antiretroviral drugs used in AIDS are enzyme inhibitors. Drugs could also inhibit other enzymes, i.e. **non-microsomal enzymes**. Such inhibition could be competitive or non-competitive inhibition.

EXCRETION

Drugs are excreted from the body after being converted to water-soluble metabolites while some are directly eliminated without metabolism. The major organs of excretion are the kidneys, the intestine, the biliary system and the lungs. Drugs are also excreted in small amounts in the saliva, sweat and milk.

Renal Excretion

Kidney is the most important organ of drug excretion. The three processes involved in the elimination of drugs through kidneys are glomerular filtration, active tubular secretion and passive tubular reabsorption.

Glomerular Filtration

The rate of filtration through the glomerulus depends on GFR, concentration of free drug in the plasma and its molecular weight. Ionised drugs of low molecular weight (<10,000) are easily filtered through the glomerular membrane.

Active Tubular Secretion

Cells of the proximal tubules actively secrete acids and bases by two transport systems. Thus acids like penicillin, salicylic acid, probenecid, frusemide; bases like amphetamine and histamine are so excreted. Drugs may compete for the same transport system resulting in prolongation of action of each other, e.g. penicillin and probenecid.

Passive Tubular Reabsorption

Passive diffusion of drug molecules can occur in either direction in the renal tubules depending on the drug concentration, lipid solubility and pH. As highly lipid-soluble drugs are largely reabsorbed, their excretion is slow. Acidic drugs get ionised in alkaline urine and are easily excreted while bases are excreted faster in acidic urine. This property is usefulin the treatment of poisoning. In poisoning with acidic drugs like salicylates and
barbiturates, forced alkaline diuresis (diuretic + sodium bicarbonate + IV fluids) is employed to hasten drug excretion. Similarly, elimination of basic drugs, like quinine and amphetamine, is enhanced by forced acid diuresis.

Faecal and Biliary Excretion

Unabsorbed portions of the orally administered drugs are eliminated through the faeces. Liver transfers acids, bases and unionised molecules into bile by specific acid transport processes. Large water-soluble conjugates are excreted in the bile. Some drugs may get reabsorbed in the lower portion of the gut and are carried back to the liver. Such recycling is called enterohepatic circulation and it prolongs the duration of action of the drug; examples are chloramphenicol, tetracycline, oral contraceptives and erythromycin.

Pulmonary Excretion

The lungs are the main route of elimination for gases and volatile liquids, viz. general anaesthetics and alcohol. The drug is eliminated with the expired air and is dependent on the rate of respiration and the blood flow to the lungs. This also has legal implications in medicolegal practice as the breath analyser is used to measure alcohol levels in the expired air in vehicle drivers.

Small amounts of some drugs are eliminated through the sweat and saliva. Excretion in saliva may result in a unique taste of some drugs like phenytoin, clarithromycin; metallic taste with metronidazole, metoclopramide and disulfiram. Drugs like iodide, rifampicin and heavy metals are excreted through sweat. The excretion of drugs in the milk is in small amounts and is of no significance to the mother. However, for the suckling infant, it may be sometimes important especially because of the infant’s immature metabolic and excretory mechanisms. Though most drugs can be taken by the mother without significant toxicity to the child, there are a few exceptions.

CLINICAL PHARMACOKINETICS

The knowledge of pharmacokinetics is clinically useful for several purposes including selection and adjustment of the dosage regimen, and to obtain optimum effects from a drug. The three most important pharmacokinetic parameters are bioavailability, volume of distribution and clearance.

Clearance (CL)

Clearance is the volume of plasma freed completely of the drug in unit time. It can be calculated by the ratio of the rate of elimination to the plasma concentration.

$$\text{Thus, CL} = \frac{\text{Rate of elimination}}{\text{Plasma concentration}}$$

Clearance is expressed as ml/litre/unit time. Clearance is the most important factor determining drug concentration and should be considered when any drug is intended for long-term administration.

Drugs are metabolised/eliminated (elimination kinetics) from the body by:

1. First order kinetics: In first order kinetics (linear kinetics), a constant fraction of the drug is metabolised/eliminated per unit time. Most drugs follow first order kinetics and the rate of metabolism/excretion is dependent on their concentration in the body, i.e. it is exponential . It also holds good for absorption of drugs.

2. Zero order kinetics (saturation kinetics or nonlinear kinetics): Here a constant amount of the drug present in the body is metabolised/eliminated per unit time. The amount remains same and does not increase with increase in dose. The metabolic enzymes get saturated and hence with increase in dose, the plasma drug level increases disproportionately resulting in toxicity. Such elimination is known as zero order kinetics.

Some drugs like phenytoin and warfarin are eliminated by both processes, i.e. by first order initially and by zero order at higher concentrations (**mixed order kinetics or Michaelis- Menten kinetics**). Hence, at higher doses, there is accumulation of the drug.

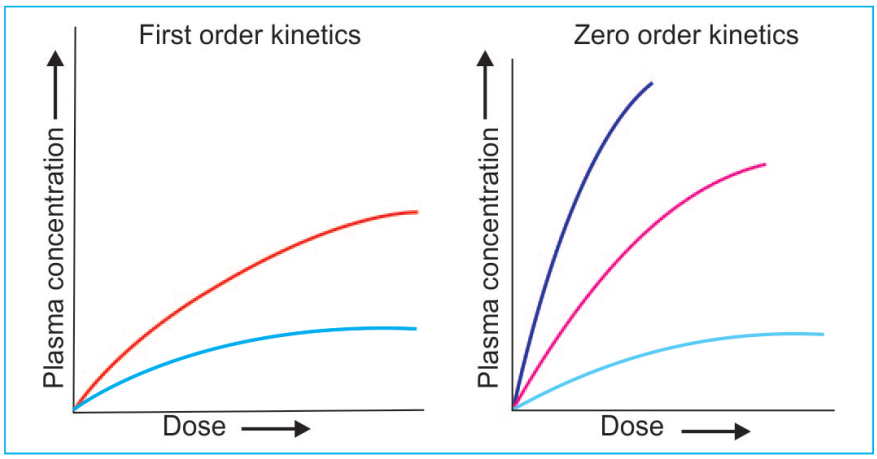
Examples of drugs that follow zero order kinetics:

- Alcohol
- Heparin
- Phenytoin
- Phenylbutazone.
- Aspirin

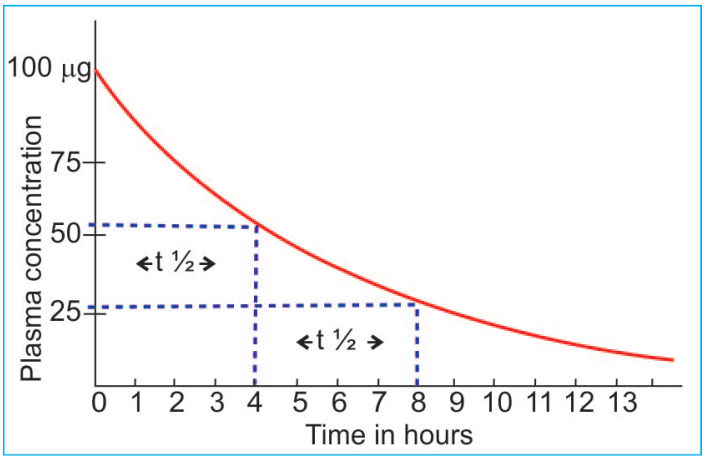
Plasma Half-life (t½)

Plasma half-life (t½) is the time taken for the plasma concentration of a drug to be reduced to half its value. For example, if a particular dose of a drug is injected intravenously and its plasma

concentration is found to be 100 □g/ml and the plasma concentration is estimated every hour and at the end of four hours it falls to 50 □g/ml, then the plasma half-life of the drug is four hours. Four to five half-lives are required for the complete elimination of a drug. Each drug has its own t½ and is an important pharmacokinetic parameter that guides the dosing regimen, e.g. esmolol has a t½ of 10 minutes, zolpidem 2 hours, aspirin 4 hours and chloroquine 10–24 days.



First order kinetics: As the plasma concentration rises, metabolism and excretion proportionately increase. Zero order kinetics: In higher doses, the drug accumulates and the plasma concentration rises resulting in toxicity.



Plasma concentration: Time curve following intravenous administration of a drug. Plasma t½ of the drug = 4 hours

Significance of Plasma t½

Plasma t½ is necessary to know:

- The duration of action of the drug
- The frequency of administration
- The time needed for attainment of steady state concentration (SSC)—longer the t½, longer is the time needed to attain SSC.
- To calculate the loading and maintenance doses of the drug.

Factors Influencing Plasma t½

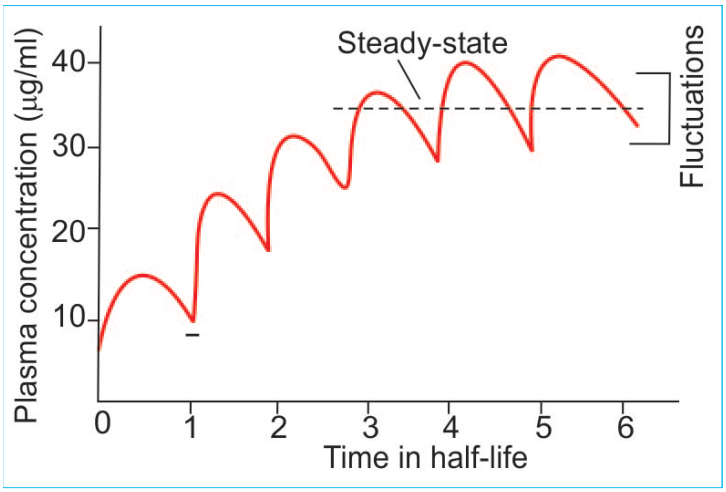
1. Plasma protein binding—drugs which are extensively bound to plasma proteins have a longer t½.
2. Enterohepatic circulation—increases the t½ of the drug.
3. Metabolism—faster the metabolism of a drug, shorter is its plasma t½.
4. Tissue storage—drugs which are sequestered in the tissues have a longer t½.
5. Clearance of the drug—drugs which are cleared faster have a shorter t½.

Terminal half-life: On long-term use, certain drugs may remain in secondary compartments and they get gradually released into the circulation as the plasma concentration of drugs fall.

Steady-state concentration (SSC)

If a drug is administered repeatedly at short intervals before complete elimination, the drug accumulates in the body and reaches a 'state' at which the rate of elimination equals the rate of administration. This is known as
the **'steady-state' or plateau level** .After attaining this level, the plasma concentration fluctuates around an average steady level. It takes 4–5 half-lives for the plasma concentration to reach the plateau level. A drug with t½ >24 hr, if given daily, accumulates on prolonged use and could lead to toxicity. Hence for such drugs, once the SSC is attained, the dose given should be equal to the dose eliminated everyday. Steady-state plasma concentration (Cpss) can be obtained as follows:

$$C = \frac{\text{Dose rate}}{\text{Clearance}}$$



Drug accumulation and attainment of steady-state concentration on oral administration.

PHARMACODYNAMICS

N.Sumanasri

UNIT-II

General Pharmacology

a. Pharmacodynamics- Principles and mechanisms of drug action. Receptor theories and classification of receptors, regulation of receptors. drug receptors interactions signal transduction mechanisms, G-protein–coupled receptors, ion channel receptor, transmembrane enzyme linked receptors, transmembrane JAK-STAT binding receptor and receptors that regulate transcription factors, dose response relationship, therapeutic index, combined effects of drugs and factors modifying drug action.

b. Adverse drug reactions.

c. Drug interactions (pharmacokinetic and pharmacodynamic)

d. Drug discovery and clinical evaluation of new drugs -Drug discovery phase, preclinical evaluation phase, clinical trial phase, phases of clinical trials and pharmacovigilance.

PHARMACODYNAMICS

Pharmacodynamics is the study of actions of the drugs on the body and their mechanisms of action, i.e. to know what drugs do and how they do it. Drugs produce their effects by interacting with the physiological systems of the organisms. By such interaction, drugs merely modify the rate of functions of the various systems. Drugs cannot bring about qualitative changes, i.e. they cannot change the basic functions of any physiological system. Thus drugs act by:

1. Stimulation
2. Depression
3. Irritation
4. Replacement
5. Anti-infective or cytotoxic action
6. Modification of immune status

Stimulation is the increase in activity of the specialised cells, e.g. adrenaline stimulates the heart.
Depression is the decrease in activity of the specialised cells, e.g. quinidine depresses the heart; barbiturates depress the central nervous system. Some drugs may stimulate one system and depress another, e.g. morphine depresses the CNS but stimulates the vagus.
Irritation can occur on all types of tissues in the body and may result in inflammation, corrosion and necrosis of cells.
Replacement: Drugs may be used for replacement when there is deficiency of natural substances like hormones, metabolites or nutrients, e.g. insulin in diabetes mellitus, iron in anaemia, vitamin C in scurvy.
Anti-infective and cytotoxic action: Drugs may act by specifically destroying infective organisms, e.g. penicillins, or by cytotoxic effect on cancer cells, e.g. anticancer drugs.
Modification of immune status: Vaccines and sera act by improving our immunity while immunosuppressants act by depressing immunity, e.g. glucocorticoids.

MECHANISMS OF DRUG ACTION

Most drugs produce their effects by binding to specific target proteins like receptors, enzymes and ion channels. Drugs may act on the cell membrane, inside or outside the cell to produce their effect. Drugs may act by one or more complex mechanisms of action. Some of them are yet to be understood. The fundamental mechanisms of drug actions may be:

1. Through receptors
2. Through enzymes and pumps
3. Through ion channels
4. Through transporters and symporters
5. By physical action
6. By chemical interaction
7. By altering metabolic processes.

1. Through receptors: A large number of drugs act by interacting with specific receptors in the body.
2. Through enzymes and pumps: A large number of drugs act by inhibition of various enzymes, thus altering the enzyme mediated reactions, e.g. allopurinol inhibits the enzyme xanthine oxidase;
• Acetazolamide inhibits carbonic anhydrase;
• Enalapril inhibits angiotensin-converting enzyme;
• Aspirin inhibits cyclo-oxygenase, neostigmine inhibits acetylcholinesterase. Methotrexate binds DHFR with high affinity and inhibits it. Sildenafil inhibits phosphodiesterase-5 to cause vasodilatation. Several enzymes are influenced by drugs and this forms one of the common models of drug action. Membrane pumps, like H+-K+-ATPase may be inhibited by omeprazole and Na+-K+ ATPase by digoxin.
3. Through ion channels: Drugs may interfere with the movement of ions across specific channels either by opening or closing them. Such channels may be voltage-gated, ligand gated or G-protein regulated channels, e.g.

i. Ca++ channels:

• Calcium channel blockers like verapamil block the voltage-sensitive L-type Ca++ channels in the myocardium.
• Ethosuximide blocks T type Ca++ channels in thalamic neurons.

ii. K+ channels:

• Nicorandil opens K+ channels in the heart and vascular smooth muscles.
• Sulfonylureas close the ATP sensitive K+ channels in the pancreatic □ cells to promote insulin release.

iii. Sodium channels*:*

• Lignocaine blocks the Na+ channels to depress nerve conduction
• Phenytoin blocks the Na+ channels to stabilize neuronal membrane for antiepileptic activity.

iv. GABA-gated chloride channels:

Diazepam acts through GABAA receptor to increase the frequency of chloride channel opening in the neurons to cause CNS depression.
4. Through transporters and symporters: Many of the endogenous substances are transported across the biological membrane with the help of carriers. The action of several of the neurotransmitters is terminated by reuptake into the presynaptic nerve terminal. Drugs may act by blocking or inhibiting the movement of these transporters, symporters or antiporters. They are explained in detail in the respective chapters.
Antidepressant imipramine acts by binding to transporters SERT and NET to inhibit the reuptake of serotonin and norepinephrine. Most diuretics act by influencing the movement of ions across the cells in the nephron by action on the symporters and transporters—thiazides inhibit Na+-Cl– symporter and furosemide inhibits Na+-K+- 2Cl cotransporter.
5. By physical action: The action of a drug could result from its physical properties like:
• Adsorption—A*ctivated charcoal in poisoning*

• Mass of the drug—*bulk laxatives like psyllium, bran*
• Osmotic property—*osmotic diuretics like* mannitol
Osmotic purgatives like magnesium sulphate
• Radioactivity—131I
• Radio-opacity:
– *Barium sulphate*
– *Contrast media.*
6. By chemical interaction: Drugs may act by chemical reaction.
• Antacids—neutralise gastric acids
• Oxidising agents—potassium permanganate and germicidal
• Chelating agents—bind heavy metals making them nontoxic.
7. By altering metabolic processes: Drugs like antimicrobials alter the metabolic pathway in the micro-organisms resulting in destruction of the micro-organism, e.g. sulfonamides interfere with bacterial folic acid synthesis.

RECEPTOR THEORIES

The works of **Langley** and **Ehrlich** put forth the concept of a 'receptor substance.' In the late 19th century, Langley noted that curare could oppose contraction of skeletal muscles caused by nicotine but did not block the contraction due to electrical stimulation. Paul **Ehrlich** observed that some organic chemicals had anti parasitic activity while others with slightly different structures did not have such activity. **Clark** put forward a theory to explain the drug action based on the drug-receptor occupation.

1. Occupation Theory (Ariëns, 1954): Drugs bind to specific receptors, triggering a response. The more receptors occupied, the greater the effect.

2. Rate Theory (Patton, 1957): The rate of drug-receptor binding determines the response, not just occupancy.

3. Induced-Fit Theory (Koshland, 1958): Receptors change shape to fit the drug, leading to activation or inhibition.

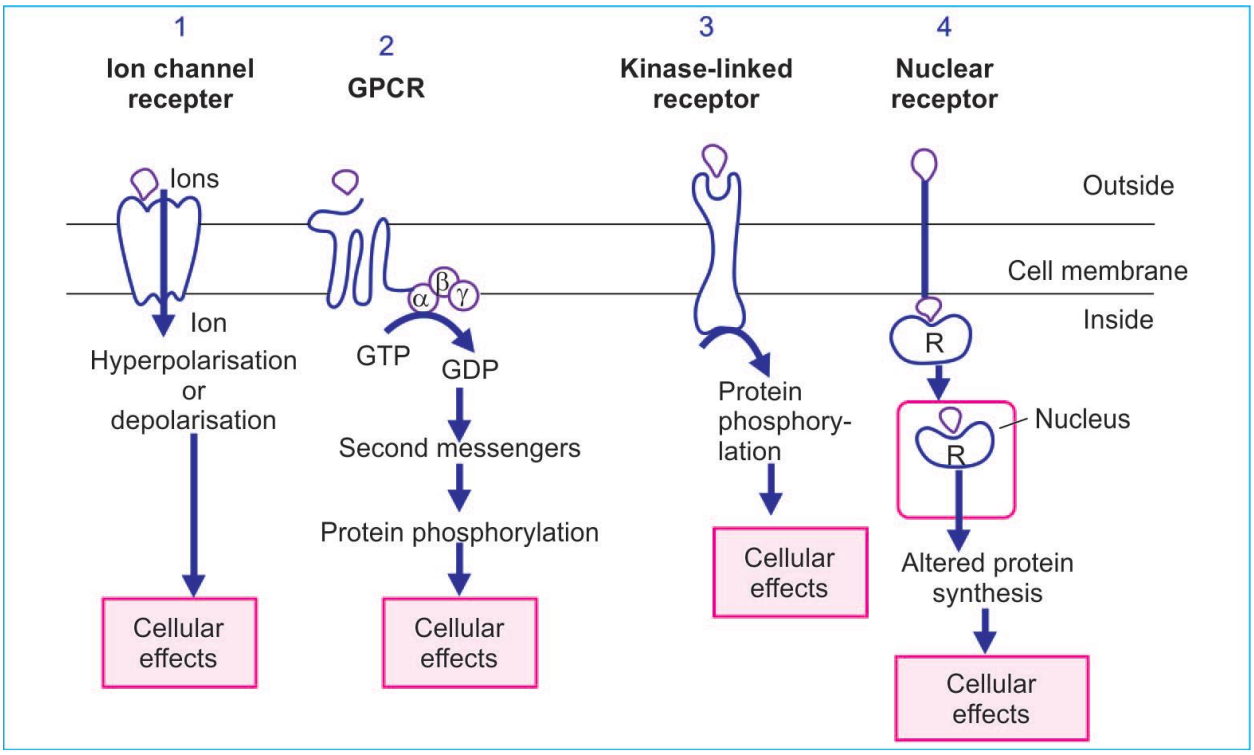
4. Two-State Theory (Monod et al., 1965): Receptors exist in active (R*) and inactive (R) states. Drugs shift the equilibrium between these states.

These theories explain how drugs interact with receptors, leading to various pharmacological effects.

CLASSIFICATION OF RECEPTORS

Receptor families: On stimulation of a receptor, the time required to elicit the response varies largely from a fraction of a second in some receptors to hours and days in others. This difference is because of the variation in mechanisms involved in linking the receptor and the effector systems (transduction mechanisms). Based on this, 5 types or super families of the cell surface receptors are identified. The receptor types are:

1. G-protein-coupled receptors (metabotropic receptor)
2. Ion channel receptors (ionotropic receptor)
3. Transmembrane enzymatic receptors (kinase-linked receptor)
4. Transmembrane non-enzymes (cytokine and TLR).
5. Nuclear receptors (transcription factors or receptors that regulate gene transcription).



Type 1: Binding of the agonist directly regulates the opening of the ion channel. Type 2: Agonist binding activates the receptor linked to an effector system by a G protein (G). Type 3: Agonist binding to extracellular domain activates enzymatic activity of its intracellular catalytic domain. Type 4: Agonist binds to the intracellular receptor, the complex moves to the nucleus and directs protein synthesis

RECEPTOR REGULATION

The number of receptors (density) and their sensitivity can be altered in many situations. Denervation or prolonged deprivation of the agonist or constant action of the antagonist, all result in an increase in the number and sensitivity of the receptors. This phenomenon is called **up regulation.** Prolonged use of a α adrenergic antagonist, like propranolol, results in up regulation of α adrenergic receptors.

On the other hand, continued stimulation of the receptors causes desensitisation and a decrease in the number of receptors—known as **down regulation** of the receptors.

Clinical Consequences and Implications of Receptor Regulation

Up regulation: After prolonged administration, a receptor antagonist should always be tapered. For example, if propranolol, α adrenoceptor blocker is suddenly withdrawn after long-term use, it precipitates angina. This is because of up regulation of α receptors. Normal amounts of noradrenaline released during any stress can stimulate the heart and cause angina. This is because of up regulation of beta receptors. Normal amounts of noradrenaline released during any stress can stimulate the heart and cause angina.

Down regulation: Constant use of α adrenergic agonists in bronchial asthma results in reduced therapeutic response due to down regulation of α 2 receptors develop tolerance.

Upregulation	Downregulation
Prolonged deprivation of agonists or Constant use of antagonists or Denervation ↓ ↑ number of receptors, ↑ sensitivity ↓ ↑↑ response Eg: Angina following sudden withdrawal of β blockers after prolonged use	Prolonged use of agonists or Continued stimulation of receptors ↓ ↓ number of receptors, ↓ sensitivity ↓ ↓↓ response Eg: Reduced response to β_2 agonists after prolonged use in bronchial asthma

DRUG RECEPTOR INTERACTION

Agonist & Antagonist (Refer in Unit-1)

RECEPTOR FAMILIES AND THEIR SIGNAL TRANSDUCTION MECHANISMS

1. Ion channel receptors or receptor channels or ionotropic receptors are proteins present on the cell surface or cell membrane. Binding of the agonist opens the channel allowing ions to cross the membrane. These are called **ligand-gated ion channels** and the ion channel acts as the target for the drug. Depending on the ion and the channel, depolarisation/hyperpolarisation occurs,

e.g. nicotinic cholinergic receptor channel permits passage of Na+ ions resulting in depolarisation while the benzodiazepines bind the GABA receptor-chloride channel complex and facilitate the opening of the channel. The chloride ions flow into the neurons and cause hyperpolarisation.

S.NO	Ion channels	Drug	Action
1.	Na+ channel	Lignocaine Quinidine Acetylcholine	Blockade Blockade Opening
2.	Ca++ channel	Nifedipine Verapamil	Blockade
3.	K+ channel	Sulfonylureas Nicorandil	Blockade Opening
4.	Cl– channel	Diazepam Barbiturates	Opening Opening

2. **G-protein-coupled receptors (GPCR)** are receptors that signal through G proteins and form a family of transmembrane proteins, present across the plasma membrane. The receptor consists of 7 helices. The G proteins are bound to the inner face of the plasma membrane and form a complex with (coupled to) the receptor. They are called G proteins because of their interaction with guanine nucleotides GTP and GDP. G proteins act as signal transducers, that is, they convey the information to the effector system when an agonist binds to the GPCR. The G proteins consist of three subunits, viz. α, β and γ (called heterotrimer meaning 3 different subunits) with GDP bound to a sub unit. The G proteins act as signal transducers, i.e. they convey the information to the effector system. When a ligand binds to the G-protein-coupled receptor, the associated G-protein gets activated. This in turn activates adenylyl cyclase or phospholipase C to generate the respective second messengers. These second messenger systems are called effector pathways. The second messengers include cAMP, IP3, DAG, Ca++ and cGMP. G-proteins acting through second messengers, bring about a chain of intracellular changes. Thus G-proteins act as links or mediators

between the receptor and the effector systems. The subunit possesses GTPase activity. G-proteins are of different classes like Gs, Gi, Gq, Go and G112/13. Gs is stimulatory and Gi is inhibitory. For example, Gs activation opens Ca++ channels in myocardium and skeletal muscles while Gi opens K+ channels in the heart and smooth muscles. Adrenergic receptors and muscarinic cholinergic receptors are examples of G-protein coupled receptors.

Effector pathways through which the G-protein-coupled receptors work are:

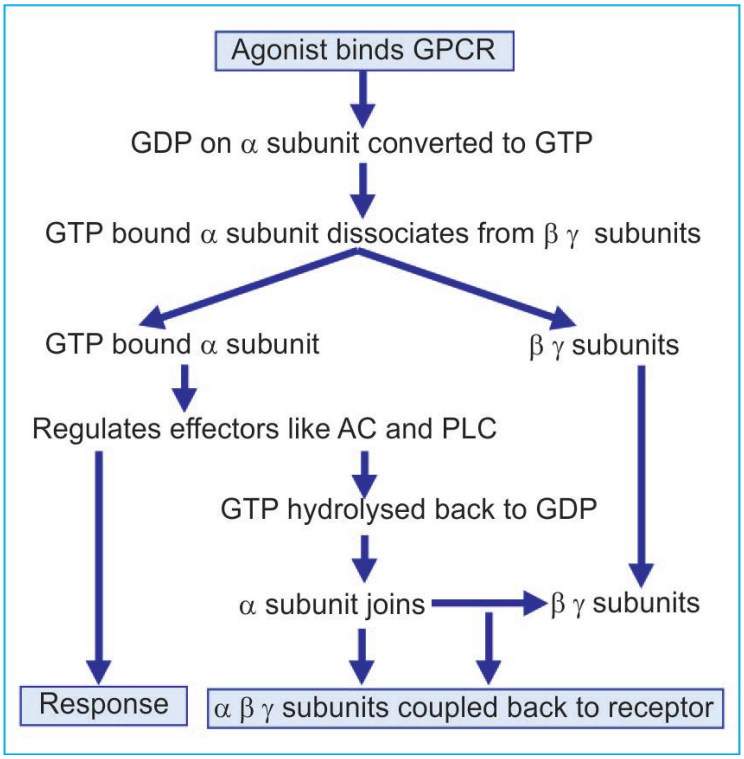
– Adenylyl cyclase/cAMP pathway

– Phospholipase C/IP3-DAG pathway

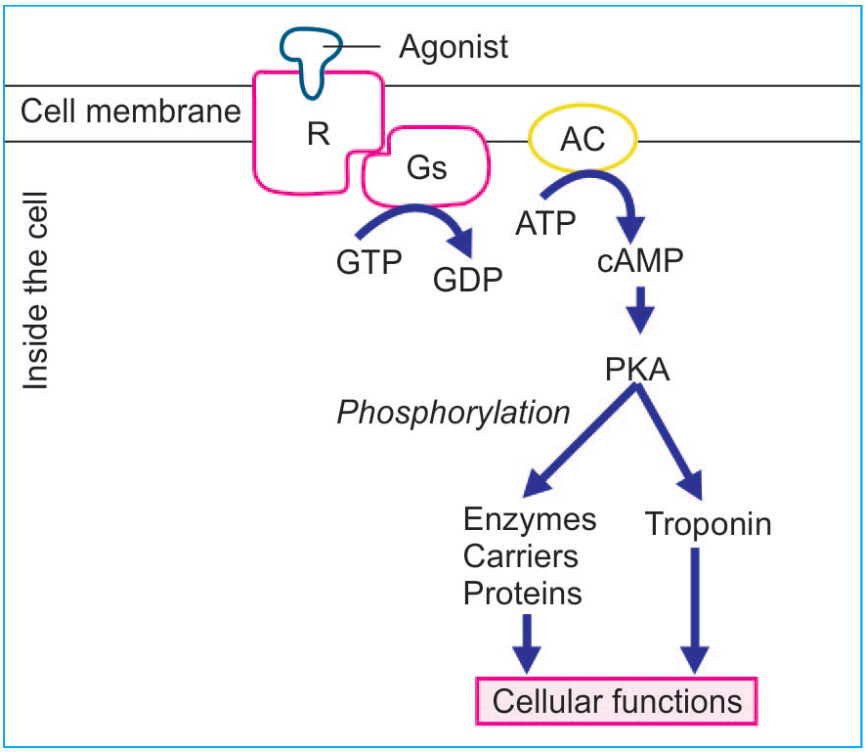
– Ion channel regulation.

Adenylyl cyclase pathway

Stimulation of adenylyl cyclase results in the formation and accumulation of cAMP within the cell. This cAMP acts through protein kinases which phosphorylate various proteins to regulate the cell function. The response may be contraction, relaxation, lipolysis or hormone synthesis



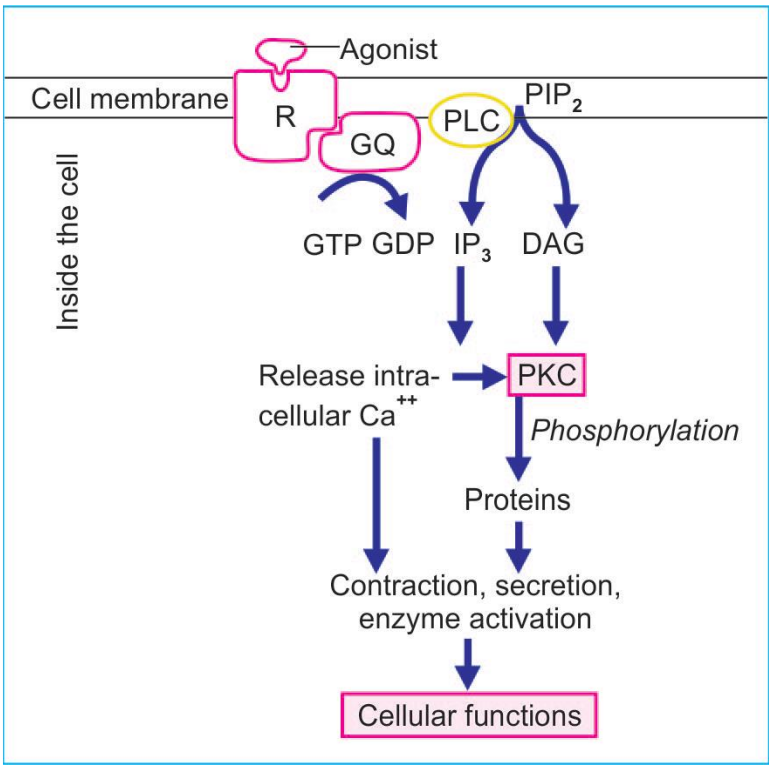
Functioning of GPCRs



G-protein-coupled receptor—transduction through adenylyl cyclase pathway with cAMP as second messenger. R = Receptor, Gs = G-protein (stimulatory)

Phospholipase C/IP3-DAG pathway

Activation of phospholipase C (PLC) results in the formation of second messengers IP3 and DAG from the membrane phospholipids phosphoinositol pyrophosphate (PIP2). IP3 mobilises Ca++ from intracellular depots and this Ca++ mediates responses like secretion, contraction, metabolism and hyperpolarization. DAG activates protein kinase C (PKC) which regulates cell function.

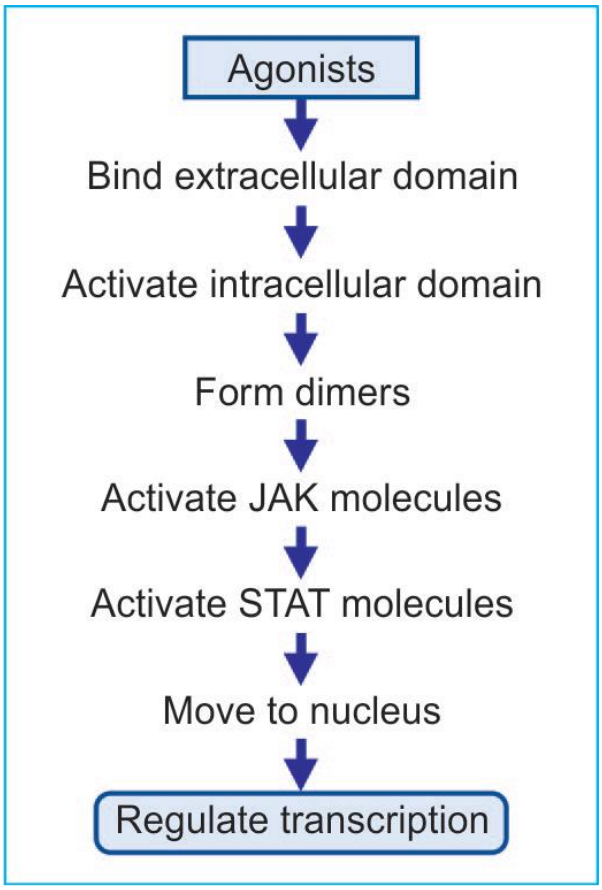


G-protein-coupled receptor acting through the second messengers IP3 and DAG. CaM-calmodulin

Ion channel regulation: The activated G-proteins can also directly (without the help of second messengers) convey the signal to some ion channels of calcium and potassium causing opening or closing of the channels. The resulting responses include depolarization / hyperpolarisation.

Enzymatic receptors

A type of non-enzymatic receptor is the **JAK-STAT binding receptor**. When an agonist binds to the extracellular domain, it activates the intracellular domain (which forms dimers, i.e. groups of two) and mobile JAK (Janus kinase) molecules are activated. These molecules in turn activate signal transducers and activation of transcription-molecules (STAT-molecules). STAT-molecules move to the nucleus and regulate transcription, e.g. growth hormones, cytokines, interferons.

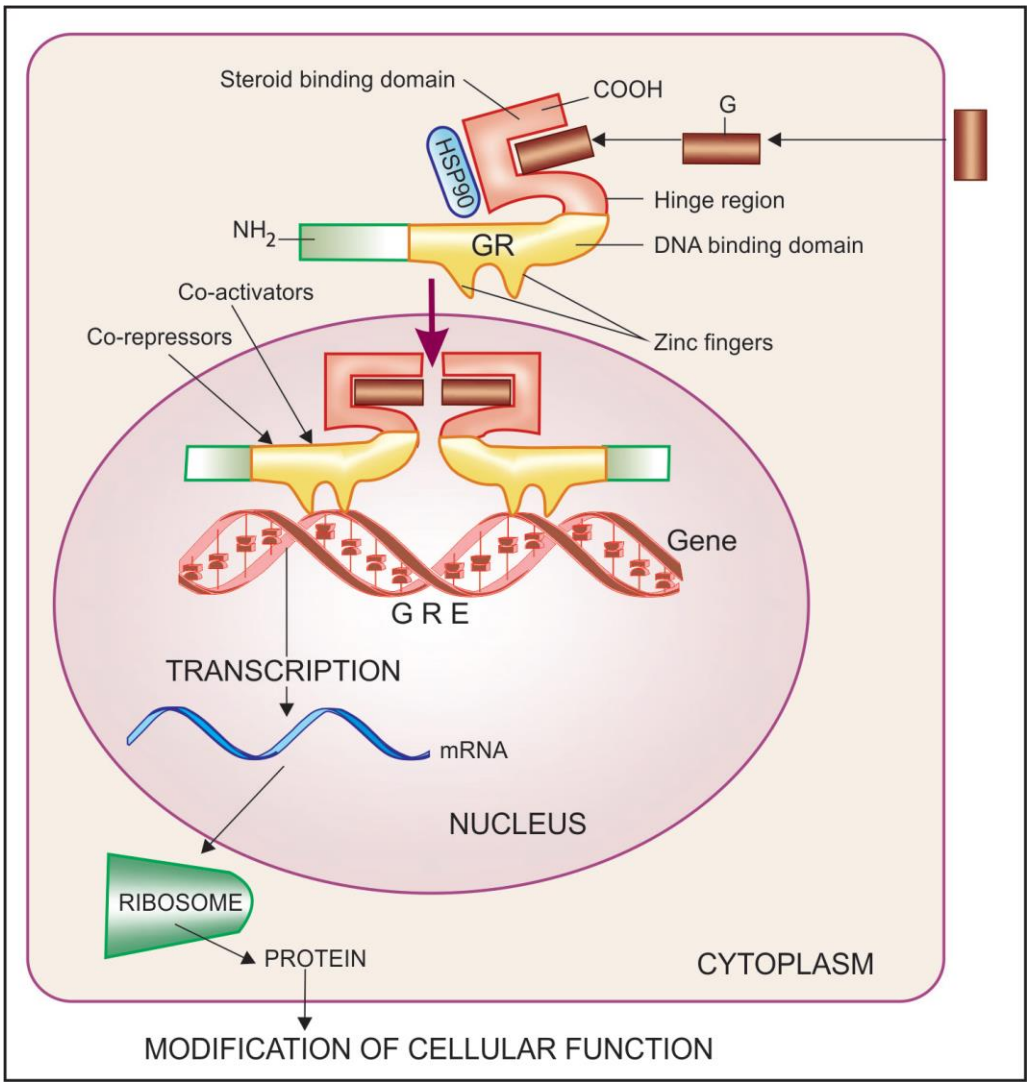


RECEPTORS THAT REGULATE TRANSCRIPTION FACTOR

Receptors exist in a dynamic state; their density and efficacy to elicit the response is subject to regulation by the level of on-going activity, feedback from their own signal output and other physiopathological influences, e.g. estrogens increase the density of oxytocin receptors on the myometrium. The sensitivity of uterus to contractile action of oxytocin increases progressively during the third trimester of pregnancy, especially near term. In tonically active systems, prolonged deprivation of the agonist (by denervation or continued use of an antagonist or a drug which reduces input) results in supersensitivity of the receptor as well as the effector system to the agonist. This has The glucocorticoid (G) penetrates the cell membrane and binds to the glucocorticoid receptor (GR) protein that normally resides in the cytoplasm in association with heat shock protein 90 (HSP90) + other proteins. The GR has a steroid binding domain near the carboxy terminus and a mid-region DNA binding domain joined by a 'hinge region'.

The DNA binding domain has two 'zinc fingers', each made up of a loop of amino acids with chelated zinc ion. Binding of the steroid to GR dissociates the complexed proteins (HSP90, etc) removing their inhibitory influence on it. A dimerization region that overlaps the steroid binding domain is exposed, promoting dimerization of the occupied receptor. The steroid bound receptor dimer translocates to the nucleus, binds coactivator/corepressor proteins and interacts with specific DNA sequences called 'glucocorticoid responsive elements' (GREs) within the regulatory region of appropriate genes. The expression of these genes is consequently altered resulting in promotion (or suppression) of their transcription. The specific mRNA thus produced is directed

to the ribosome where the message is translated into a specific pattern of protein synthesis, which in turn modifies cell function.



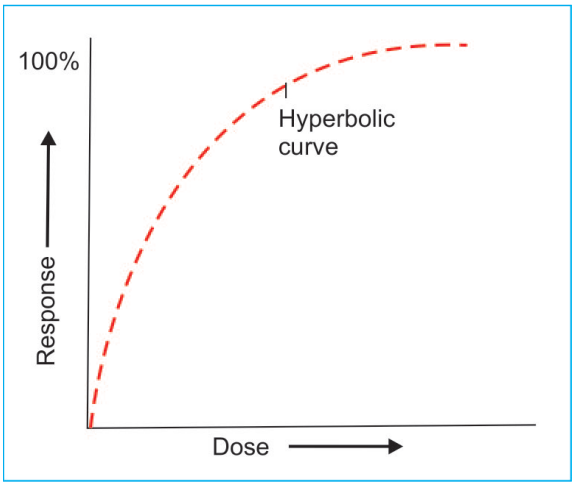
Operational scheme of intracellular (glucocorticoid) receptor

DOSE RESPONSE RELATIONSHIP

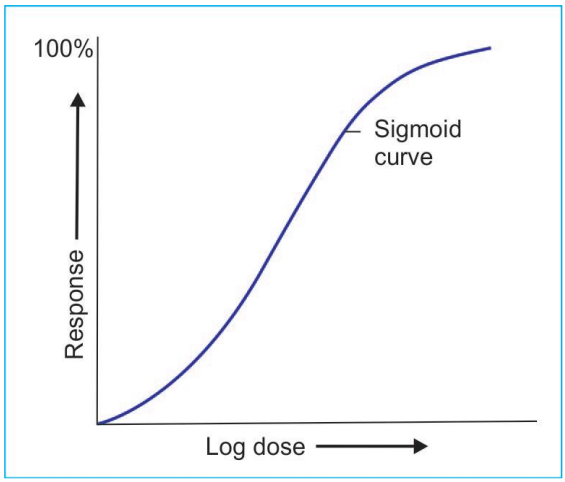
The clinical response to the increasing dose of the drug is defined by the shape of the dose response curve (DRC). Initially, the extent of response increases with increase in dose till the maximum response is reached.

There are 2 types of dose response relationships, viz. **graded dose response relationship** and **quantal dose response relationship**.

Graded DRC: The graded dose response curve has the shape of a rectangular **hyperbola**. After the maximum effect has been obtained, further increase in doses does not increase the response. If the dose is plotted on a logarithmic scale, the curve becomes **sigmoid.**

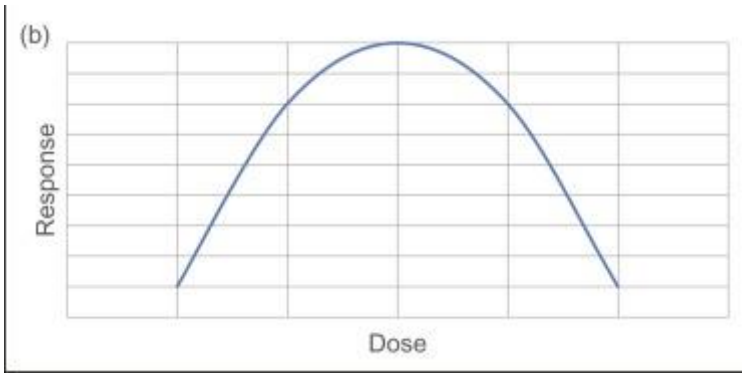


Log dose response curve



Dose response curve

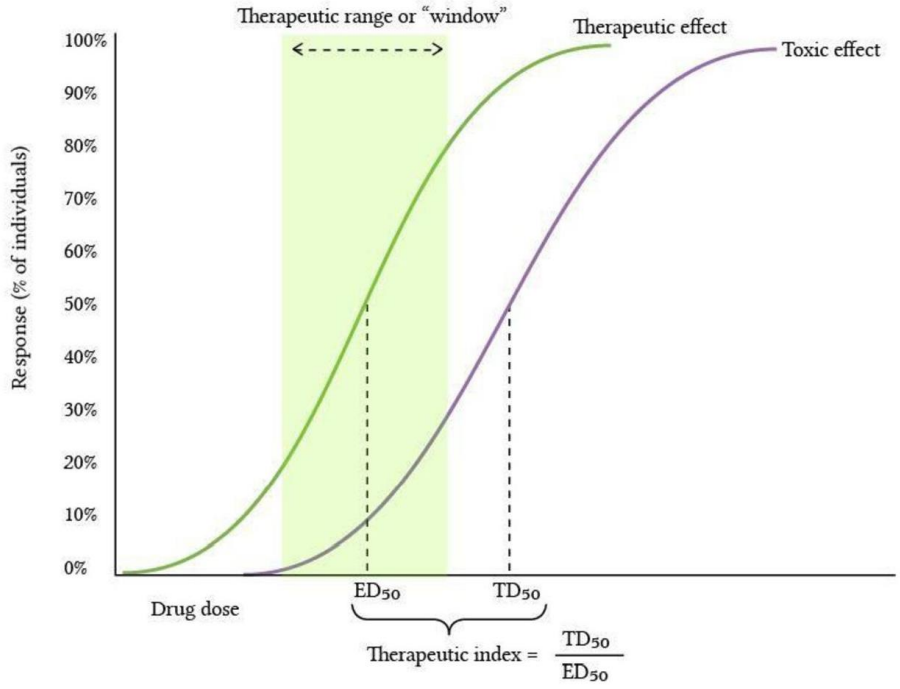
Quantal DRC: Certain responses can only be all-or-none (e.g. vomiting) and when represented on the dose response curve, the curve appears bell-shaped and it indicates the percentage of responders.



Quantal DRC

THERAPEUTIC INDEX

The dose response curves for different actions of a drug could be different. Thus salbutamol may have one DRC for bronchodilation and another for tachycardia. The distance betweenbeneficial effect DRC and unwanted effect DRC indicates the safety margin of the drug.



Dose response curve for therapeutic index

Median lethal dose (LD50): Dose which is lethal to 50% of the population.
Median effective dose (ED50): Dose that produces a desired effect in 50% of the test population.
Therapeutic index (TI) in experimental animals is obtained by the ratio of the median lethal dose to the median effective dose.

$$\text{Therapeutic index} = \frac{LD50}{ED50}$$

COMBINED EFFECTS OF DRUGS

When two or more drugs are given concurrently, the effect may be additive, synergistic or antagonistic.

1) Additive Effect

The effect of two or more drugs get added up and the total effect is equal to the sum of their individual actions.

Examples
Ephedrine + theophylline in bronchial asthma; nitrous oxide + ether as general anaesthetics.

2) Synergism

When the action of one drug is enhanced or facilitated by another drug, the combination is synergistic. In Greek, *ergon* = work; *syn* = with. Here, the total effect of the combination is greater than the sum of their independent effects. It is often called 'potentiation' or 'supra-additive' effect.

Examples
• Acetylcholine + physostigmine
• Levodopa + carbidopa.
Thus additive effect can be understood as
2 + 2 = 4 while synergistic effect is 2 + 2 = 5!

3) Antagonism

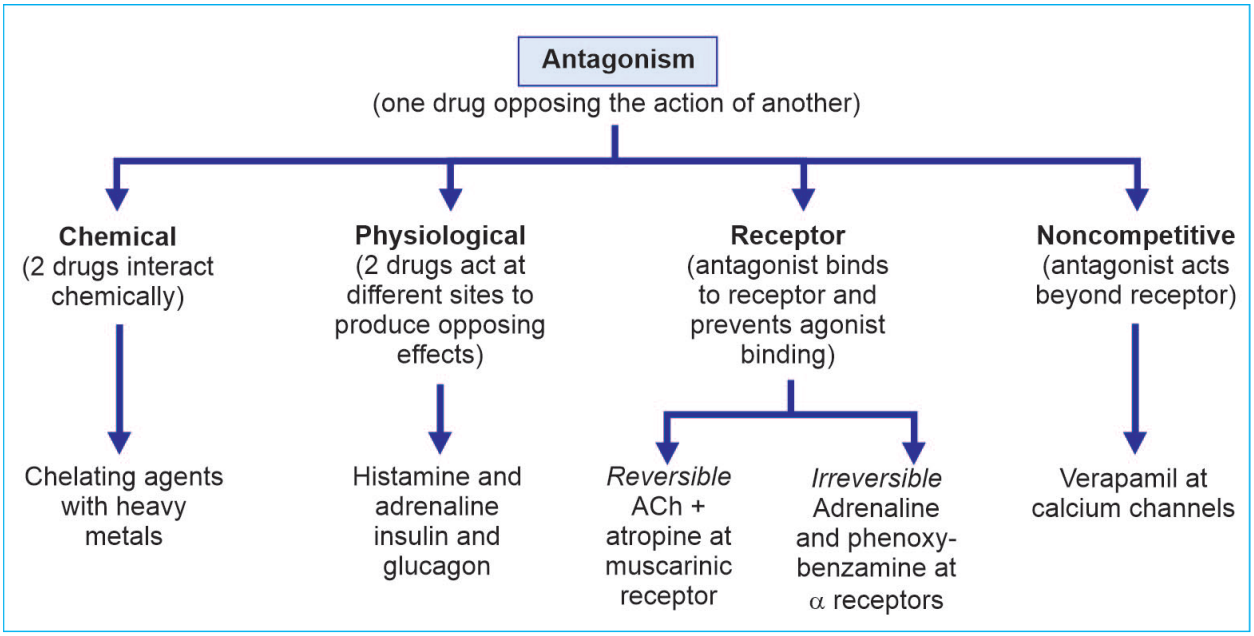
One drug opposing or inhibiting the action of another is antagonism. Based on the mechanisms, antagonism can be:

1. Chemical Antagonism

Two substances interact chemically to result in inactivation of the effect.
e.g. chelating agents inactivate heavy metals like lead and mercury to form inactive complexes; antacids like aluminium hydroxide neutralize gastric acid.

2. Physiological Antagonism

Two drugs act at different sites to produce opposing effects. For example, histamine acts on H1 receptors to produce bronchospasm and hypotension while adrenaline reverses these effects by acting on adrenergic receptors. Insulin and glucagon have opposite effects on the blood sugar level.



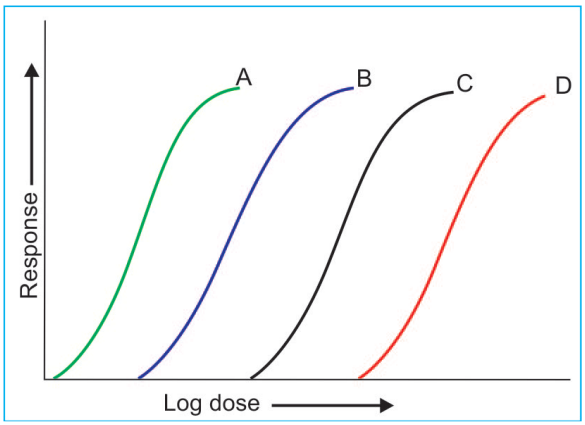
Types of antagonism with examples

3. Antagonism at the Receptor Level

The antagonist binds to the receptor and inhibits the binding of the agonist to the receptor. Such antagonism may be reversible or irreversible.

Reversible or competitive antagonism:

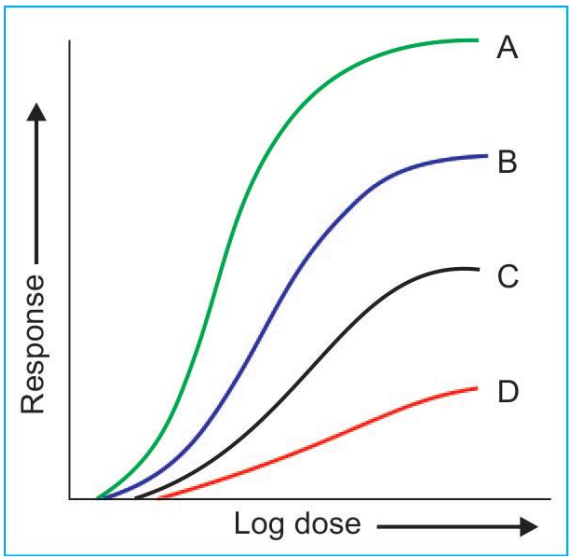
The agonist and antagonist compete for the same receptor. When a fixed concentration of an agonist is employed and the dose of the antagonist is progressively increased, the response to the agonist is progressively diminished. However, by increasing the concentration of the agonist, the antagonism can be overcome. It is thus reversible antagonism. The same maximal response can still be obtained by increasing the dose of the agonist. It is also called **surmountable** or **equilibrium type** of antagonism. This is the most common type of antagonism. Acetylcholine and atropine compete at muscarinic receptors. The antagonism can be overcome by increasing the concentration of acetylcholine at the receptor. Tubocurarine and acetylcholine compete for the nicotinic receptors at the neuromuscular junction. The dose response curve of the agonist shifts to the right in the presence of competitive antagonists.



Dose response curves of an agonist: A in the absence of competitive antagonist; B, C and D in the presence of increasing doses of a reversible competitive antagonist.

Irreversible antagonism: The antagonist binds by covalent bonds to the receptor and it binds so firmly that it dissociates very slowly or not at all. Thus it blocks the action of the agonist and the blockade cannot be overcome by increasing the dose of the agonist and hence it is irreversible antagonism. In this type of antagonism, the duration of action is usually long since the effect remains till the new receptors are synthesized.

e.g. adrenaline and phenoxybenzamine at alpha adrenergic receptors. This antagonism is also called **non equilibrium** type of antagonism. There is progressive flattening of the dose response curve.

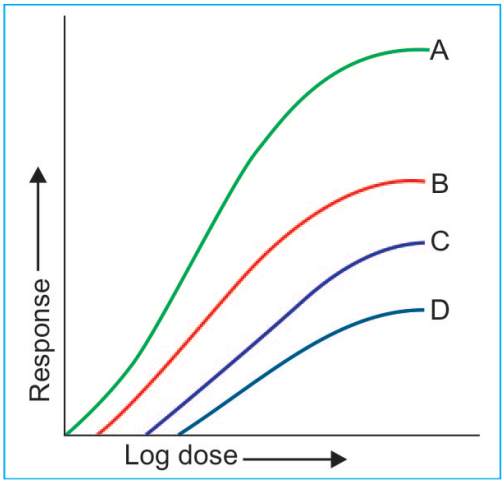


Dose response curves of an agonist A, in the absence of antagonist, B, C, and D in the presence of increasing doses of an irreversible antagonist.

4. Noncompetitive Antagonism

The antagonist blocks at the level of the receptor–effector linkage, i.e. at a different site beyond the receptor and not on the receptor. There is flattening as well as some rightward shift of the dose response curve.

For example, verapamil blocks the cardiac calcium channels and inhibits the entry of Ca++ during depolarisation. It thereby antagonises the effect of cardiac stimulants like isoprenaline and adrenaline. Since non-competitive antagonism is often confused with irreversible antagonism.



Non-competitive antagonism—there is flattening as well as some rightward shift of DRC

FACTORS THAT MODIFY THE EFFECTS OF DRUGS

The same dose of a drug can produce different degrees of response in different patients and even in the same patient under different situations. Various factors modify the response to a drug. They are:

1. Body weight: The recommended dose is calculated for medium built persons. For the obese and underweight persons, the dose has to be calculated individually. Though body surface area is a better parameter for more accurate calculation of the dose, it is inconvenient and hence not generally used.

Formula:

$$\text{Dose} = \frac{\text{Body weight (kg)} \times \text{average adult dose}}{70}$$

2. Age: The pharmacokinetics of many drugs change with age resulting in altered response in extremes of age.

Newborn and infants: In the newborn, the liver and kidneys are not fully mature to handle the drugs, e.g. chloramphenicol can produce grey baby syndrome. The blood–brain barrier is not well-formed and drugs can easily reach the brain. The gastric acidity is low, intestinal motility is slow, skin is delicate and is permeable to drugs applied topically. Hence calculation of the appropriate dose, depending on the body weight is important to avoid toxicity. Also pharmacodynamics differences could exist, e.g. barbiturates which produce sedation in adults may produce excitation in children.

Formula for calculation of dose for children.

1. *Young's formula*

$$\text{Child's dose} = \frac{\text{Age (years)}}{\text{Age} + 12} \times \text{Adult dose}$$

2. Dilling's formula

$$\text{Child's dose} = \frac{\text{Age}}{20} \times \text{Adult dose}$$

In the elderly, the capacity of the liver and kidney to handle the drug is reduced and they are more susceptible to adverse effects. Hence, lower doses are recommended.

e.g. elderly are at a higher risk of ototoxicity and nephrotoxicity by streptomycin.

3. Sex: There are no gross gender differences in response to drug. However, the hormonal effects and smaller body size may influence the drug response in women. Special care is necessary while prescribing for pregnant and lactating women and during menstruation.

For example, purgatives cause pelvic congestion and if they are administered during menstruation, they may increase the menstrual blood loss. Adult male rats metabolize drugs at a much faster rate than their female counterparts.

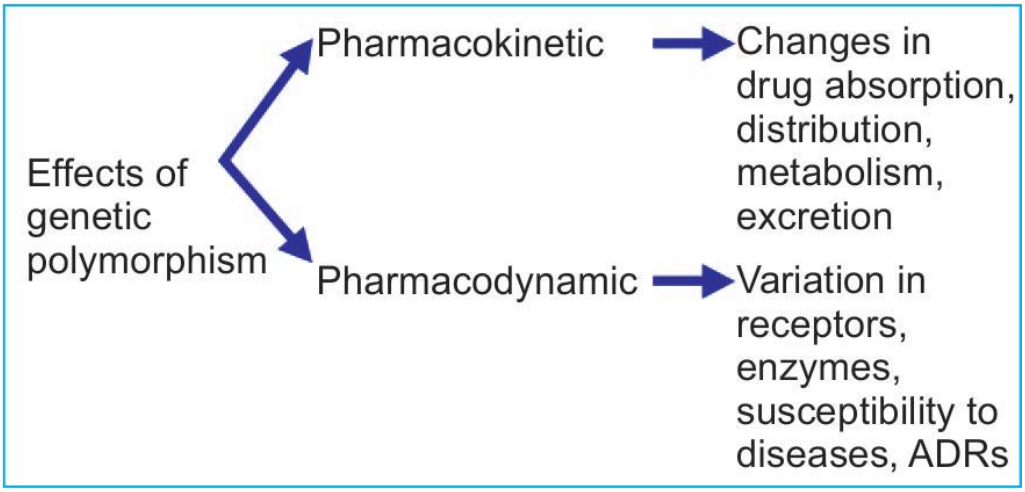
4. Species and race: Response to drugs may vary with species and race.

For example, rabbits are resistant to atropine. Such variation makes it difficult to extrapolate the results of animal experiments. Variation in response to drugs is also noted among different races. Blacks need higher doses of atropine to produce mydriasis. The antipsychotic clozapine may cause a higher incidence of agranulocytosis in people of Finland. Hence most countries now approve a drug to be used in their country only after it has undergone trials on its own population.

5. Diet and environment: Food interferes with the absorption of many drugs and such drug–food interactions should be borne in mind.

For example, tetracyclines form complexes with calcium present in the food and are poorly absorbed. Polycyclic hydrocarbons present in the cigarette smoke may induce microsomal enzymes resulting in enhanced metabolism of some drugs.
Examples of drug–food interactions:
Absorption increased by food—spironolactone, chloroquine, riboflavin, lithium, albendazole.
Absorption reduced by food—ampicillin, rifampicin, tetracycline, INH.

6. Route and time of administration: Occasionally route of administration may modify the pharmacodynamic response, e.g. magnesium sulphate given orally is a purgative. But given IV it causes CNS depression and has anticonvulsant effects for which it is used in eclampsia of pregnancy. Applied topically
(poultice), it reduces local oedema. Hypertonic magnesium sulphate retention enema reduces intracranial tension. N-acetylcysteine is another similar example. When given orally and IV it acts as an antidote in paracetamol overdosage—acetylcysteine replenishes glutathione stores in the liver. If inhaled as a solution, it acts as a mucolytic while if irrigated into the urinary bladder, it counters cystitis caused by cyclophosphamide.
Time of administration: There are several diurnal variations in the body and the time of drug administration is important to obtain the benefit of such variations. For example, secretion of glucocorticoids is highest in the
morning. Hence, if exogenous glucocorticoids are also administered in the morning, the HPA axis suppression is much less. The study of such correlation of drug effects to the circadian rhythm has emerged as chronopharmacology
7. Genetic factors: Variations in an individual's response to drugs could be genetically mediated. **Pharmacogenetics** is the study of genetically mediated variations in drug responses. Variation in nucleotide sequences could result in differences in response to drugs.
Pharmacogenomics and pharmacogenetics are often used to mean the same (as synonyms) but difference is pharmacogenetics deals with monogenetic variants while pharmacogenomics involves the entire spectrum of genes that could modify drug response.



Genetic **polymorphisms/variations** could result in changes in pharmacokinetics or pharmacodynamics.

i. ***Pharmacokinetic variations:*** Production of drug metabolizing enzymes is genetically controlled and variations are common.

Examples

a. *Oxidation of drugs* genetic polymorphism in cytochrome P450 enzymes result in variation in the rate of metabolism (oxidation, hydroxylation) of drugs metabolized by these enzymes, e.g. SSRIs, phenytoin, warfarin.

b. *Acetylation of drugs:* The rate of drug acetylation differs among individuals who may be fast or slow acetylators, e.g. INH, sulfonamides, hydralazine, procainamide and dapsone are metabolized by acetylation.

Slow acetylators treated with hydralazine are more likely to develop lupus erythematosus.

c. *Atypical pseudocholinesterase:* Succinylcholine is metabolised by the enzyme pseudocholinesterase. Some people inherit an atypical pseudocholinesterase which cannot quickly metabolise succinylcholine. When succinylcholine is given to such people, they develop a prolonged apnoea due to persistant action of succinylcholine.

ii. *Pharmacodynamic variations:* Variations in receptor, enzymes, susceptibility to ADRs and diseases:

a. *G6PD deficiency:* Deficiency of G6PD in RBCs leads to NADPH deficiency resulting in accumulation of glutathion. Exposure of such RBCs to drugs like primaquine, sulphones, and quinolones leads to hemolysis.

b. *Malignant hyperthermia:* Halothane and succinylcholine can trigger malignant hyperthermia in some genetically predisposed individuals.

c. *Hepatic porphyrias:* Some people lack an enzyme required for haeme synthesis, and this results in accumulation of porphyrin containing haeme precursors. Some drugs, like barbiturates, griseofulvin and carbamazepine, induce the enzyme required for porphyrin synthesis resulting in accumulation of porphyrins. In both the above cases, neurological, gastrointestinal and behavioural abnormalities can occur due to excess porphyrins.

8. Dose: It is fascinating that the response to a drug may be modified by the dose administered. Generally as the dose is increased, the magnitude of the response also increases proportionately till the 'maximum' is reached. Further increases in doses may with some drugs produce effects opposite to their lower-dose effect, e.g.

i. In myasthenia gravis, neostigmine enhances muscle power in therapeutic doses, but in high doses it causes muscle paralysis.

ii. Physiological doses of vitamin D promotes calcification while hypervitaminosis D leads to decalcification.

9. Diseases: Presence of certain diseases can influence drug responses.

e.g.

• *Gastrointestinal diseases:* Drugs are poorly absorbed in malabsorption syndrome.

• *Liver diseases:* Rate of drug metabolism including first pass metabolism is reduced due to dysfunction of hepatocytes. Also protein binding is reduced due to low serum albumin, because albumin is synthesized in the liver and blood levels of the free form of the drug increases in liver failure.

• *Cardiac diseases:* In CCF, there is oedema of the gut mucosa and decreased perfusion of liver and kidneys. These may result in cumulation and toxicity of drugs like propranolol and lignocaine.

• *Renal dysfunction:* Drugs mainly excreted through the kidneys are likely to accumulate and cause toxicity, e.g. streptomycin, amphotericin B. Doses of such drugs need to be reduced. Several drugs are totally eliminated unchanged only by the kidneys and such drugs can cause more toxicity. Also, the diseased kidneys are more susceptible to the toxic effects of nephrotoxic drugs like gold, penicillamine and aminoglycosides.

• *Endocrine diseases:* Hypothyroid patients are more sensitive to the effects of certain drugs like CNS depressants. Patients with benign prostatic hypertrophy are more susceptible to urinary retention with anticholinergics and tricyclic antidepressants.

10. Repeated dosing: Repeated dosing can result in:

a. Cumulation

b. Tolerance

c. Tachyphylaxis

d. Resistance

a. *Cumulation:* Drugs like digoxin which are slowly eliminated may cumulate resulting in toxicity.

b. *Tolerance:* It is the requirement of higher doses of a drug to produce a given response.

Tolerance may be natural or acquired.

• *Natural tolerance:* The species/race shows less sensitivity to the drug, e.g. rabbits show tolerance to atropine; black race are tolerant to mydriatics.

• *Acquired tolerance* develops on repeated administration of a drug. The patient who was initially responsive becomes tolerant,

e.g. tolerance develops to barbiturates, opioids, nitrites. Tolerance may develop to some actions of the drug and not to others, e.g. morphine— tolerance develops to analgesic and euphoric effects of morphine but not to its constipating and miotic effects. Barbiturates—tolerance develops to sedative but not antiepileptic effects of barbiturates.

c. *Tachyphylaxis:* It is the rapid development of tolerance. When some drugs are administered repeatedly at short intervals, tolerance develops rapidly and is known as tachyphylaxis or acute tolerance, e.g. ephedrine,

amphetamine, tyramine and 5-hydroxytryptamine. This is thought to be due to depletion of noradrenaline stores as the above drugs act by displacing noradrenaline from the sympathetic nerve endings. Other
mechanisms involved may be slow dissociation of the drug from the receptor thereby blocking the receptor. Thus ephedrine given repeatedly in bronchial asthma may not give the desired response.
d. ***Resistance:*** Repeated administration of an antibiotic can result in reduced or no response to it and this could lead to life-threatening infections.

11. Psychological factor: The doctor–patient relationship influences the response to a drug often to a large extent by acting on the patient's psychology. The patient's confidence in the doctor may itself be sufficient to relieve a suffering, particularly the psychosomatic disorders. This can be substantiated by the fact that a large number of patients respond to placebo.

12. Presence of other drugs: The concurrent use of two or more drugs can influence the response of each other.

B. ADVERSE DRUG REACTIONS.

DEFINITION

Adverse effect is 'any undesirable or unintended consequence of drug administration'. It is a broad term, includes all kinds of noxious effect—trivial, serious or even fatal.

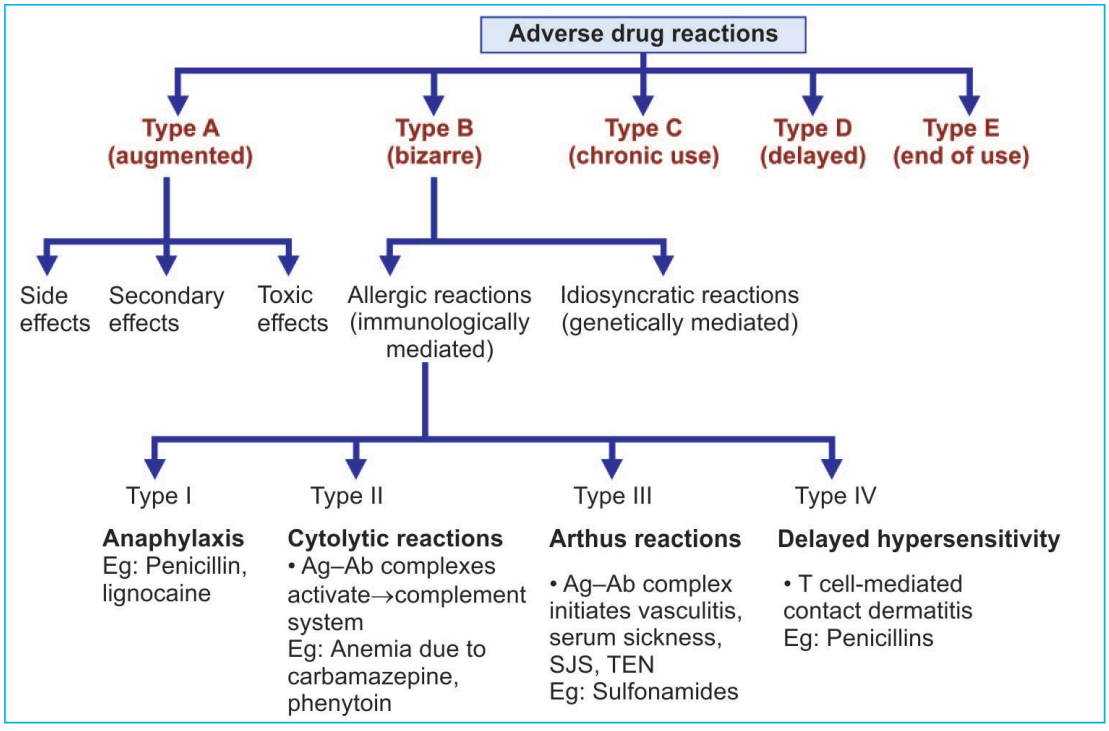
(OR)

Adverse drug reaction (ADR) has been defined as 'any noxious change which is suspected to be due to a drug, occurs at doses normally used in man, requires treatment or decrease in dose or indicates caution in the future use of the same drug'.

- An adverse drug event is "an injury resulting from the use of a drug. Under this definition, the term ADE includes harm caused by the drug (adverse drug reactions and overdoses) and harm from the use of the drug (including dose reductions and discontinuations of drug therapy)."1 Adverse Drug Events may results from medication errors but most do not.

TYPES:

1) Type A (Augmented)
2) Type B (Bizarre)
3) Type C (Chronic)
4) Type D (Delayed)
5) Type E (End-of-treatment)



1) **Type A (Augmented):** Dose-dependent, predictable reactions

Example: Bleeding with warfarin (increased anticoagulation effect)

2) **Type B (Bizarre):** Unpredictable, dose-independent reactions

Example: Stevens-Johnson syndrome with sulfonamides (severe skin and mucous membrane reaction)

3) **Type C (Chronic):** Dose- and duration-dependent reactions

Example: Tardive dyskinesia with long-term antipsychotic use (involuntary movements)

4) **Type D (Delayed):** Reactions occurring after drug discontinuation

Example: Withdrawal symptoms with opioid cessation (anxiety, tremors, nausea)

5) **Type E (End-of-treatment):** Reactions occurring when treatment is stopped

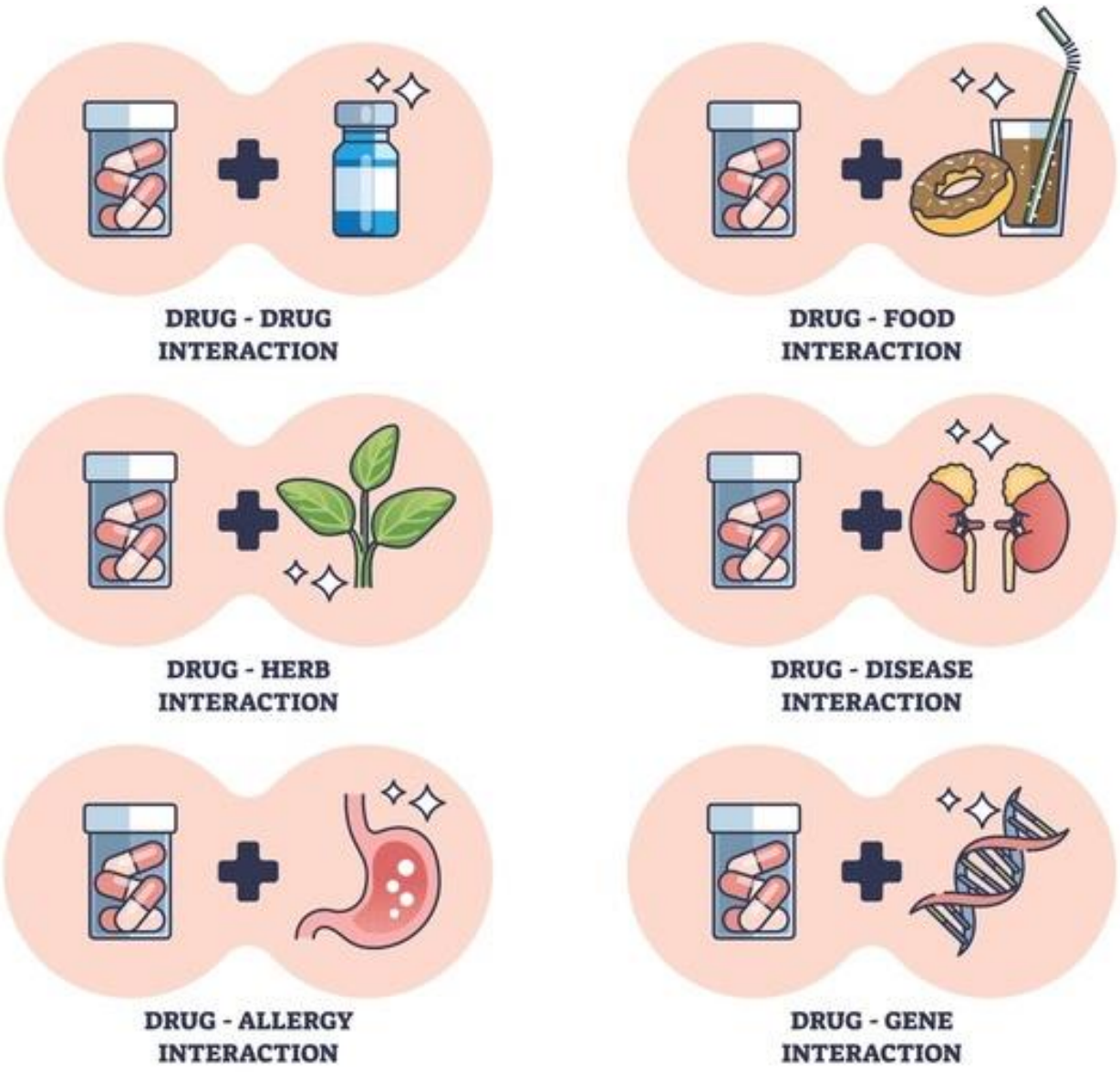
Example: Rebound hypertension with sudden withdrawal of clonidine (blood pressure increase)

Teratogenic effect: Some drugs given in the first three months of pregnancy may cause congenital abnormalities and are said to be teratogenic. The best known example is thalidomide which results in early easily recognizable abnormalities such as absent or grossly abnormal limbs.

Allergic reactions: Most of the drugs and sera used in therapeutics are capable of causing allergic or hypersensitive reactions. These reactions may be mild or very severe like anaphylaxis. When an individual has been sensitized to an antigen (allergen) further contact with that antigen can some times lead to tissue damaging reactions.
These allergic reactions are 4 types.
• Type-I reactions or anaphylactic reactions (Immediate hypersensitive reaction).
• Type-II reactions or cytotoxic reactions.
• Type-III reactions or immune complex mediated reactions.
• Type-IV reactions or cell mediated reactions (Delayed hypersensitive reactions).

Hepatotoxicity: Liver is the major organ of drug metabolism and most drugs are metabolized by it. Drug induced hepatotoxicity is a serious problem accounting for nearly 10% of all cases of hepatitis. It is also a common cause of acute hepatic failure. Hepatotoxicity can complicate treatment because it can result in reduced metabolism of drugs, which in turn increases their plasma levels, further worsening toxicity.

C) DRUG INTERACTION



DEFINITION

- A drug interaction is a change in the action or side effects of a drug caused by concomitant administration with a food, beverage, supplement, or another drug.
- Every time a drug is administered with any other prescription medicine, OTC medicine, food item, or herb, we expose ourselves to the risk of a potentially dangerous interactions.
- The risk of a drug-drug interaction increases with the number of drugs used. The drug whose activity is effected by such interaction is called as “Object Drug” and the agent which precipitates such an interaction is called as the “Precipitant”.

Drug interactions are thus-

•Mostly undesirable

•Rarely desirable (beneficial) for ex. Enhancement of activity of penicillin when administered with probenecid

Types of Drug Interactions:

1. Drug-drug interactions

2. Drug -food interactions

3. Drug-chemical interactions

4. Drug-laboratory test interactions

5. Drug-disease interactions

1. Drug-drug interactions

A drug-drug interaction occurs when two or more medications taken together alter the effectiveness, safety, or toxicity of one or both drugs.

Ex: 1. Warfarin + Aspirin: Increased risk of bleeding due to additive anticoagulant effects.

2. Beta-blockers + Verapamil: Increased risk of bradycardia, hypotension, and heart failure due to additive negative inotropic effects.

3. Opioids + Benzodiazepines: Increased risk of respiratory depression, sedation, and death due to additive CNS depressant effects.

2. Drug -food interactions

A drug-food interaction occurs when food or nutrients affect the absorption, metabolism, or effectiveness of a medication, or when medications affect the body's utilization of nutrients.

Examples:

1. Food reducing drug absorption:
   - Tetracycline antibiotics + Dairy products = Reduced antibiotic absorption due to calcium binding.
   - Quinolone antibiotics + Food = Reduced antibiotic absorption due to insoluble complex formation.

2. Food increasing drug absorption:
   - Graprefruit juice + Statins (e.g., atorvastatin) = Increased statin levels and risk of toxicity due to CYP3A4 inhibition.
   - High-fat meal + Oral anticoagulants (e.g., warfarin) = Increased anticoagulant absorption and risk of bleeding.

3. Drug-chemical interactions

A drug-chemical interaction occurs when a chemical substance (e.g., environmental toxin, industrial chemical, or recreational drug) affects the pharmacokinetics, pharmacodynamics, or toxicity of a medication, or when medications affect the body's handling of chemicals.

Examples:

1. Chemicals increasing drug toxicity:
   - Alcohol + Sedatives (e.g., benzodiazepines) = Increased risk of respiratory depression and overdose.
   - Tobacco smoke + Theophylline = Increased theophylline metabolism and reduced effectiveness.

2. Chemicals reducing drug effectiveness:
   - Activated charcoal + Oral medications = Reduced medication absorption due to binding.
   - Antacids + Tetracycline antibiotics = Reduced antibiotic absorption due to calcium binding.

4. Drug-laboratory test interactions

A drug-laboratory test interaction occurs when a medication or its metabolite affects the accuracy or interpretation of a laboratory test result, or when a laboratory test result affects the safe and effective use of a medication.

Examples:

1. Drugs altering laboratory test results:

- Aspirin + Fasting blood sugar test = Falsely elevated glucose levels.

- Corticosteroids + Blood glucose test = Elevated glucose levels due to increased gluconeogenesis.

- Lithium + Thyroid function tests = Altered thyroid hormone levels.

2. Laboratory tests affecting drug therapy:

- International Normalized Ratio (INR) + Warfarin therapy = Adjusted warfarin dosing based on INR results.

- Liver function tests (LFTs) + Hepatotoxic medications = Monitoring for liver damage and adjusted dosing.

- Renal function tests + Nephrotoxic medications = Monitoring for kidney damage and adjusted dosing.

5. Drug-disease interactions

A drug-disease interaction occurs when a medication exacerbates or worsens an underlying medical condition, or when a medical condition affects the safe and effective use of a medication.

Examples:

1. Drugs worsening disease conditions:
   - Beta-blockers + Asthma = Exacerbated bronchospasm.
   - NSAIDs + Hypertension = Increased blood pressure.
   - Thiazide diuretics + Diabetes mellitus = Worsened glucose control.

2. Diseases affecting drug pharmacokinetics:

- Liver disease + Hepatotoxic medications = Reduced drug clearance and increased toxicity risk.
- Kidney disease + Nephrotoxic medications = Reduced drug excretion and increased toxicity risk.
- Heart failure + Cardiodepressant medications = Reduced cardiac output and worsened heart failure.

CLASSIFICATION OF DRUG INTERACTIONS

1) Pharmacokinetics
2) Pharmacodynamics

1) Pharmacokinetics

Pharmacokinetic drug interactions occur when one drug affects another drug's pharmacokinetic parameters, leading to altered plasma concentrations and potentially clinically significant effects.

Absorption:

- Food reduces absorption of:
  - Tetracycline antibiotics (e.g., doxycycline)
  - Quinolone antibiotics (e.g., ciprofloxacin)
- Antacids reduce absorption of:
  - Tetracycline antibiotics
  - Fluoroquinolone antibiotics

Distribution:

- Warfarin displaced from blood proteins by:
  - Phenytoin (increased anticoagulation effect)
  - Valproic acid (increased anticoagulation effect)
- Highly protein-bound drugs (e.g., warfarin, phenytoin) may be displaced by:
  - Other highly protein-bound drugs

Metabolism:

- Enzyme induction (increased metabolism):
  - Rifampicin induces CYP3A4, reducing levels of:
    - Oral contraceptives
    - Cyclosporine
  - Phenytoin induces CYP2C9, reducing levels of:
    - Warfarin
- Enzyme inhibition (decreased metabolism):
  - Grapefruit juice inhibits CYP3A4, increasing levels of:
    - Calcium channel blockers (e.g., nifedipine)
    - Statins (e.g., atorvastatin)
  - Fluoxetine inhibits CYP2D6, increasing levels of:
    - Tricyclic antidepressants (e.g., imipramine)

Excretion:

- Probenecid increases levels of:
  - Penicillin (reduced renal excretion)
  - Cephalosporins (reduced renal excretion)
- Diuretics increase excretion of:
  - Lithium (increased risk of toxicity)

These interactions can lead to:

- Increased toxicity (e.g., grapefruit juice + statins)
- Reduced efficacy (e.g., food + tetracycline)
- Altered drug response (e.g., warfarin + phenylbutazone)

2) Pharmacodynamics

Pharmacodynamic drug interactions occur when two or more drugs act on the same physiological system, leading to additive, synergistic, or antagonistic effects.

Additive Effects:

- Opioids (e.g., morphine) + Benzodiazepines (e.g., diazepam) = Increased risk of respiratory depression and sedation

- Antihypertensives (e.g., beta-blockers, ACE inhibitors) + Diuretics = Increased risk of hypotension

Synergistic Effects:

- MAOIs + SSRIs = Increased risk of serotonin syndrome

- Warfarin + Aspirin = Increased risk of bleeding

Antagonistic Effects:

- Beta-blockers + Beta-agonists (e.g., salbutamol) = Reduced effectiveness of both drugs

- Opioid agonists + Opioid antagonists (e.g., naloxone) = Reduced opioid effect

Agonist-Antagonist Interactions:

- Partial agonists (e.g., buprenorphine) + Full agonists (e.g., methadone) = Reduced effect of full agonist

- Alpha-blockers + Alpha-agonists (e.g., phenylephrine) = Reduced effect of alpha-agonist

Indirect Interactions:

- Diuretics + Digitalis glycosides = Increased risk of digitalis toxicity due to hypokalemia

- Corticosteroids + Warfarin = Increased risk of bleeding due to hypoprothrombinemia

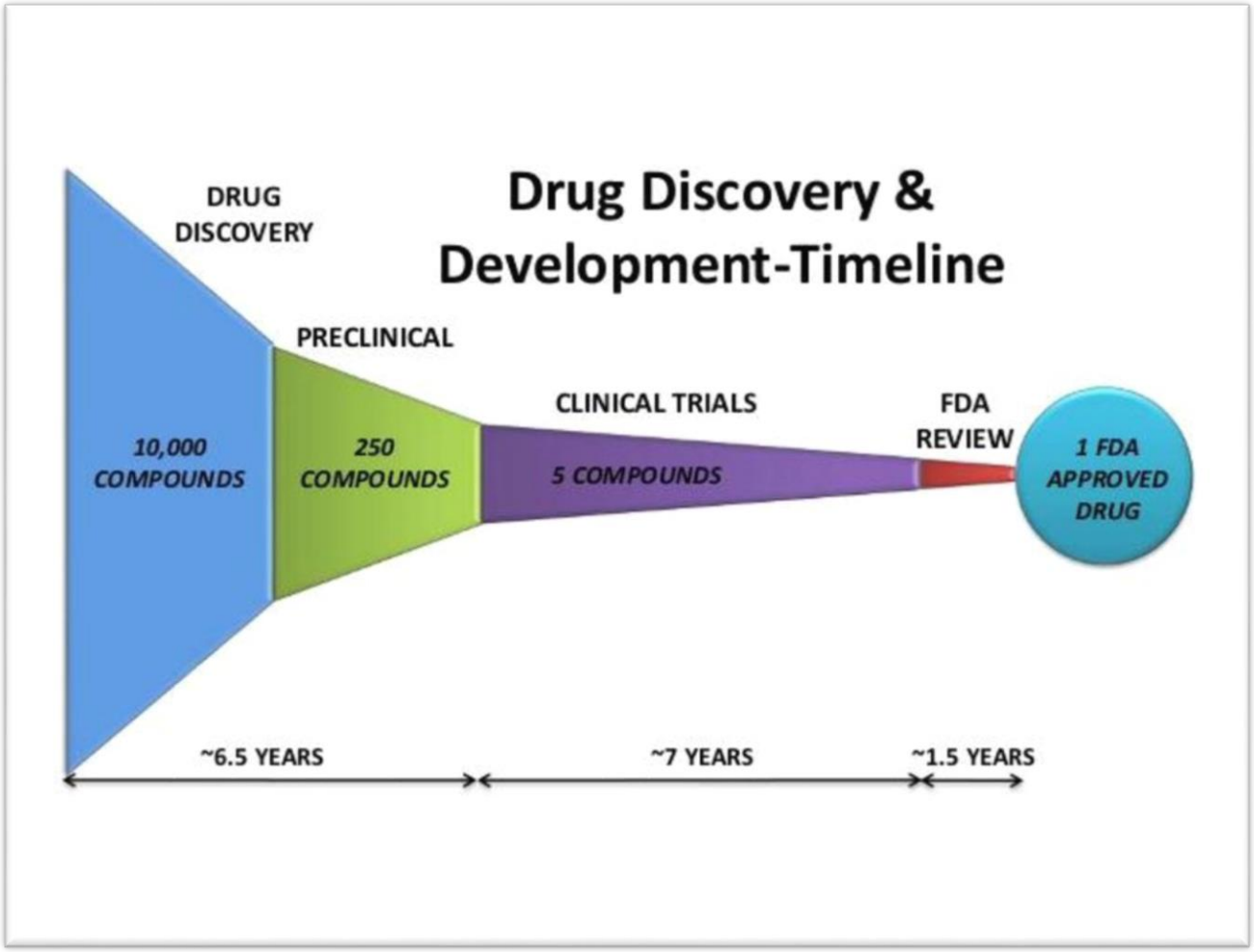
These interactions can lead to:

- Increased toxicity (e.g., opioids + benzodiazepines)

- Reduced efficacy (e.g., beta-blockers + beta-agonists)

- Altered drug response (e.g., warfarin + aspirin)

DRUG DISCOVERY AND CLINICAL EVALUATION OF NEW DRUGS



DEFINITION

Drug discovery is the process to which likely new medicines are identify by the process of clinical trial. It was a wide range of scientific disciplines including biology, chemistry and pharmacology. In the past most drugs have been discovered at their identifying the active ingredient from tradition remedies for by the discovery. A new approach has been to a understand how disease and infections are control at the molecular and physiological level and target specific on this knowledge. The process of drug discovery in was the identification of candidate, synthesis, characterization and assay for therapeutic efficiency.

It involves:

1. Target identification: Identifying a biological target (e.g., protein, gene) involved in a disease.
2. Target Validation: Confirming that a potential drug
3. Lead discovery: Finding a lead compound that interacts with the target.
4. Lead optimization: Modifying the lead compound to improve efficacy, safety, and pharmacokinetics.
5. Preclinical testing: Testing the optimized compound in vitro and in vivo.
6. Clinical trials: Evaluating the drug's safety and efficacy in humans.

1) Target identification:

Target identification is the first step in the drug discovery process. It involves identifying a biological target, such as a protein, gene, or molecular pathway, that is involved in a disease process and can be modified by a drug to produce a therapeutic effect.

Steps involved in target identification:

1. Disease understanding: Understanding the disease mechanisms, pathology, and biology.

2. Literature review: Reviewing existing research and data to identify potential targets.

3. Genomics and proteomics: Analyzing genomic and proteomic data to identify potential targets.

4. High-throughput screening: Using high-throughput screening techniques to identify potential targets.

5. Target validation: Validating the target using various experimental approaches.

Types of targets:

1. Protein targets: Enzymes, receptors, ion channels, transporters.

2. Gene targets: Genes involved in disease pathways.

3. Molecular pathway targets: Signaling pathways, metabolic pathways.

Characteristics of a good target:

1. Involved in disease pathology

2. Druggable: Can be modified by a drug

3. Specific: Has a specific role in the disease process

4. Validated: Has been validated through experimental approaches

2. Target Validation

Target validation is the process of confirming that a potential drug target is indeed involved in the disease process and can be modified by a drug to produce a therapeutic effect.

Steps involved in target validation:

1. In vitro assays: Using cell-based or biochemical assays to study target function.
2. In vivo models: Using animal models or human tissues to study target function.
3. Genetic manipulation: Using gene knockout or knockdown techniques to study target function.
4. Pharmacological inhibition: Using small molecules or biologics to inhibit target function.
5. Biomarker analysis: Measuring biomarkers to confirm target modulation.

Types of target validation:

1. Functional validation: Confirming target function in disease pathology.
2. Mechanistic validation: Understanding target mechanism of action.
3. Pharmacological validation: Confirming target can be modified by a drug.

Techniques used in target validation:

1. RNA interference (RNAi)
2. CRISPR-Cas9 gene editing
3. Small molecule inhibitors
4. Antibodies and biologics
5. Imaging and diagnostics

Outcomes of target validation:

1. Confirmation of target involvement in disease

2. Identification of potential biomarkers
3. Optimization of drug discovery strategies
4. Increased confidence in target druggability

Target validation is a critical step in drug discovery, ensuring that the target is relevant to the disease and can be effectively modified by a drug.

3. Lead discovery

Lead discovery is the process of identifying and selecting potential lead compounds that can be developed into drugs.

Steps involved in lead discovery:

1. High-throughput screening (HTS): Testing large libraries of compounds against a target.
2. Virtual screening: Using computational models to predict compound-target interactions.
3. Fragment-based drug discovery (FBDD): Identifying small fragments that bind to a target.
4. Structure-based drug design (SBDD): Designing compounds based on target structure.
5. Lead optimization: Modifying lead compounds to improve properties.

Techniques used in lead discovery:

1. Bioassays: Measuring compound activity in biological systems.
2. Binding assays: Measuring compound-target binding affinity.
3. Computational modeling: Predicting compound properties and interactions.
4. X-ray crystallography: Determining target structure.

Types of lead compounds:

1. Small molecules: Oral drugs, typically <500 Da.
2. Biologics: Large molecules, such as proteins or antibodies.
3. Natural products: Compounds derived from natural sources.

Characteristics of lead compounds:

1. Potency: Effective at low concentrations.
2. Selectivity: Specific for the target.
3. Solubility: Able to dissolve in biological fluids.
4. Stability: Resistant to degradation.
5. ADME (Absorption, Distribution, Metabolism, Excretion) properties.

Lead discovery is a critical step in drug discovery, identifying potential lead compounds that can be developed into effective drugs.

4) Lead optimization

Lead optimization is the process of modifying lead compounds to improve their properties, such as potency, selectivity, solubility, stability, and ADME (Absorption, Distribution, Metabolism, Excretion).

Goals of lead optimization:

1. Improve potency: Increase compound activity.

2. Enhance selectivity: Reduce off-target effects.

3. Optimize solubility: Improve aqueous solubility.

4. Increase stability: Reduce metabolic degradation.

5. Improve ADME properties: Optimize absorption, distribution, metabolism, and excretion.

Techniques used in lead optimization:

1. Structural modification: Modify chemical structure to improve properties.

2. SAR (Structure-Activity Relationship) studies: Analyze relationships between structure and activity.

3. Medicinal chemistry: Apply chemical principles to improve properties.

4. Computational modeling: Use computational tools to predict property improvements.

5. In vitro and in vivo testing: Evaluate optimized compounds in biological systems.

Types of lead optimization:

1. Chemical optimization: Modify chemical structure.

2. Biological optimization: Optimize biological activity.

3. Pharmacokinetic optimization: Optimize ADME properties.

Outcomes of lead optimization:

1. Improved lead compounds: Enhanced prop erties.

2. Increased confidence: In lead compound's potential.

3. Reduced risk: Of failure in later development stages.

4. Streamlined development: Focus on most promising compounds.

Lead optimization is a critical step in drug discovery, refining lead compounds to increase their potential for success in later development stages.

5) Pre-Clinical Trails

Pre-clinical trials, also known as preclinical studies, are a crucial stage in the drug development process. They are conducted before clinical trials in humans and involve testing the drug candidate in vitro (in a laboratory dish) and in vivo (in animals).

Objectives of pre-clinical trials:

1. Evaluate safety: Assess toxicity and potential risks.
2. Assess efficacy: Determine if the drug candidate is effective.
3. Pharmacokinetics: Study how the drug is absorbed, distributed, metabolized, and excreted.
4. Pharmacodynamics: Study how the drug affects the body.

Types of pre-clinical trials:

1. In vitro studies: Cell-based assays, receptor binding, and enzyme inhibition.
2. In vivo studies: Animal models, such as mice, rats, and primates.
3. Toxicology studies: Acute, sub-acute, and chronic toxicity testing.
4. ADME studies: Absorption, Distribution, Metabolism, and Excretion.

Preclinical studies

After synthesizing/identifying a prospective compound, it is tested on animals to expose the whole pharmacological profile. Experiments are generally performed on a rodent (mouse, rat, guinea pig, hamster, rabbit) and then on a larger animal (cat, dog, monkey). As the evaluation progresses unfavourable compounds get rejected at each step, so that only a few out of thousands reach the stage when administration to man is considered.

The following types of tests are performed.

1. **Screening tests :** These are simple and rapidly performed tests to indicate presence or absence of a particular pharmacodynamic activity that is sought for, e.g. analgesic or hypoglycaemic activity.
2. **Tests on isolated organs, bacterial cultures, etc :** These also are preliminary tests to detect specific activity, such as antihistaminic, anti-secretory, vasodilator, antibacterial, etc.
3. **Tests on animal models of human disease**: Such as kindled seizures in rats, spontaneously (genetically) hypertensive rats, experimental tuberculosis in mouse, alloxan induced diabetes in rat or dog, etc.

4. **Confirmatory tests and analogous activities**: Compounds found active are taken up for detailed study by more elaborate tests which confirm and characterize the activity. Other related activities, e.g. antipyretic and anti-inflammatory activity in an analgesic are tested.

5. **Systemic pharmacology**: Irrespective of the primary action of the drug, its effects on major organ systems such as nervous, cardiovascular, respiratory, renal, g.i.t are worked out. Mechanism of action, including additional mechanisms, e.g. α adrenergic blockade, calcium channel blockade, nitro-vasodilatation, etc. in a β adrenergic blocker antihypertensive, are elucidated.

6. **Quantitative tests***:* The dose-response relationship, maximal effect and comparative potency/efficacy with existing drugs is ascertained.

7. **Pharmacokinetics**: The absorption, volume of distribution, metabolism, excretion, pattern of tissue distribution and plasma half-life of the drug are quantified.

8. **Toxicity tests:** The aim is to determine safety of the compound in at least 2 animal species, one rodent and one non rodent, e.g. mouse/rat and dog by oral and parenteral routes.

TOXICITY TESTS

Acute toxicity: Single escalating doses are given to small groups of animals that are observed for overt effects and mortality for 1–3 days. The dose which kills 50% animals (LD50) is calculated. Organ toxicity is examined by histopathology on all animals.

Sub-acute toxicity: Repeated doses are given for 2–12 weeks depending on the duration of intended treatment in man. Doses are selected on the basis of ED50 and LD50. Animals are examined for overt effects, food intake, body weight, haematology, etc. and organ toxicity.

Chronic toxicity: The drug is given for 6–12 months and effects are studied as in subacute toxicity. This is generally undertaken concurrently with early clinical trials.

Reproduction and teratogenicity: Effects on spermatogenesis, ovulation, fertility and developing foetus are studied.

Mutagenicity: Ability of the drug to induce genetic damage is assessed in bacteria (Ames test), mammalian cell cultures and in intact rodents.

Carcinogenicity: Drug is given for long-term, even the whole life of the animal and they are watched for development of tumours. Standardised procedures under ‘Good Laboratory Practices’ (GLP) have been laid down for the conduct of animal experiments, especially toxicity testing.

Phases of Clinical Trials

Clinical trials are generally conducted in 4 phases though phase 0 is also included in some situations

Phase 0:

Phase 0, also called **microdosing**, is a recent approach in clinical trials to cut cost in drug development. It is conducted in a small number of subjects (10–15) for a short duration (<7 days). A very small dose is used to evaluate the pharmacodynamics and pharmacokinetics in human beings (the first exposure in humans) and are exposed to the drug for a short period. Analysis is done by highly sensitive methods like accelerated mass spectrometry and positron emission tomography (PET).

Phase I:

Less than 50 normal healthy volunteers are given the drug to establish safety, to know the actions, determine pharmacokinetic profile and to design a safe dose for further use.

Phase II:

If phase I is successful, the compound undergoes phase II evaluation in order to establish efficacy, to detect any adverse effects, appropriate dose and detailed pharmacology of the chemical in 100–300 patients suffering from diseases for which the drug under trial has therapeutic prospects.

Phase III:

If the phase II establishes that the drug is useful and generally safe, phase III clinical trials are undertaken. A large number of selected patients is given the drug to establish the benefits of the drug in the target disease, to identify the latent side effects, susceptibility to tolerance and to design ideal dosage regimen for different groups of patients.

Phase IV:

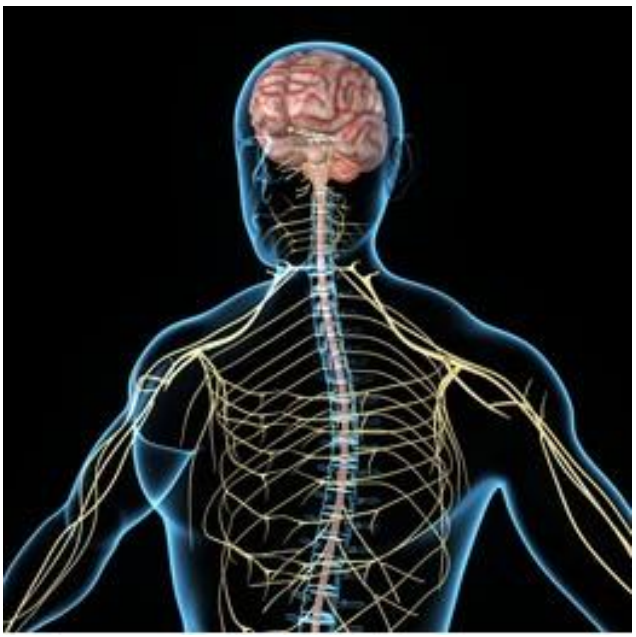
Postmarketing surveillance—If phase III studies are satisfactory, the new drug is marketed. Since the earlier phases involve a relatively smaller number of patients (3000) for short periods (<1 year), they cannot be expected to provide full safety information. Thus post marketing surveillance is done for systematic detection and evaluation of long term safety of the drug. It is done by collection and evaluation of data based on information sent by medical practitioners prescribing the drug. Phase IV trials are thus conducted by medical practitioners.

PHARMACOVIGILANCE

Definition: Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems. It deals with the epidemiologic study of adverse drug effects. The aim of pharmacovigilance is to ensure safe and rational use of medicines. Since clinical trials are done on a limited number of patients, many potential adverse effects go undetected.

- Hence reporting adverse reactions is the **duty of all medical professionals**. The adverse reactions reported and related data is collected and assessed by the pharmacovigilance system consisting of ADR reporting centres, regional and national pharmacovigilance centres which in turn report to the Uppsala Monitoring Centre at Sweden.
- In India, the Central Drugs Standard Control Organization (CDSCO) in collaboration with Indian Pharmacopoeia Commission, located at Ghaziabad has initiated a pharmacovigilance programme of India **(PVPI)**, which consists of peripheral, regional and zonal centres for coordinating the activity.
- Under theADR monitoring centre, various medical colleges and hospitals function to report ADRs. The data collected is uploaded into the pharmacovigilance software **Vigiflow**. Effective pharmacovigilance activity and awareness of toxic effects of drugs has resulted in the withdrawal of several potential toxic drugs from the market.

ADR analysis: The reported ADRs are assessed to know whether they were actually drug induced. Several scales are available for the purpose but the most preferred are the Naranjo's scale and WHO scale.



UNIT-III

Pharmacology of drugs acting on peripheral nervous system

N. Sumanasri

UNIT-III

2. Pharmacology of drugs acting on peripheral nervous system

a. Organization and function of ANS.

b.Neurohumoral transmission,co-transmission and classification of neurotransmitters.

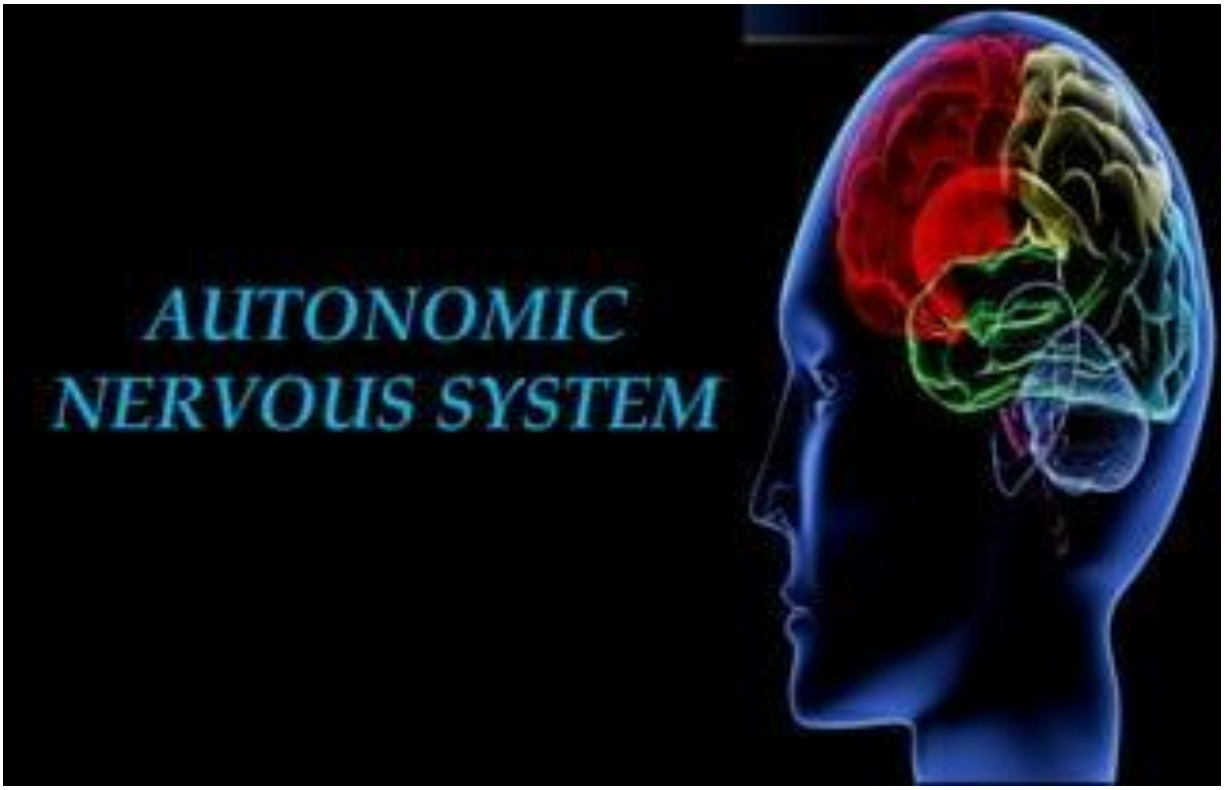
c. Parasympathomimetics, Parasympatholytics, Sympathomimetics, sympatholytics.

d. Neuromuscular blocking agents and skeletal muscle relaxants (peripheral).

e. Local anesthetic agents.

f. Drugs used in myasthenia gravis and glaucoma

A) ORGANIZATION AND FUNCTION OF ANS

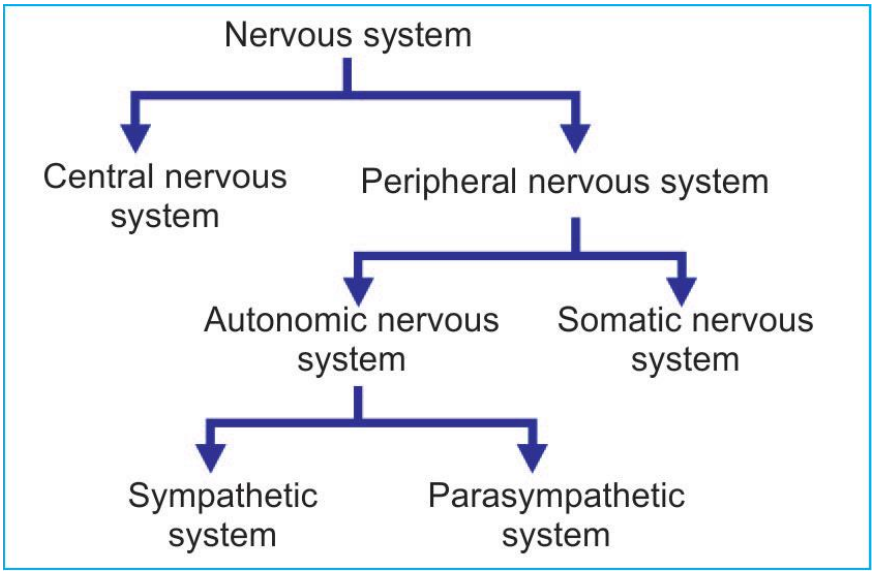


ORGANIZATION AND FUNCTION OF ANS

The autonomic nervous system (ANS) functions largely below the level of consciousness and controls visceral functions. The major differences between the somatic and autonomic nervous systems. consists of afferents, centre and efferents.

Autonomic afferents

Most visceral nerves are mixed nerves and carry non-myelinated visceral afferent fibres as well. The cell bodies of these afferent fibres are located in the dorsal root ganglion of spinal nerves and in the sensory ganglia (e.g. nodose ganglion of vagus) of cranial nerves. They mediate visceral pain as well as cardiovascular, respiratory and other visceral reflexes.



Nervous system

Central autonomic connections

- There are no exclusively autonomic areas in the CNS; considerable intermixing and integration of somatic and autonomic innervation occurs.
- The highest seat regulating autonomic functions is in the hypothalamus— posterior and lateral nuclei are primarily sympathetic while anterior and medial nuclei are primarily parasympathetic. Many autonomic centres (pupillary, vagal, respiratory, etc.) are located in the mid-brain and the medulla in relation to the cranial nerves.
- The lateral column in the thoracic spinal cord contains cells which give rise to the sympathetic outflow.

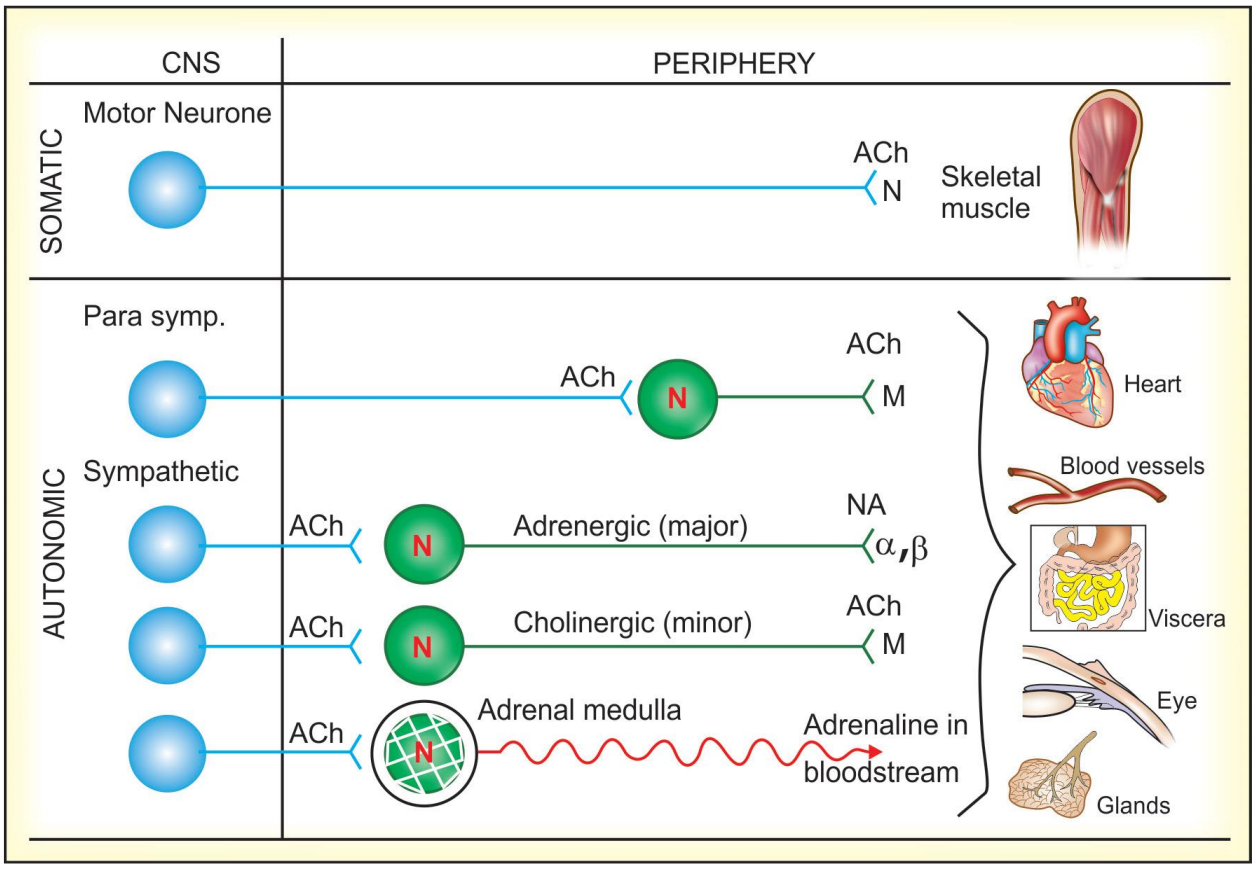
Autonomic efferents

- The motor limb of the ANS is anatomically divided into sympathetic and parasympathetic. Many organs receive both sympathetic and parasympathetic innervation and the two subdivisions are functionally antagonistic in majority of these.
- The level of activity of innervated organ at a given moment is the algebraic sum of sympathetic and parasympathetic tone. However, refractory period of atrial fibres is decreased by sympathetic as well as parasympathetic influences. Most blood vessels, spleen, sweat glands and hair follicles receive only

sympathetic, while ciliary muscle, bronchial smooth muscle, gastric and pancreatic glands receive only parasympathetic innervation. Thus, the two divisions of ANS are not merely check-and-balance physiological antagonists of each other.

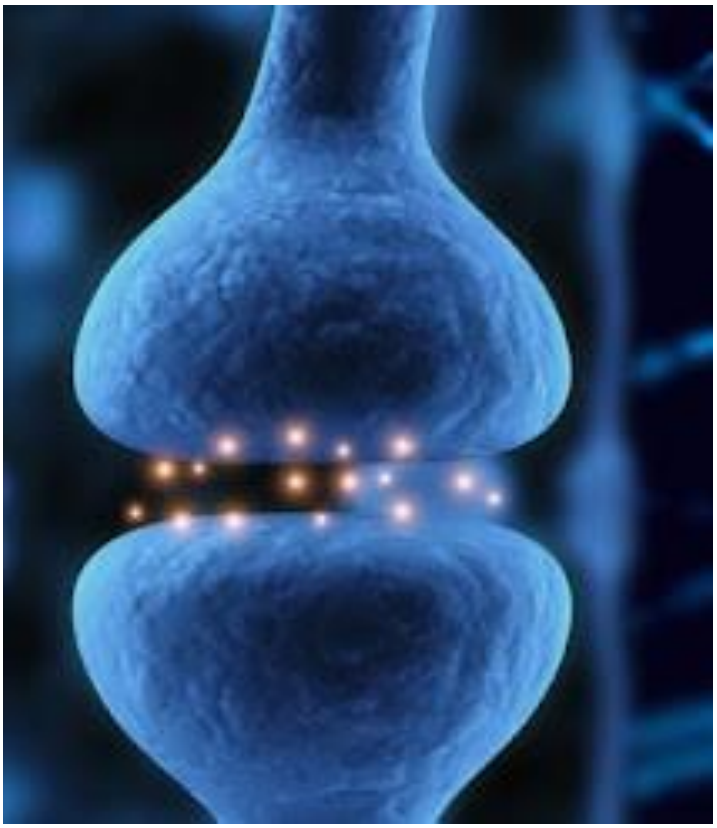
Enteric nervous system

- The enteric nervous system (ENS) located in the gut wall consists of a submucosal (Meissner's) and a myenteric (Auerbach's) plexus along with its afferent and efferent neurons whose fibres travel anterograde, retrograde as well as in a circular manner.
- It receives inputs from both sympathetic and parasympathetic divisions of ANS, but in addition functions independently to integrate bowel movements as well as regulate secretion and absorption. As such, it has also been labelled as a distinct 'enteric nervous system'.



The general outlay of efferent autonomic nervous system. The transmitter released and the primary postjunctionalreceptor subtype is shown at each synapse/neuroeffector junction

B. NEUROHUMORAL TRANSMISSION



NEUROHUMORAL TRANSMISSION

- Neurohumoral transmission implies that nerves transmit their message across synapses and neuroeffector junctions by the release of humoral (chemical) messengers.
- Junctional transmission was thought to be electrical (it does occur in some lower animals and probably in certain areas of mammalian brain) but observations at the turn of last century prompted Elliott (1905) to suggest that sympathetic nerves functioned by the release of an adrenaline-like substance, and Dixon (1907) to propose that vagus released a muscarine like chemical.
- Otto Loewi (1921) provided direct proof of humoral transmission by perfusing two frog hearts in series. Stimulation of vagus nerve of the first heart caused arrest of both. Thus, a chemical must have been released by vagal stimulation in the first heart which passed in the perfusate and arrested the second heart.
- This vagusstoff was found in 1926 to be acetylcholine, which earlier Dale (1914) had characterised as 'parasympathomimetic'.
- The sympathetic transmitter was eventually shown to be noradrenaline in 1946 by Von Euler. Many humoral transmitters (dopamine, 5-HT, GABA, glutamic acid, purines, peptides, etc.) are now known. To be considered as a postjunctionally acting neurohumoral transmitter a substance must fulfill the following criteria:

(i) It should be present in the presynaptic neurone (usually along with enzymes synthesizing it).
(ii) It should be released in the medium following nerve stimulation.
(iii) Its application should produce responses identical to those produced by nerve stimulation.
(iv) Its effects should be antagonized or potentiated by other substances which similarly alter effects of nerve stimulation.

Steps in neurohumoral transmission

I. Impulse conduction

The resting transmembrane potential (70 mV negative inside) is established by high K+ permeability of axonal membrane and high axoplasmic concentration of this ion coupled with low Na+ permeability and its active extrusion from the neurone. Stimulation or arrival of an electrical impulse causes a sudden increase in Na+ conductance.

→ Depolarization and overshoot (reverse polarization: inside becoming 20 mV positive); K+ ions then move out in the direction of their concentration gradient and repolarization is achieved. The ionic distribution is normalized during the refractory period by the activation of Na+ K+ pump. The action potential (AP) thus generated sets up local circuit currents which activate ionic channels at the next excitable part of the membrane (next node of Ranvier in myelinated fibre) and the AP is propagated without decrement. Tetrodotoxin (from puffer fish) and saxitoxin (from certain shell-fish) selectively abolish increase in Na+ conductance in nerve fibres and thus block impulse conduction.

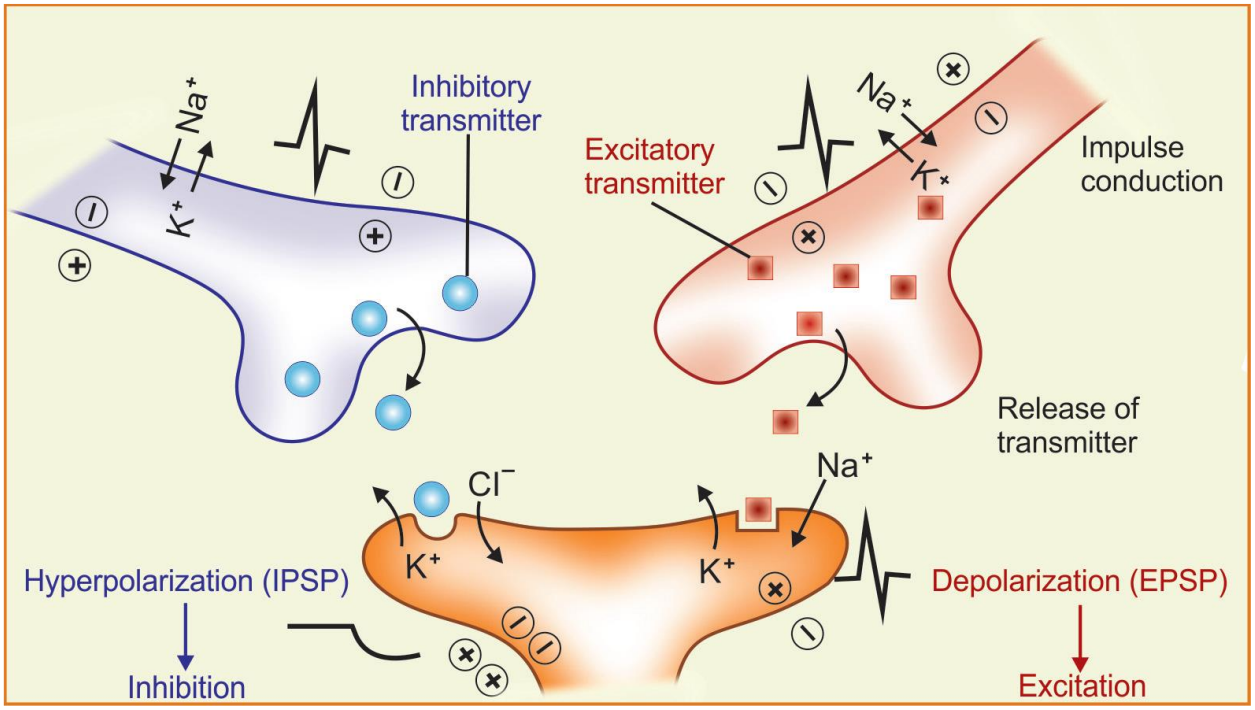
II. Transmitter release

- The transmitter (excitatory or inhibitory) is stored in prejunctional nerve endings within 'synaptic vesicles'. Nerve impulse promotes fusion of vesicular and axonal membranes through Ca2+ entry which fluidizes membranes. All contents of the vesicle (transmitter, enzymes and other proteins) are extruded by exocytosis in the junctional cleft.

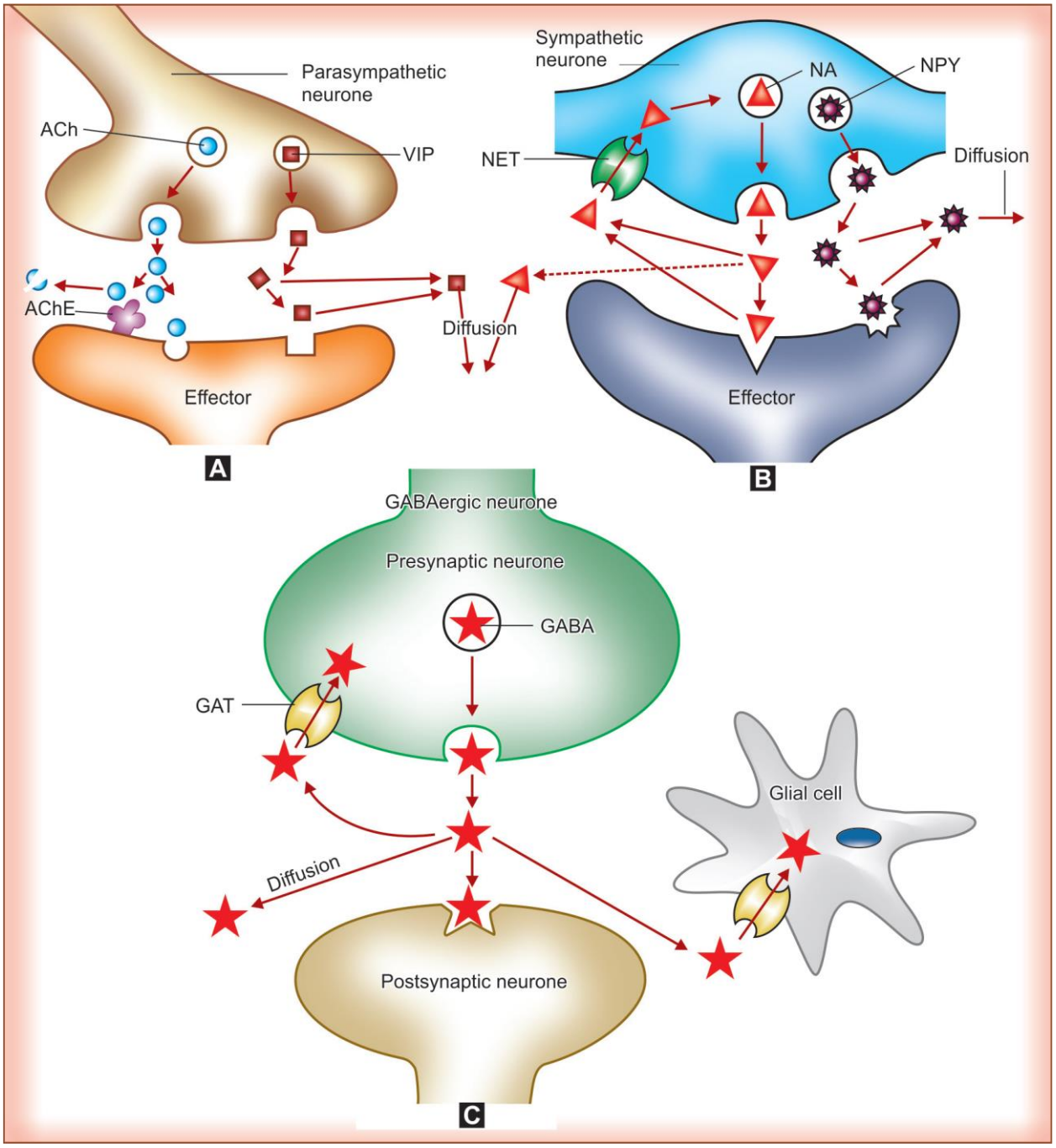
- While majority of the neurotransmitters are preformed, kept stored in synaptic vesicles and released on activation by exocytosis as outlined above, some mediators like NO, prostaglandins, endocannabinoids are synthesized on demand and reach their target by diffusion or by active transport.
- The release process can be modulated by the transmitter itself and by other agents through activation of specific receptors located on the prejunctional membrane, e.g. noradrenaline (NA) release is inhibited by NA (α2 receptor), dopamine, adenosine, prostaglandins and enkephalins while isoprenaline (β2 receptor) and angiotensin (AT1 receptor) increase NA release. Similarly, α2 and muscarinic agonists inhibit acetylcholine (ACh) release at autonomic neuro effector sites (but not in ganglia and skeletal muscles).

III. Transmitter action on post junctional membrane

- The released transmitter combines with specific receptors on the post junctional membrane and depending on its nature induces an excitatory postsynaptic potential (EPSP) or an inhibitory postsynaptic potential (IPSP).
- EPSP Increase in permeability to cations → Na+ or Ca2+ influx (through fast or slow channels) causes depolarization followed by K+ efflux. These ionic movements are passive as the flow is down the concentration gradients.
- IPSP Increase in permeability to anions, so that Cl^- ions move in (axonal Cl^- concentration is lower than its extracellular concentration) and tend to hyperpolarize the membrane → an IPSP is generated. Stabilization of the membrane or hyperpolarization can also result from selective increase in permeability to K+ ions, which move out carrying +ive charges. In addition, a trophic influence on junctional morphology and functional status is exerted by the background basal release of the transmitter.



Diagrammatic representation of steps in excitatory and inhibitory neurohumoral transmission: EPSP—Excitatory postsynaptic potential; IPSP—Inhibitory postsynaptic potential



Mechanisms of termination of transmitter action

III. Postjunctional activity

- A supra threshold EPSP generates a propagated post junctional AP which results in nerve impulse (in neurone), contraction (in muscle) or secretion (in gland). An IPSP stabilizes the post junctional membrane and resists depolarizing stimuli.

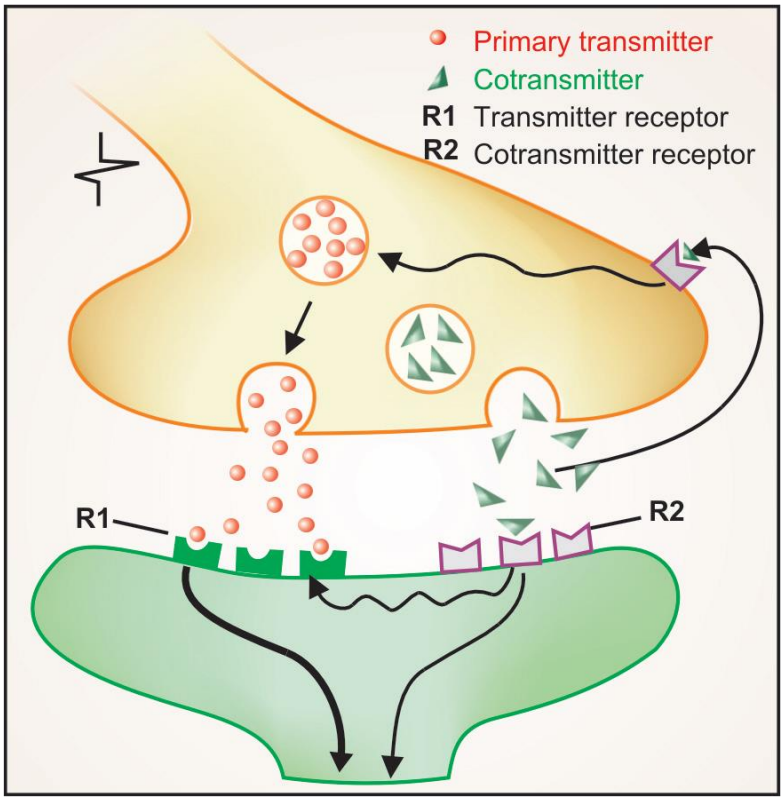
IV. Termination of transmitter action

- The various mechanisms of termination of transmitter action are depicted in its combination with the receptor, the transmitter is either locally degraded (e.g. ACh) or is mainly taken back into the prejunctional neurone by active reuptake and partly diffuses away (e.g. NA). Specific monoamine

transporter proteins like norepinephrine transporter (NET), dopamine transporter (DAT), serotonin transporter (SERT) are expressed on the axonal membrane for this purpose. The rate of termination of transmitter action governs the rate at which responses can be transmitted across a junction (1 to 1000/sec). Aminoacid transmitters (glutamate, GABA) are also partly taken up by active transport into neuronal and neighbouring glial cells, but no active reuptake of peptide neurotransmitters (VIP, NPY, enkephalins, etc.) occurs. They diffuse away and are broken down by peptidases at distant sites.

CO-TRANSMISSION

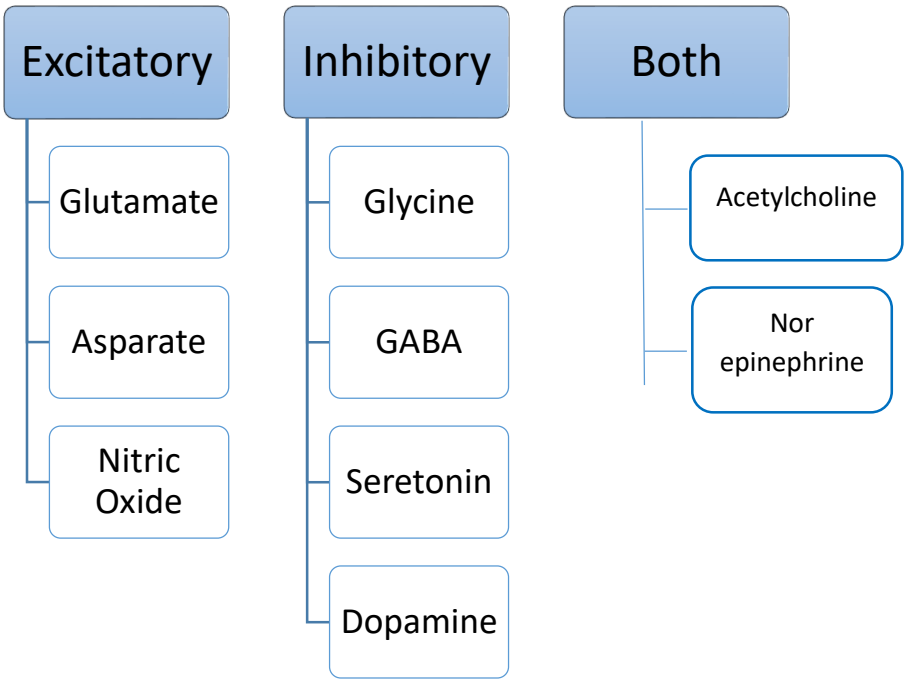
- It has become apparent that the classical 'one neurone—one transmitter' model is an over simplification. On stimulation, most peripheral and central neurones have been shown to release more than one active substance. In the ANS, besides the primary transmitters ACh and NA, neurones have been found to elaborate purines (ATP, adenosine), peptides (vasoactive intestinal peptide or VIP, neuropeptide-Y or NPY, substance P, enkephalins, somatostatin, etc.), nitric oxide (NO) and prostaglandins as cotransmitters.
- In most autonomic cholinergic neurones VIP is associated with ACh, while ATP is associated with both ACh and NA. The transmitter at some parasympathetic sites is NO, and these are called nitrergic nerves. Vascular adrenergic nerves contain NPY which causes long lasting vasoconstriction.
- The co-transmitter is stored in the same neurone but in distinct synaptic vesicles or locations. However, ATP is stored with NA in the same vesicle. On being released by nerve impulse the cotransmitter may serve to regulate the presynaptic release of the primary transmitter and/or postsynaptic sensitivity to it (neuromodulator role). The cotransmitter may also serve as an alternative transmitter in its own right and/or exert a trophic influence on the synaptic structures. Non-adrenergic, non-cholinergic (NANC) transmission has been demonstrated in the autonomic innervation of the gut, vas deferens,

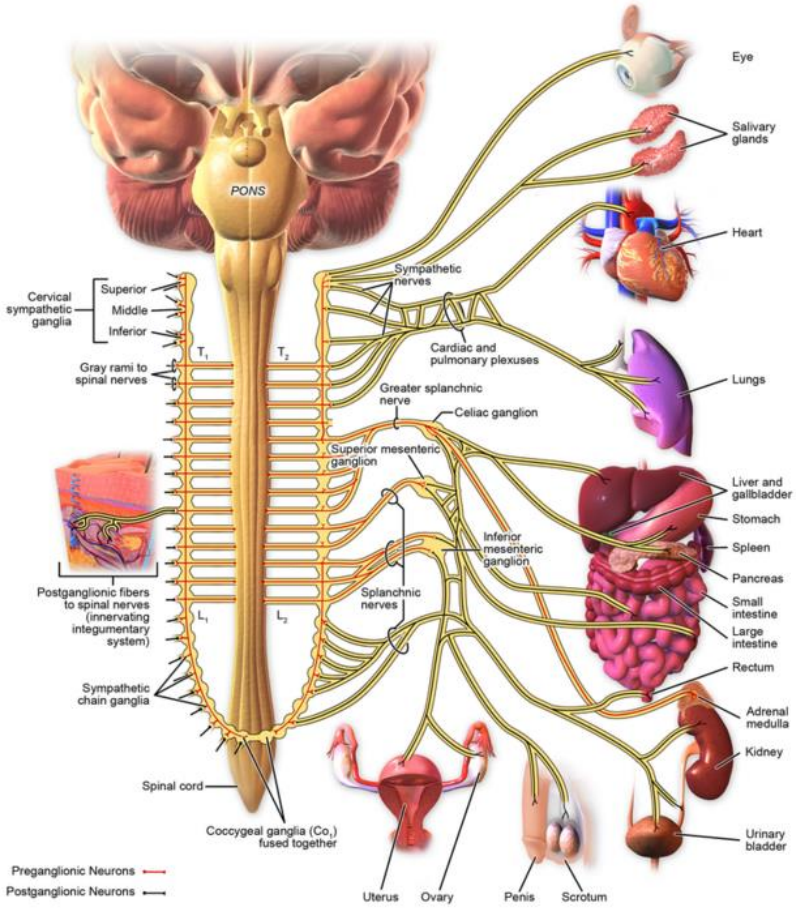


Co-transmission

- The co transmitter is stored in the prejunctional nerve terminal along with the primary transmitter, but in separate vesicles (in some cases in the same vesicle itself). Nerve impulse releases both the transmitters concurrently. Acting on its own receptors, the co-transmitter modifies responsiveness of the effector to the primary transmitter or substitutes for it.
- Co transmitter may also act on pre junctional receptors and modulate release of the transmitters urinary tract, salivary glands and certain blood vessels, where nerve stimulation is able to evoke limited responses even in the presence of total adrenergic and cholinergic blockade. For example, it has been shown that stimulation of sympathetic nerve to guinea pig vas deferenselicits a biphasic contractile response, the initial short-lasting phase of which is mediated by ATP (through P2 receptors) and the second longer lasting phase by NA (through α1 receptors).

CLASSIFICATION OF NEUROTRANSMISSTORS





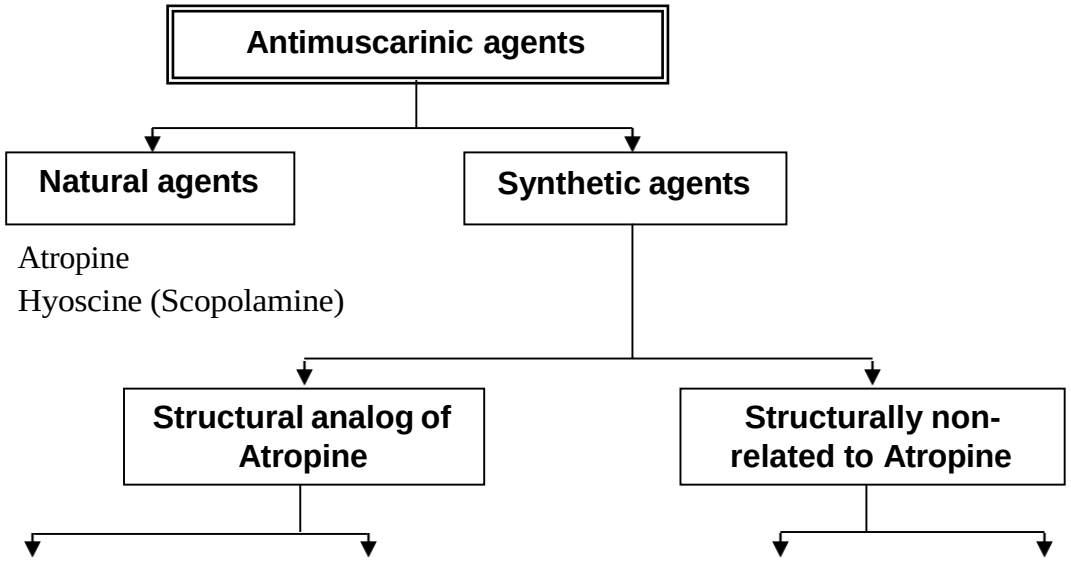
Parasympathomimetics, Parasympatholytics, Sympathomimetics, Sympatholytics

ANTICHOLINERGIC DRUGS (Parasympatholytics)

These drugs block muscarinic receptors only, so better known as antimuscarinic agents.

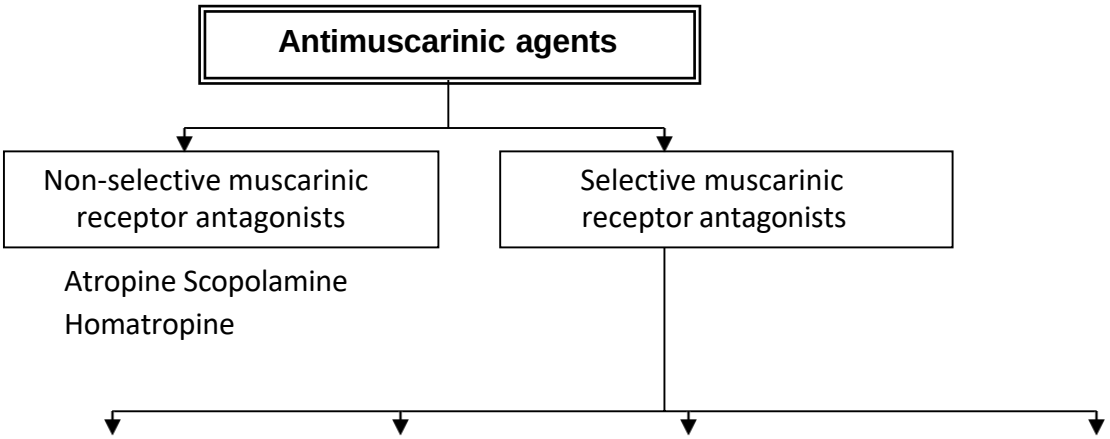
CLASSIFICATION:

(I) Classification based on Origin & Structure:



Tertiary ammonium Compounds	Quaternary ammonium Compounds	Tertiary amine	Quaternary amine
Homatropine	Atropine methylnitrite	Pirenzepine	Methantheline
	Homatropine methyl bromide	Dicyclomine	Propantheline
	Methscopolamine bromide	Cyclopentolate	Isopropamide
	Ipratropium bromide	Oxyphenecyclimine	Glycopyrrolate
	Tiotropium bromide	Tropicamide	

(II) Classification based on Mode of Action:



M_1 Antagonist	M_2 Antagonist	M_3 Antagonist	M_4 Antagonist
Pirenzepine	Methoctramine	Hexahydrosiladenifenidol	Himbacine
Telenzepine	Gallamine		

Mechanism of action of muscarinic blockers:

Atropine and related drugs block the cholinergic muscarinic receptors by acting as competitive antagonists of ACh or other direct acting cholinergic drugs.

PHARMACOLOGICAL ACTIONS OF PARASYMPATHOLYTICS:

(1) vascular system: Small doses of atropine cause an initial temporary bradycardia (agonistic action due to vagal stimulation and/ or momentary stimulation of cardiac muscarinic receptors prior to their blockade). High doses cause tachycardia. Atropine like drugs antagonize the fall in blood pressure caused by choline esters. Atropine alone does not affect blood pressure.

(2) t: Smasmolytic effect on GI smooth muscles by preventing the effect of endogenous ACh. Block the increase in tone and motility of GIT caused by cholinergic drugs. Rumen motility is reduced. GI secretions including salivation are blocked.

(3) piratory tract: Inhibition of bronchial secretions and dilatation of bronchi (temporary relief of dyspnoea/ asthma/ heaves in horses).

(4) : Mydriasis and cycloplegia (paralysis of accommodation) following local or systemic use. Mydriasis is due to blockade of cholinergic influence and dominance of adrenergic effect. Cycloplegia is due to paralysis of ciliary muscle of the lens.

(5) ry tract: Spasmolytic effect on ureters (useful in the treatment of renal colic) and urinary retention (relaxation of bladder).

(6) Anhydrotic action in man (cholinergic) and consequently rise in body temperature but does not prevent sweating in horses (adrenergic).

(7) Atropine has no significant effect. Scopolamine in small doses produces depression & excitement and delirium at high doses in cats and dogs.

ATROPINE & SCOPOLAMINE:

- Atropine is an alkaloid extracted from the leaves of belladonna plants Atropa belladonna (deadly nightshade), Datura stramonium (Jimson weed) and Hyoscyamus niger (Henbane). Scopolamine is also an alkaloid extracted from the leaves Hyoscyamus niger and Scopolia carniolica.
- **The name "Atropa belladonna":** During the time of the Roman Empire and in the Middle Ages, the deadly nightshade shrub was frequently used to produce an obscure and often prolonged poisoning, prompting Linnaeus to name the shrub Atropa belladonna, after Atropos, the oldest of
  the three Fates (goddesses) in Greek mythology, who cuts the thread of life. The name belladonna derives from the alleged use of this preparation by Italian women to dilate their pupils; modern-day fashion models are known to use this same device for visual appeal.
- Atropine is a racemic mixture of d-hyoscyamine and l-hyoscyamine. The laevo form of hyoscyamine is biologically active.
- An atropine poisoning, physostigmine is used as it is better able to enter CNS than other parasympathomimetics. It is the central effects of atropine which is lethal.

- bbits possess an esterase (atropinase) which hydrolyses atropine and is thereby able to feed on deadly nightshade with freedom without showing any toxic symptom.
- The laevo isomer of hyoscine is called scopolamine which is the active form. Its main difference from atropine is its slight sedative effect on the CNS at therapeutic dosage.

- **fects of atropine in relation to dose:**

Dose	Effects
0.5 mg/kg	Slight cardiac slowing; some dryness of mouth; inhibition of sweating.
1 mg/kg	Definite dryness of mouth; thirst; acceleration of heart, sometimes preceded by slowing; mild dilation of pupils.
2 mg/kg	Rapid heart rate; palpitation; marked dryness of mouth; dilated pupils; some blurring of near vision.
5 mg/kg	All the above symptoms marked. Difficulty in speaking and swallowing; restlessness and fatigue; headache; dry, hot skin; difficulty in micturition; reduced intestinal peristalsis.
10 mg/kg or more	Above symptoms more marked, pulse rapid & weak; iris practically obliterated; vision very blurred; skin flushed, hot dry & scarlet; ataxia; restlessness, excitement, hallucinations and delirium; coma and finally death.

THERAPEUTIC USES OF PARASYMPATHOLYTICS:

(i) Atropine:

- As preanaesthetic
- As antidote in organophosphate and carbamate poisoning (0.2 to 0.5 mg/kg : $1/4^{th}$ of the total dose should be given i.v. and rest by i.m. route).
- For relief of heaves in horses.
- Eye drops (1%) – during eye examination.

(ii) Homatropine: 2 – 5 % solution topically in the eye for ophtalmological use (mydriatic or cycloplegic). Its effects are of shorter duration as compared to those of atropine which causes persistent mydriasis and cycloplegia.

(iii) Glycopyrrolate: Preanaesthetic.

ADRENERGIC NEUROTRANSMISSION

ADRENERGIC TRANSMISSION:

The impulse transmission that is mediated by norepinephrine (post-ganglionic sympathetic nerve terminals and CNS), dopamine (CNS) and epinephrine (adrenal medulla) is in general called as adrenergic transmission. All these transmitters are also called as catecholamines.

CATECHOLAMINES:

Norepinephrine, epinephrine and dopamine are endogenous catecholamines; they are sympathetic neural and humoural transmitter substances in most mammalian species.

Norepinephrine: It acts as transmitter at most peripheral sympathetic neuroeffector junctions and in the CNS.

Epinephrine: It is the major hormone released from adrenal medulla.

Dopamine: It is believed to transmit impulse information in specific areas within the CNS (basal ganglia, limbic system, CTZ, anterior pituitary etc.).

SYNTHESIS OF CATECHOLAMINES:

Norepinephrine is synthesized from the amino acid phenylalanine in a stepwise process summarized below:

(i) The aromatic ring of phenylalanine is hydroxylated by action of an enzyme, phenylalanine hydroxylase. The reaction yields tyrosine.

(ii) Tyrosine is converted to dihydroxyphenylalanine (DOPA) by the enzyme tyrosine hydroxylase. This reaction involves additional hydroxylation of the benzene ring, and it is believed to represent the rate limiting step in catecholamine synthesis.

(iii) DOPA is decarboxylated by the enzyme L-amino acid decarboxylase (dopa decarboxylase) to dihydrophenylethylamine (dopamine). Dopamine is then taken up in the storage granule.

Conversion of tyrosine to DOPA to dopamine is believed to occur within the axonal cytoplasm (axoplasm). In some central anatomic sites (e.g. mammalian extrapyramidal system), dopamine seems to act as the primary neurotransmitter rather than its metabolites norepinephrine and epinephrine.

(iv) In peripheral adrenergic neurons and adrenal medullary chromaffin cells, intragranular dopamine is hydroxylated in the □-position of the aliphatic side chain by dopamine-□-hydroxylase to form norepinephrine.

(i) he adrenal medulla, norepinephrine is released from the granules of chromaffin cells and is N-methylated within the cytoplasm by phenylethanolamine N-methyltransferase to form epinephrine. Epinephrine is subsequently localized in another type of intragranular storage granule prior to its release from the adrenal medulla.

STORAGE OF CATECHOLAMINES:

Catecholamines are taken up from the cytoplasm into vesicles or granules by an active transport system which is ATP and Mg^{2+} dependent. Storage within the granular vesicles is accomplished by complexation of the catecholamines with ATP (in molecular ratio of 4:1)

which is adsorbed on a protein, chromogranin. This complexation renders the amine inactive until their release. The intragranular pool of NE is the principal source of neurotransmitter released upon nerve stimulation. The cytoplasmic pool of catecholamines is kept low by the enzyme monoamine oxidase (MAO) present in neuronal mitochondria.

[**NB:** Reserpine is a drug which depletes catecholamine stores by inhibiting monoamine transport into vesicles].

RELEASE OF CATECHOLAMINES:

The nerve impulse coupled release of catecholamines from adrenergic nerve terminals takes place by exocytosis and is dependent upon an inward movement of Ca^{2+}. Released norepinephrine migrates across the synaptic cleft and interacts with specific adrenergic receptor sites on the post-junctional membrane.

[**NB:** Bretylium inhibits norepinephrine release].

TERMINATION OF CATECHOLAMINES ACTION:

Uptake of Catecholamines:

There is a very efficient mechanism by which norepinephrine released from the nerve terminal is recaptured. Exogenously administered norepinephrine and epinephrine are taken up into sympathetic nerve endings by this uptake process. Conservation of catecholamine neurotransmitters by reuptake is one of the first examples of recycling used products. There are following two uptake mechanisms:

Axonal uptake (Uptake - 1)	**Extraneuronal uptake (Uptake -2)**
(i) The adrenergic neuronal uptake is referred to as uptake-1. This uptake is the most important mechanism for terminating the action post-junctional action of NE.	(i) It signifies the extraneuronal uptake of catecholamines into surrounding tissue.
(ii) Uptake-1 is saturable and operates at very low physiological concentrations of transmitter.	(ii) Uptake-2 has very large capacity and accumulation operates most effectively at high concentrations of NE.
(iii) Uptake-1 requires Na^+ ions, K^+ ions and ATP and is blocked by cocaine, desipramine & its congeners guanethidine and many H1 antihistaminics.	(iii) Uptake-2 is less selective, and is not blocked by cocaine but is sensitive to cortisol. It is not of pharmacological importance.

Metabolism of Catecholamines:

The duration of action of catecholamines can be terminated either by reuptake mechanisms or metabolism by enzymes monoamine oxidase (MAO) and catechol o-methyl transferase (COMT).

Cytoplasmic NE is attacked by MAO. The extraneuronal NE which diffuses into circulation is destroyed by COMT in liver and other tissues like kidney, brain etc.

However, metabolism does not play an important role in terminating the action of endogenous catecholamines.

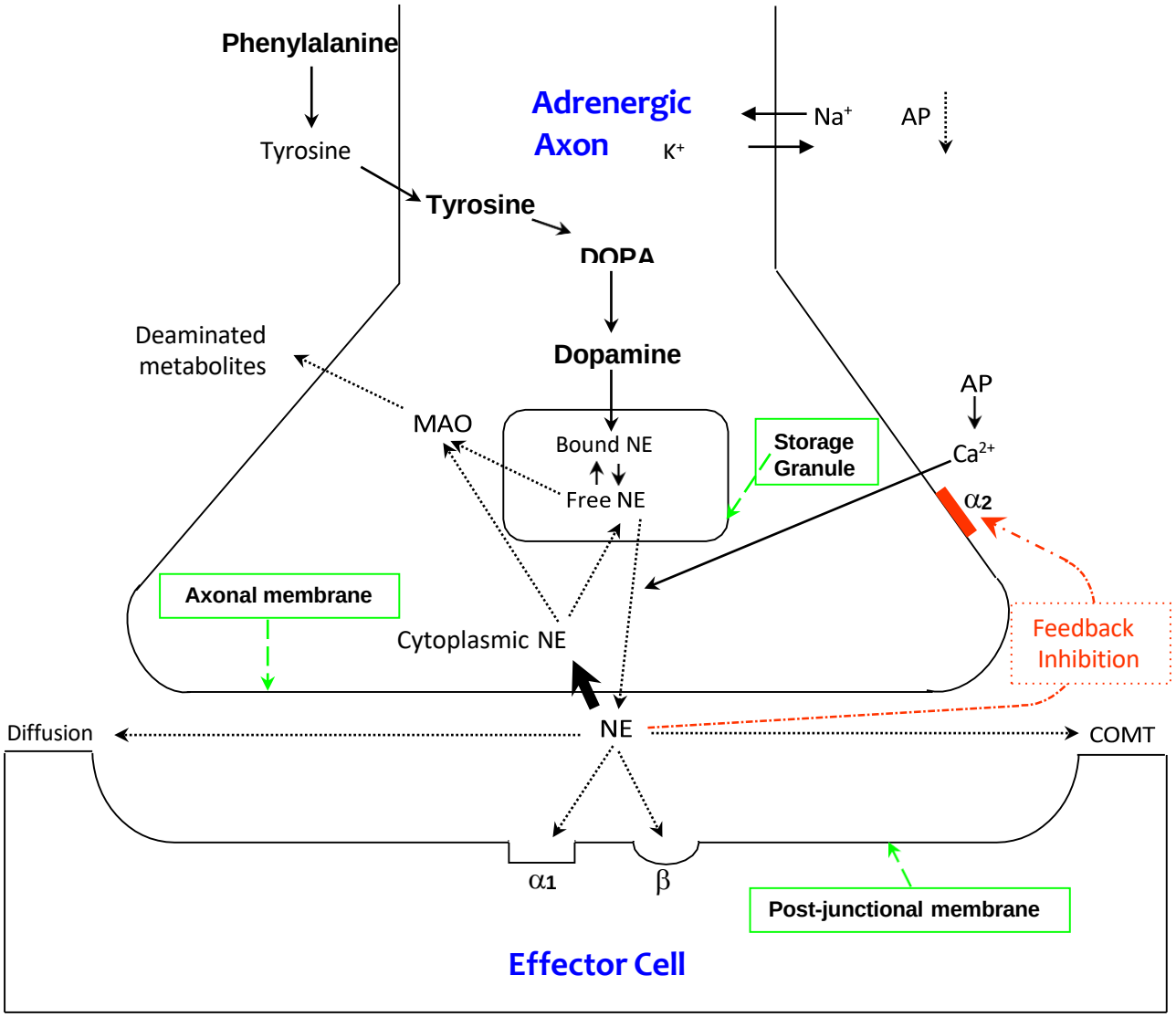


Fig.: Showing neurohumoural transmission at the adrenergic neuroeffector junction

ADRENERGIC DRUGS (Sympathomimetics)

These are drugs which mimic the effects of sympathetic stimulation or those of catecholamines. Their effects are due to stimulation of adrenergic receptors (directly or indirectly) on the effector cells, hence also called as adrenergic drugs.

CLASSIFICATION:

(I) Classification based on chemical structure:

(1) Catecholamines: Epinephrine, Norepinephrine, Dopamine and Isoproterenol.

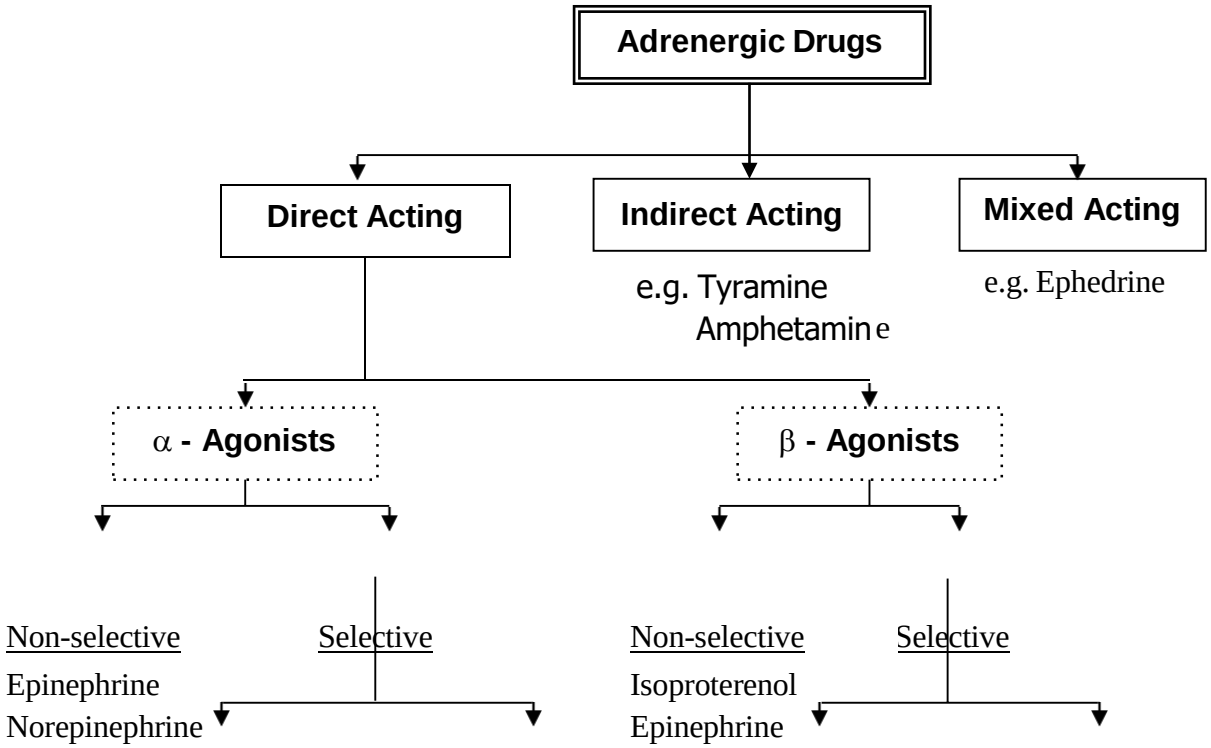
(2) Non-catecholamines: Phenylephrine, Ephedrine, Amphetamine, Tyramine etc.

(II) Classification based on mechanism of action:

(1) Indirectly acting agents: They act directly as agonists on α and/ or α -adrenergic receptors. e.g. Epinephrine, NE, Isoproterenol.

(2) Directly acting agents: They act on adrenergic neurons to release noradrenaline which then acts on the adrenergic receptors. e.g. Tyramine.

(3) mixed acting agents: They act directly as well as indirectly. e.g. Ephedrine.



α1 Agonists	α2 Agonists	β1 Agonists	β2 Agonists
Phenylephrine	Clonidine	Dobutamine	Terbutaline
	Detomidine		Salbutamol (Albuterol)
	Medetomidine		Clenbuterol

PHARMACOLOGICAL EFFECTS OF ADRENERGIC DRUGS:

(1) Heart (□1 & □1): Increase in heart rate (positive chronotropic effect) and increase in force of cardiac contraction (positive inotropic effect).

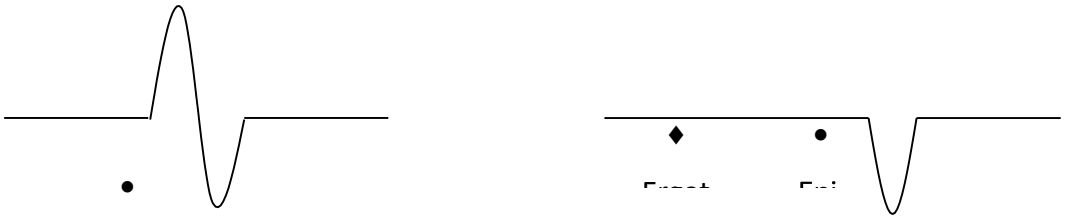
(2) Blood vessels (Mainly □1 but also □2): Both vasoconstriction (□1 mediated) and vasodilatation (□2 mediated) can occur depending on the drug, its dose and vascular bed. There is dilatation of blood vessels in skeletal muscles, lungs and mesentery (□2 action).

Dale's Reversal Phenomenon or Epinephrine reversal:

Blood vessels contain both □ and □2 receptors. □ receptors are more abundant whereas α 2 receptors are less but more powerful and sensitive. Epinephrine causes increase which is followed by decrease in blood pressure. The rise in blood pressure is mediated by α receptors which are more in number. Though □2 receptors are also occupied by epinephrine, their effect is suppressed by activation of large number of □ receptors. As the concentration of epinephrine decreases by metabolism or elimination, it dissociates first from the less sensitive α receptors. So, at later stage, the number of activated □2 receptors remains more than the activated □ receptors which cause decrease in blood pressure.

Now, the presence of α receptor blockers like ergot etc. renders α receptors inactive and inhibits the rising phase of epinephrine induced blood pressure. But, □2 receptor

mediated action (i.e. fall in blood pressure) predominates even at higher concentration of epinephrine as their suppressors (□ receptors) are blocked. As the effect of epinephrine is reversed by the presence of □ receptor blockers and this phenomenon was first observed by Dale, the phenomenon is called as Dale's Reversal Phenomenon.



(3) Respiratory tract (□2): Inhibitory effect on smooth muscles of respiratory passages causing relaxation of bronchi and trachea. Epinephrine and isoproterenol (but not norepinephrine) are potent bronchodilators.

(4) Gastrointestinal tract (Both □1 & □2): Inhibitory effect on smooth muscles of GI tract causing decrease in tone and motility.

(5) Eye (□1): Mydriasis due to contraction of radial muscles. Decrease Intraocular Pressure by enhancing both conventional (via a β2-receptor mechanism) and uveoscleral outflow (perhaps via prostaglandin production) from the eye.

(6) Sex organ (□1): Ejaculation of male sex organ.

(7) Metabolism: Metabolic effects like hyperglycaemia (□1 & □2) due to glycogenolysis and hyperlipaemia (□3) due to lipolysis.

(8) Splenic capsule: Contracts (□) and more RBCs are poured into circulation.

(9) CNS: CNS stimulation causing respiratory stimulation, wakefulness, increase in psychomotor activity and anorectic effect.

SYMPATHOMIMETIC AGENTS AND THEIR CLINICAL USES:

(1) Adrenaline (Epinephrine) and Noradrenaline (Norepinephrine): Classically these agents have been used to reverse hypotension, hence, the group name 'pressoramines'.

Noradrenaline – is best used by continuous i.v. infusion (8 □g/ml, 2 ml/min). It causes generalized vasoconstriction with increased peripheral resistance and increased systolic and diastolic blood pressure.

Adrenaline – Myocardial stimulation induced by adrenaline is often accompanied by disordered rhythm of the heart, esp. under trichloroethylene, chloroform, cyclopropane or halothane anaesthesia. For this reason, adrenaline is not given intravenously. Subcutaneously injected adrenaline is still used to relieve the severe hypotension and bronchoconstriction of acute hypersensitivity reactions.

Uses:

(i) With local anaesthetics: Epinephrine and norepinephrine potentiate local anaesthetic action by decreasing absorption of local anaesthetics.

(ii) As local haemostatic: By applying epinephrine moistened gauge or sponge (1 lakh to

1.2 lakh dilutions) over the bleeding surfaces, mucosae or subcutaneous tissues, arrests bleeding due to local vasoconstriction.

(iii) In allergic/ anaphylactic reactions and acute bronchial asthma: Epinephrine reverses the acute hypotension and dilates the respiratory passages.
Cattle & Horses – 4 to 8 ml of 1:1000 dilution i.m. or s.c. Sheep & Swine – 1 to 3 ml of 1:1000 dilution i.m. or s.c. Dog & Cat – 1 to 5 ml of 1:10,000 dilution i.m. or s.c.

(iv) As cardiac stimulant: Used in the treatment of acute cardiac arrest AV blocks.

(2) Ephedrine: It is a naturally acting alkaloid obtained from Ephedra vulgaris.

- Mixed acting - Mainly acts indirectly but also has some direct action on □ & □ receptors also.
- It is resistant to MAO and COMT.
- It is 100 times less potent than adrenaline but longer lasting (4 - 6 hour).
- It was the first agent to be used clinically in management of asthma.
- The drug was previously used as bronchodilator, vasoconstrictor, a heart stimulant, a mydriatic and a CNS stimulant. Now-a-days, for most of these purposes, there are preferred drugs which are pharmacologically cleaner, more potent alternatives.

(3) Amphetamine {CNS stimulant}**:** It is a synthetic, orally active, largely indirect acting □ & □ agonist having euphoriant & habit forming properties in man. It has been used by athletes and given to race horses to improve performance illegally (Doping). The central effects of amphetamine include alertness, increased concentration & attention span, euphoria, talkativeness and increased work capacity. Fatigue is allayed. Hence, athletic performance is improved temporarily followed by deterioration.

(4) Phenylephrine {vasoconstrictor}**:** It is an □1 agonist (less potent but more long lasting than noradrenaline). It is used in hypotension, in local anaesthetic formulations, in decongestants and in ophthalmology (as 10% solution when pupillary dilatation without loss of accommodation is required).

(5) Isoprenaline (Isoproterenol) {bronchodilator & cardiostimulant}**:** It is a synthetic, mixed □ agonist. The drug is resistant to MAO but metabolized by COMT.

- Bronchodilator (□2) action to asthma in man.
- Powerful cardiostimulatory action (□1) to accelerate ventricular rate in heart block.

(6) Salbutamol (Albuterol) {bronchodilator}**:** It is a selective □2 agonist (i.e. acting on bronchial muscle, vasculature and the uterus). □2 selectivity is only relative. Salbutamol has □2:□1 action ratio of 10.

- The drug is lacking the undesirable cardio-excitation side effects of isoprenaline in asthmatics.
- The drug is resistant to MAO and COMT and is having longer duration of action as compared to isoprenaline.
- It is used as **inhaler** by asthmatics. Inhaled salbutamol produces

bronchodilatation within 5 minutes and the action lasts for 2 – 4 hours.

(7) Terbutaline {bronchodilator}**:** It is similar to salbutamol in properties and use. Inhaled salbutamol and terbutaline are currently the most popular drugs.

(8) Isoxuprine {tocolytic or uterine relaxant}**:** Selective □2 agonist. Depresses smooth muscle contraction in gravid uterus. So, useful in threatened abortion.

(9) Clenbuterol: Selective □2 agonist. It is having tocolytic and bronchodilator actions.

ANTIADRENERGIC DRUGS (Sympatholytics)

These are the drugs which antagonize the pharmacological action of sympathomimetic agents or alter the function of sympathetic nervous system inside the body.

CLASSIFICATION:

(1) Direct acting adrenergic receptor blockers or adrenergic antagonists: These drugs interact with adrenergic receptors and by occupying these sites do not allow an adrenergic agonist access to the receptor.

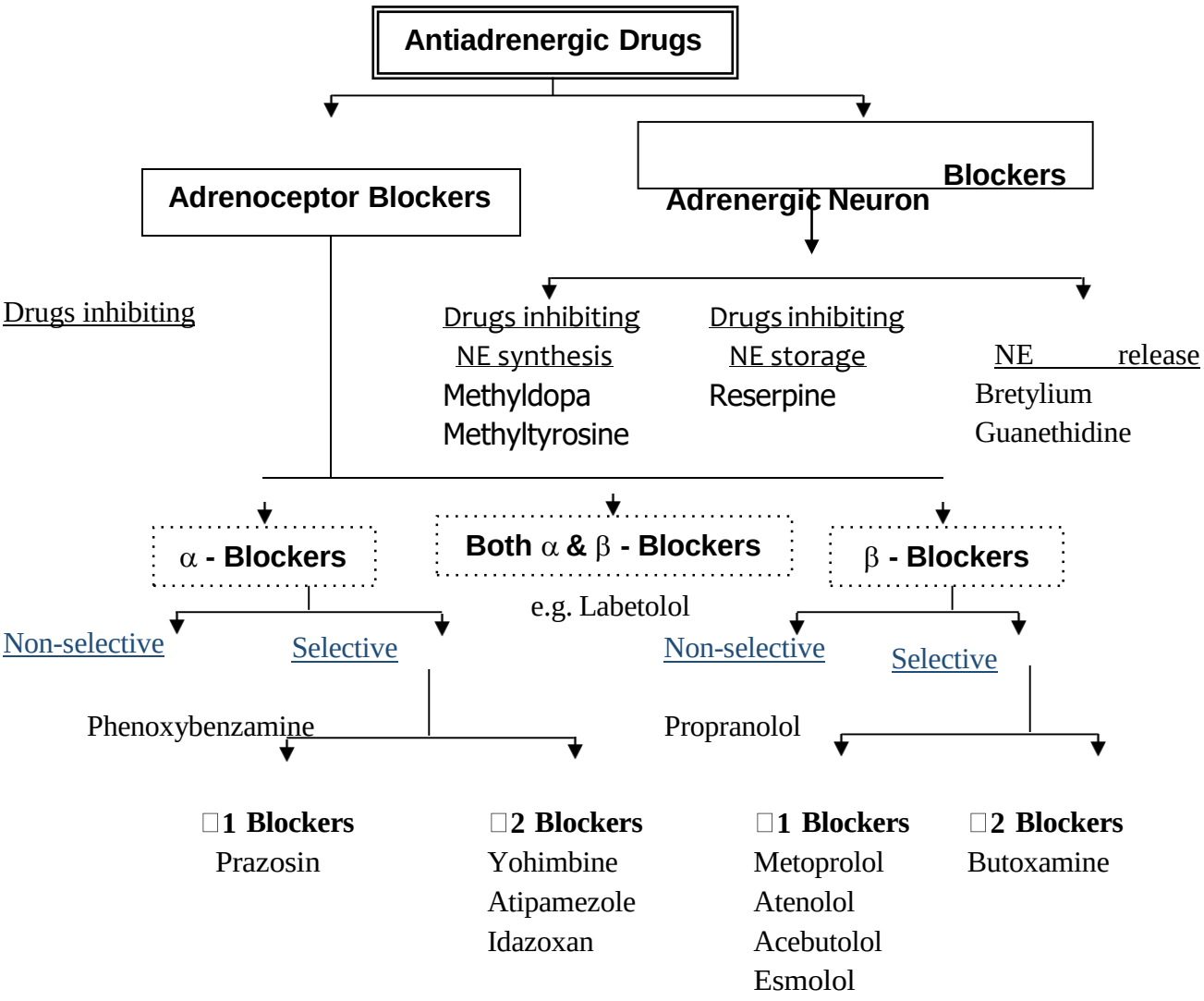
(2) Indirect acting adrenergic neuron blockers: These drugs do not block receptors; instead, they act presynaptically at the nerve terminal to cause a decreased release of the endogenous neurotransmitter norepinephrine.

The adrenergic neuron blockers interfere with the transmitter function of adrenergic neurons by the following mechanisms:

(i) By interfering with the synthesis of catecholamines: e.g. Methyldopa and methyltyrosine.

(ii) By interfering with storage of norepinephrine: e.g. Reserpine (It depletes NE stores in adrenergic neurons).

(iii) By preventing the release of norepinephrine: e.g. Guanethidine.



PHARMACOLOGICAL ACTIONS OF SYMPATHOLYTICS:

(1) CVS: Heart rate, force of cardiac contraction and cardiac output decreases.

[NB: The effect on a normal resting heart is not appreciable, but becomes prominent under sympathetic over-activity (exercise, vomition).**]**

(2) B.P.: Epinephrine reversal (net result - hypotension).

(3) Respiratory tract: Bronchoconstriction.

(4) Skeletal muscles: Relaxation.

(5) Eye: Reduces secretion of aqueous humour and intraocular tension. Thus, helpful in glaucoma.

ANTIADRENERGIC DRUGS AND THEIR CLINICAL USES:

□ Blockers:

(1) □ blockers (like Prazosin etc.) are used in human therapeutics as <u>vasodilators</u> in emergency control of dangerously high blood pressure or in peripheral ischaemic diseases.

(2) The ability of □ **blockers** to reverse the effects of **xylazine** has now given these drugs a veterinary role.

- Atipamezole (□2 blocker) selectively antagonizes medetomidine (□2 agonist).
- Idazoxan (□2 blocker) selectively antagonizes xylazine (□2 agonist).
- Yohimbine is in general used as □2 antagonist.

□ - Blockers:

(1) **Pronethalol:** It was the first □ blocker to be marketed. Although, effective in controlling arrhythmias and hypotension, it was found a carcinogen in mice and was later withdrawn.

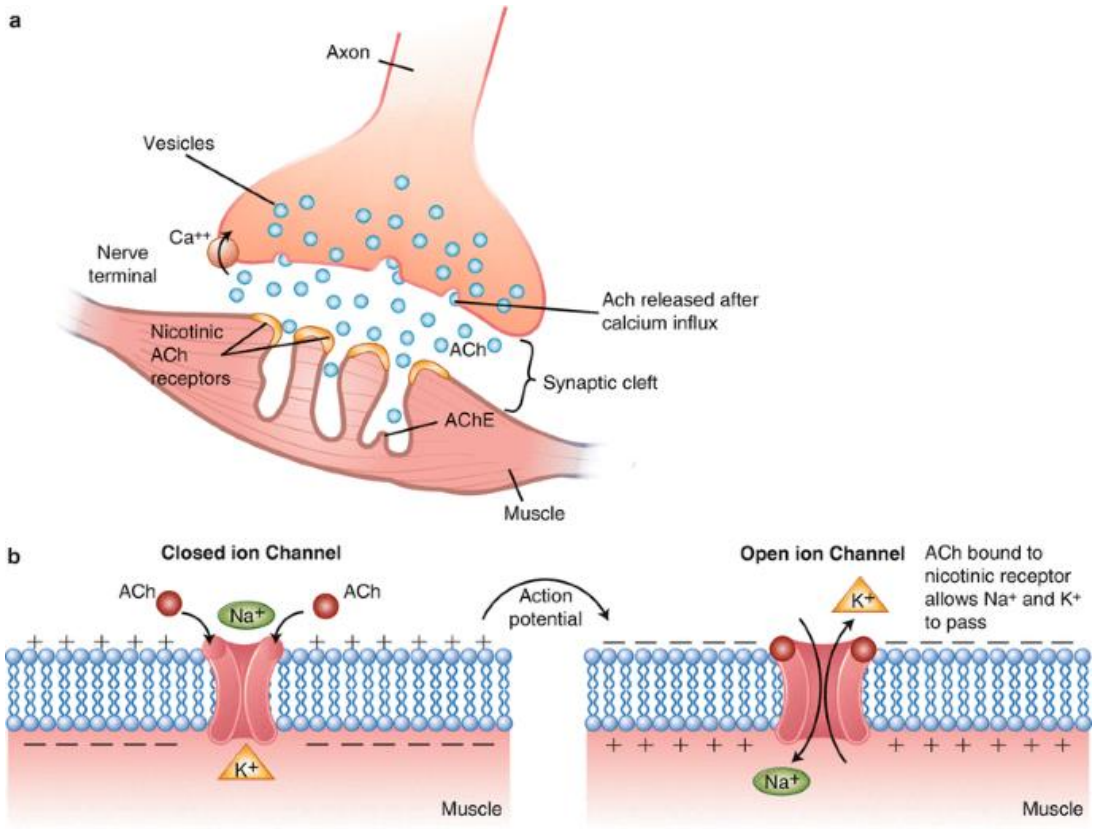
(2) **Propranolol:** It is a non-selective □ (□1+□2) antagonist.

- The drug is a competitive antagonist of isoprenaline at □ adrenoceptors. Useful in angina pectoris and protects the heart from sympathetic drive.
- Inhibits the metabolic actions of adrenaline like muscle and liver glycogenolysis & lipolysis.
- Bronchoconstrictor and antiarrhythmic for heart.

(3) **Acebutolol, Metoprolol, Atenolol:** (Cardioselective □1 blockers)

- Used for – **Angina pectoris**, **hypertension**, **cardiac arrhythmias** etc.

D) NEUROMUSCULAR BLOCKING AGENTS

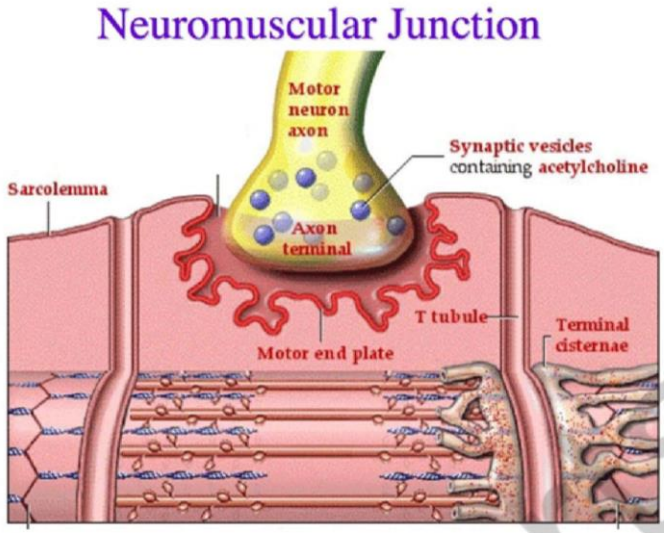


NEUROMUSCULAR BLOCKING AGENTS

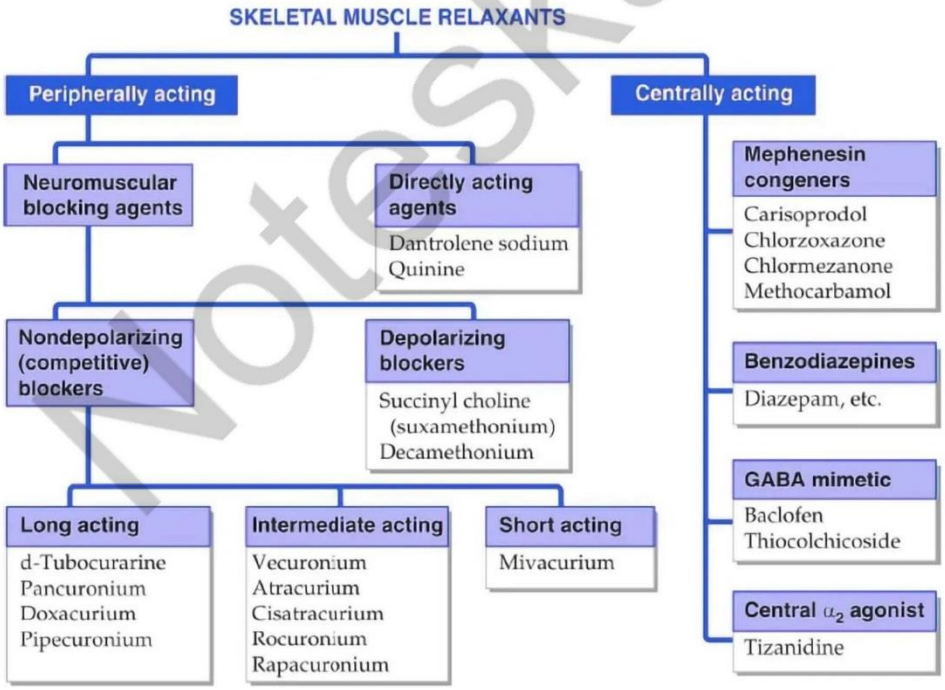
These are those agents which are used to block the neuromuscular junction and inhibit the contraction of muscle and cause relaxation of muscles. They are also known as Skeletal muscle relaxants.

Neuromuscular Junction:

- The neuromuscular junction (NMJ) is a synaptic connection between the terminal end of a motor nerve and a muscle (skeletal/ smooth/cardiac).
- It is the site for the transmission of action potential from nerve to the muscle. It is also a site for many diseases and a site of action for many pharmacological drugs.



Classification of Skeletal muscle relaxants (peripheral).



A. Non-depolarizing Blockers:

- Non-depolarizing blockers are a type of neuromuscular blocking agent (NMBA) that act on the neuromuscular junction (NMJ) to induce muscle relaxation.
- Unlike depolarizing blockers, they do not directly trigger muscle contraction.
- They work by competitively inhibiting the binding of acetylcholine (ACh), the natural neurotransmitter responsible for muscle activation, to the nicotinic acetylcholine receptors (nAChRs) on the postsynaptic membrane of the muscle fiber.

Mechanism of Action:

1. ACh release: An action potential travels down the motor neuron, leading to the 2. release of ACh from the presynaptic terminal.
2. Competition for binding: ACh and the non-depolarizing blocker compete for binding sites on the nAChRs
3. Blocked ACh binding: The blocker molecule occupies the binding site, preventing ACh from effectively activating the receptor

Pharmacological Action:

1. Skeletal Muscles:

- Induced flaccid paralysis
- Paralysis according to this onder-Muscles of f neck oleskarts eye finger limb
- Recovery occurs in reverse order

2. Histamine Release:

- d-TC has a greater tendency to liberate histamine from most cells
- 3. Cardiovascular system
- d-TC produce hypotension due to histamine release.
- Calamine cause tachycardia

Adverse Effect:

- Respiratory Paralysis

• Hypotension Constipation

B. Depolarizing blockers:

- Depolarizing blockets are a type of neuromuscular blocking agent (NMBA) that act

- on the neuromuscular junction (NMI te induce muscle relaxation non-depolarizing blockers, they directly trigger muscle contraction but with a prolonged blocking effect leading to paralysis

Mechanism of Action:

- The mechanism of action of depolarning blockers involves mimicking the action of acetylcholine Ach at the neuromuscular junction.
- Specifically, succinylcholine binds to nicotinic cholinergic receptors on the motor endplate, initiating depolarization of the muscle cell membrane.
- This depolarization initially causes muscle fasciculations due to the sustained + activation of the receptors. However, succinylcholine is resistant to degradation by acetylcholinesterase, the enzyme responsible for metabolizing ACh.
- As a result, succinylcholine remains bound to the receptors for an extended period, leading to sustained depolarization and subsequent muscle paralysis.

Pharmacological Action:

- Muscle twitching
- Muscle soreness

Adverse effect:

- Muscle rigidity
- prolonged apnoea
- Nausea and Vomiting

E) LOCAL ANESTHETIC AGENTS

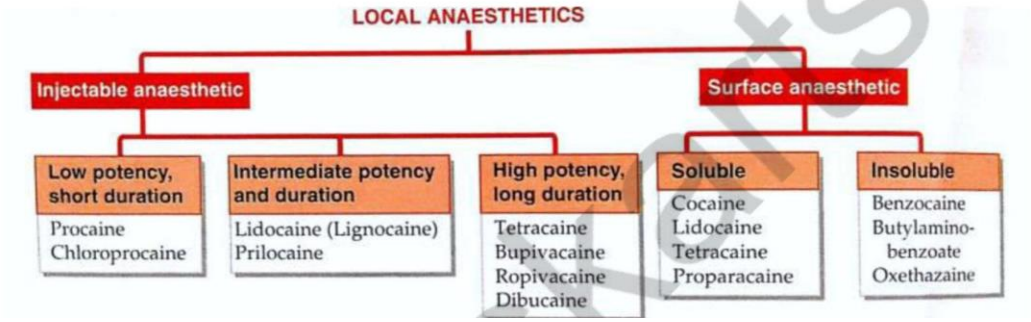
LOCAL ANESTHETIC AGENTS

Local anaesthetics are drugs which upon topical application or local injection cause reversible loss of sensory perception, especially of pain, in a restricted area of the body.

Or

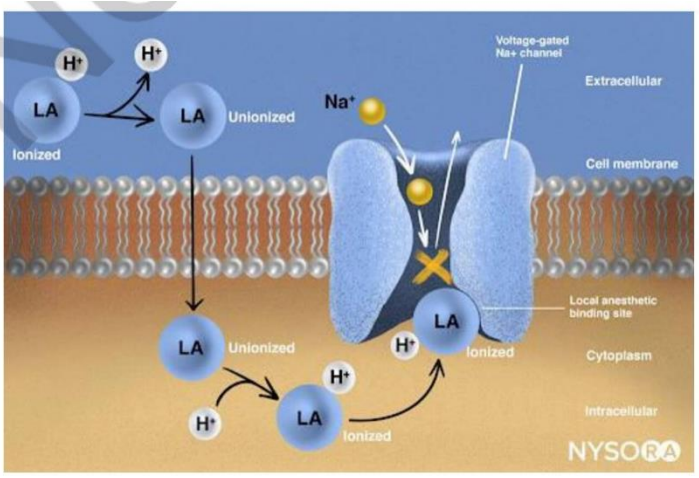
Local Anesthetic are those drugs which blocks the neuronal condition at local particular area. And it is helpful for miner surgery.

Classification of Local Anesthetic agents:



Mechanism of action

Local anesthetics work by binding to the a subunit of the voltage-gated Na+ channels, thus preventing the generation and conduction of nerve impulses. Subsequently, Na+ ions cannot flow into the cell, thereby halting the transmission of the advancing wave of depolarization down the length of the nerve. The fraction of local anesthetic molecules are in the ionized form. Local anesthetic molecules change from ionized to unionized in a fraction of a second.



Cocaine:

Definition: A highly addictive and illegal stimulant drug derived from the coca plant. It is important to note that cocaine is a dangerous and illegal substance with no legitimate medical use.

Misuse: Cocaine is a powerful stimulant that disrupts the central nervous system, producing intense feelings of pleasure followed by a crash. It is highly addictive and can lead to severe health problems, including:

- Increased heart rate, blood pressure, and body temperature
- Chest pain, heart attack, stroke
- Seizures, coma, and death
- Respiratory failure
- Damage to the heart, lungs, liver, and kidneys
- Mental health problems, including psychosis and depression

Procaine:

A medication used as a local anesthetic to numb a specific area of the body. It was one of the first synthetic substitutes for cocaine.

Medical Uses:

- Procaine has been used in various medical procedures, including:
- Dental anesthesia (less common today due to better alternatives)
- Infiltration anesthesia for minor surgeries
- Spinal anesthesia (limited use due to potential allergic reactions)

Adverse Effects:

Procaine can cause side effects, including

- Allergic reactions (rare)
- Dizziness
- Headache
- Nausea and vomiting
- Nervous system problems (in high doses)

Lidocaine:

A widely used medication that acts as a local anesthetic to numb a specific area of the body It is considered a safer and more effective alternative to procaine

Medical Uses:

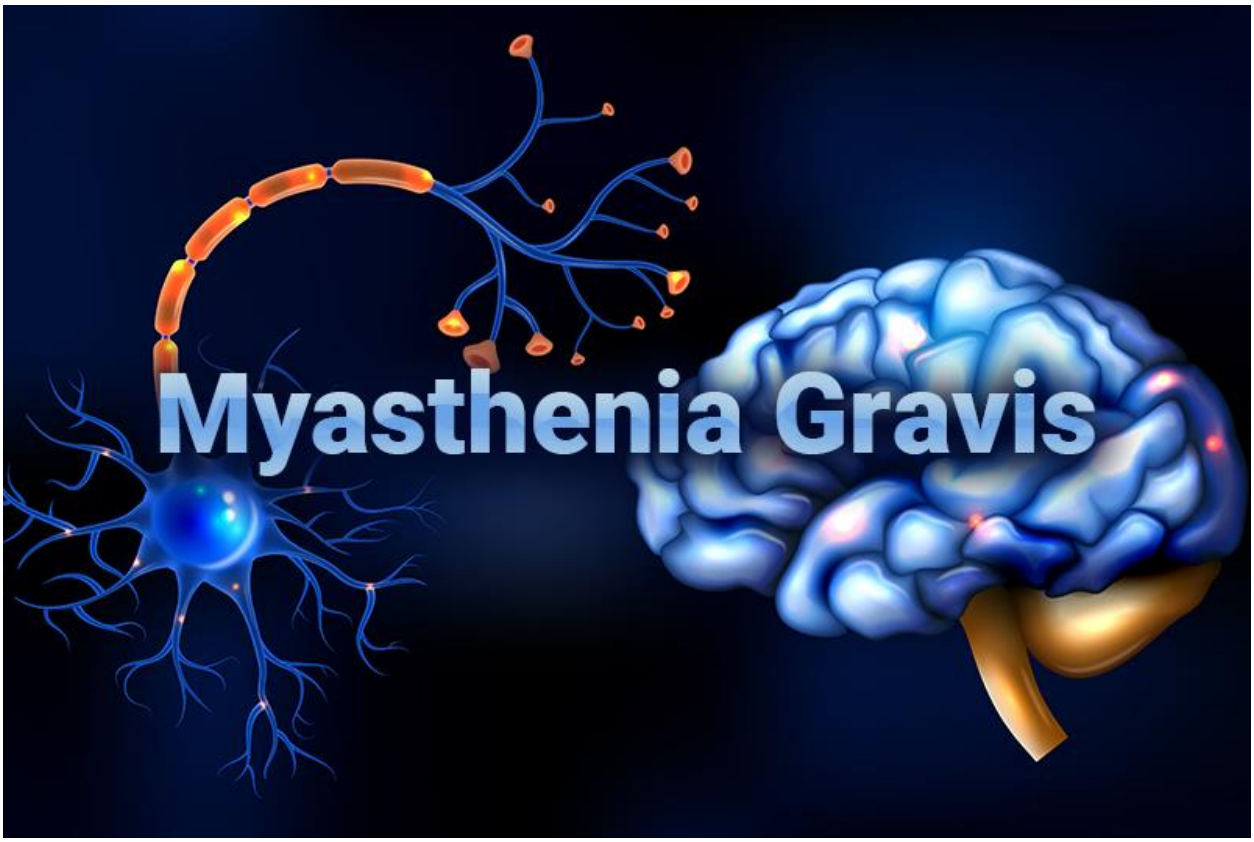
Lidocaine is commonly used in various medical procedures including

- Dental anesthesia
- Topical anesthetic for minor skin procedures (e.g., stitches, injections)
- Treatment of certain heart rhythm problems

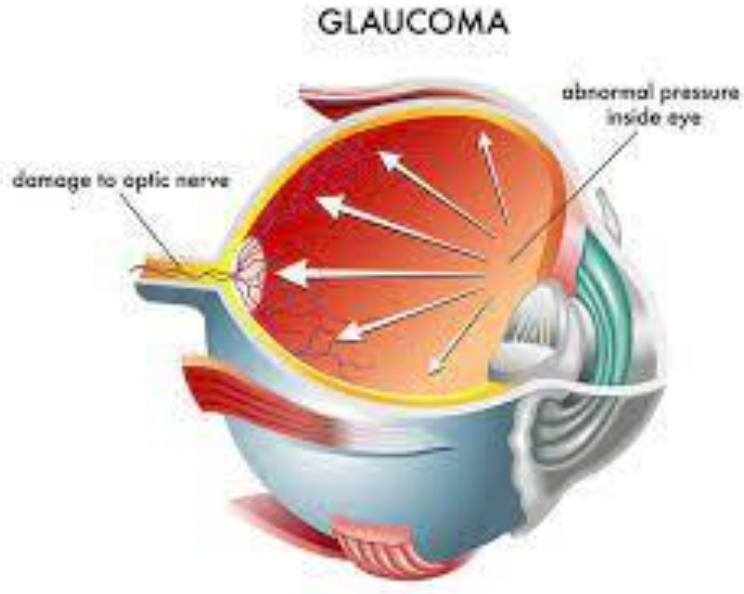
Adverse Effects:

Lidocaine can cause side effects, including:

- Dizziness
- Lightheadedness
- Drowsiness
- Numbness or tingling at the injection site
- Seizures (in high doses)



DRUGS USED IN MYASTHENIA GRAVIS & GLAUCOMA



DRUGS USED IN MYASTHENIA GRAVIS

Myasthenia Gravis

- It is an autoimmune disorder affecting about 1 in 10,000 population, due to development of antibodies directed to the nicotinic receptors (NR) at the muscle endplate.
- The number of free Nm cholinoceptors may be reduced to 1/3 of normal or less a structural damage to the neuromuscular junction.
- It is an auto-immune disorder in which our immune system produce antibioties the block or destroy muscle's receptor.
- Break down in communication between nerves and muscles.

Mechanism of action of Myasthenia Gravis

- It is an auto-immune disorder. In this disorder our immune system produce antibo to block/ destroy the Nicotinic receptor.
- Because according to immune system these receptor are harmful for body. So thes receptor and block them.
- Now due to blockage of receptor acetycholine (Ach) does not bind on receptor. Due to this there are loss of communication between nerves (Ach) and muscle.
- Which further decrese the contraction of muscles.
- Also muscle become weak and fatigue. These antibodies also destroy or kill the receptor. Due to this there are also decrease in the no. of receptors.

Drugs used in myasthenia gravis:

1. Cholinesterase Inhibitors:

Pyridostigmine: This is the most commonly used cholinesterase inhibitor. It works. by inhibiting the breakdown of acetylcholine, thereby increasing its availability at th neuromuscular junction and improving muscle strength. Pyridostigmine is usually administered orally and may be adjusted based on individual response and tolerance

Neostigmine: Neostignine is a cholinesterase inhibitor, prescribed for Myasthenia Gravis. It inhibits the chemicals which brings non-communication between the nervous and the muscular system Neostigmine enhances the muscular movements in case of Myasthenia Gras is condition

Immunosuppressant: Use these drugs to suppress the immune system to decrees the formation of antibodies

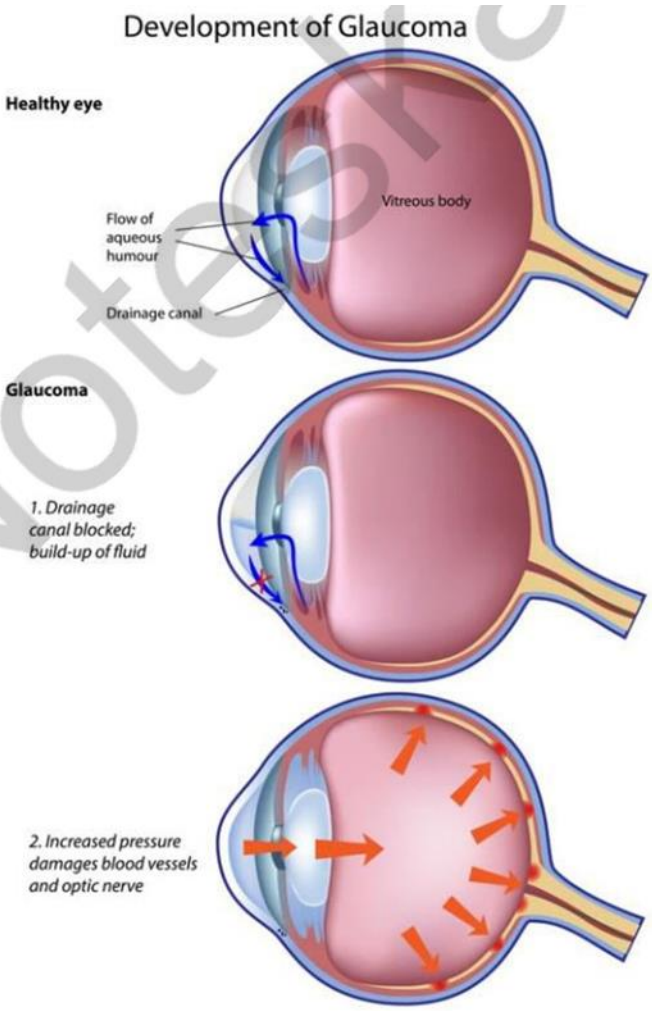
Eg: Cyclosparoine A. Methotrexate, Azathioprine etc

Plasmapheresis: (Plasma exchange) : The plasma of the blood is exchange with substitute plasma, So Antibodies remove from body and immune system does not attack the body's own tissue.

Drugs used in glaucoma:

Glaucoma: (Vision loss and blindness)

- Glaucoma are eye conditions associated with damage of the optic nerve (which connects the eye to the brain) and the nerve fibres from the retina (the light-sensitive nerve tissue that lines the back of the eye). Glaucoma often affects both eyes, usually to varying degrees. ↑
- The optic nerve sends visual inte gation from your eye to good vision. Damage to the optic nerve is often related to your brain and is vital for high pressure in your eye.
- But glaucoma can happen even with normal eye pressure Glaucoma can occur at any age but is more common in older adults. It is one of the leading causes of blindness for people over the age of 60.



Symptoms:

- Eye Pain
- Redness of the Eye
- Vision loss, Blurred Vision

Types of Glaucoma:

1. Open Angle Glaucoma

2. Close angle Glaucoma

1. Open Angle Glaucoma: It is also known as chronic and wide angle glaucoma.

Symptoms:

- Gradual Vision loss.
- Optic nerve damage
- Most common type of glaucoma.

2. Close angle Glaucoma: It is also known as acute and narrow angle glaucoma

Drug used in Glaucoma:

1) Atropine-

- Naturally obtain from Atropa belladonna
- It is competitive antagonists of all five muscarine receptor
- It gives temporary relief from bradycardia
- Antidote for cholinesterase poisoning Poisoning from mashrum containing muscarine

2) Scopolamine-

- It is belladonna alkaloids
- Well absorb through skin
- Crosses BBB
- It prevent motion sickness and nausea associated with the use of opioid analgesics

3) Tropicamide

- Short acting anti muscarinc drug
- Applied at eye drops prior to retinal exam
- They produce mydriasis by inhibiting the contraction of the spincter muscles
- They are sometimes co-administered with phenylephrine 4) Ipratropium bromide-
- It is quaternary analog of atropine
- Used to prevent bronchospasm assosiated with COPD and asthma. 16

4) Glycopyrrolate-

- It is quaternary analog of atropine.
- Used as preoperative medication to reduce salivary and respiratory secretion.
- In combination with neostigmine to reserve the effect of non-depolarizing skeletal muscle relaxant at the end of surgery

UNIT-IV

Pharmacology of drugs acting on central nervous system

N.Sumanasri

UNIT-IV

3. Pharmacology of drugs acting on central nervous system

a. Neurohumoral transmission in the C.N.S.special emphasis on importance of various neurotransmitters like with GABA, Glutamate, Glycine, serotonin, dopamine.

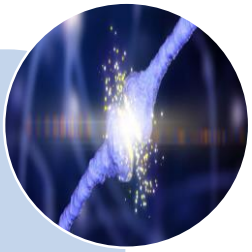
b. General anesthetics and pre-anesthetics.

c. Sedatives, hypnotics and centrally acting muscle relaxants.

d. Anti-epileptics.

e. Alcohols and disulfiram.

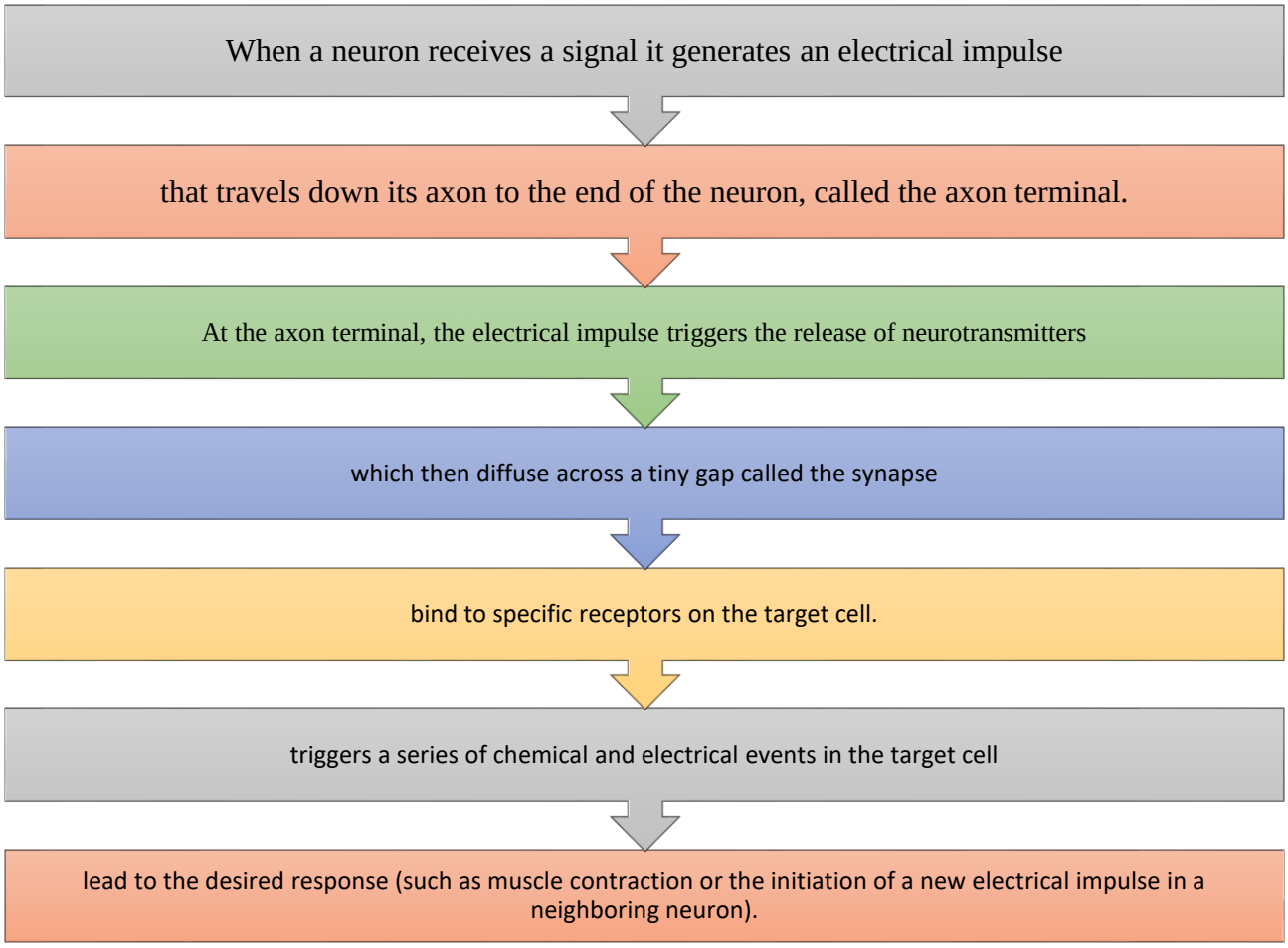
a. Neurohumoral transmission in the C.N.S.special emphasis on importance of various neurotransmitters like with GABA, Glutamate, Glycine, serotonin, dopamine.



DEFINITION

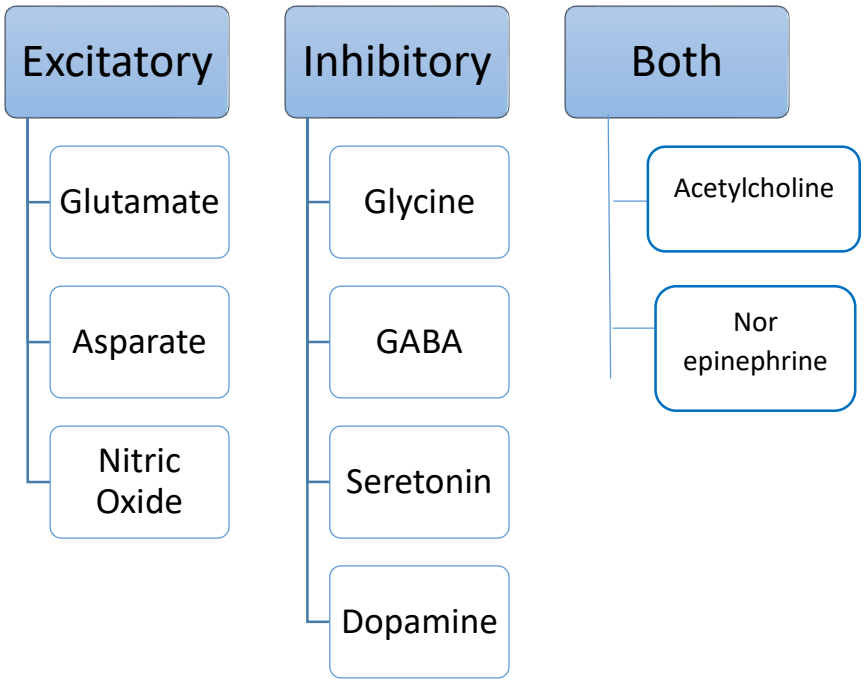
Neurohumoral transmission refers to the process by which nerve cells, also known as neurons, communicate with other cells in the body, such as muscle cells or other neurons through the release of chemicals called neurotransmitters and hormones.

PROCESS OF NEUROHUMORAL TRANSMISSION



- The term "neurohumoral" refers to the combination of both neural and humoral (meaning involving hormones or other bodily fluids) signals that work together to coordinate and regulate many physiological processes in the body movement, digestion, and the regulation of body temperature.

CLASSIFICATION



ROLE OF GABA IN NEUROHUMORAL TRANSMISSION

• Gamma-amino butyric acid (GABA) is an inhibitory neurotransmitter.
• When released by neurons GABA binds to specific receptors on the target cell causing an influx of negatively charged ions (such as chloride ions) into the cell which makes the target cell less likely to generate an electrical impulse. Less electrical impulses Inhibition of response.
GABA is widely distributed throughout the brain and spinal cord.
Functions of GABA
• It is involved in the regulation of muscle tone, sleep, and anxiety. • In addition, GABA is also involved in the regulation of other neurotransmitter systems, including dopamine and serotonin.

Abnormalities in GABA function:
• It have been linked to a variety of neurological and psychiatric disorders epilepsy, anxiety disorders, and schizophrenia.

Drugs modulating GABA effect:

• The drugs that enhance GABA function, such as benzodiazepines are commonly used to treat anxiety and sleep disorders

• While drugs that reduce GABA function, such as some stimulants can lead to increased arousal and wakefulness

ROLE OF GLUTAMATE IN NEUROHUMORAL TRANSMISSION

• Glutamate main excitatory neurotransmitter in the central nervous system.

• Glutamate binds to specific receptors on the target cells causing an influx of positively charged ions (such as sodium and calcium ions) into the cell which makes the target cell to generate more electrical impulse Na+ More electrical impulses Excitatory response Na+ Na+ Na+ Na+

• It is involved in many important functions learning and memory, synaptic plasticity (the ability of synapses to change in strength), and the regulation of mood and behaviour.

Role of Glutamate:

• Excessive activation of glutamate receptors can be harmful to neurons contribute to a variety of neurological disorders stroke, traumatic brain injury, and neurodegenerative diseases such as Alzheimer's and Parkinson's.

• Glutamate is also involved in the regulation of the hyothalamic-pituitary-adrenal (HPA) axis. It involved in the body's response to stress.

• The drugs that enhance glutamate function, such as the NMDA receptor agonist D-cycloserine potential treatments for depression

• While drugs that inhibit glutamate function, such as ketamine have shown promise as rapid-acting antidepressants.

Drugs modulating Glutamate function:

•The drugs that enhance glutamate function, such as the NMDA receptor agonist D-cycloserine potential treatments for depression • while drugs that inhibit glutamate function, such as ketamine have shown promise as rapid-acting antidepressants.

ROLE OF GLYCINE IN NEUROHUMORAL TRANSMISSION

• Glycine is an inhibitory neurotransmitter that plays an important role in the regulation of neurohumoral transmission particularly in the spinal cord and brainstem.

• Glycine binds to specific receptors on the target cell causing an influx of negatively charged ions (such as chloride ions) into the cell which makes the target cell to generate an electrical impulse.

Glycine is mainly found in inhibitory neurons in the spinal cord and brainstem plays a key role in the regulation of reflexes, sensory processing, and the control of muscle tone.

• It is particularly important for regulating the activity of motor neurons that control muscle contraction, and abnormalities in glycine function lead to a variety of neurological disorders, including hyperekplexia.
• Glycine is also involved in the regulation of pain perception, particularly in the spinal cord. Inhibiting glycine release in the spinal cord can enhance pain sensitivity.

Drugs modulating Glycine function:
• While enhancing glycine release can reduce pain sensitivity.
• This makes glycine a potential target for the development of new pain medications.
• Overall, the role of glycine in neurohumoral transmission is primarily inhibitory plays a key role in regulating a variety of physiological processes particularly in the spinal cord and brainstem.

ROLE OF SEROTONIN IN NEUROHUMORAL TRANSMISSION:

- Serotonin, also known as 5-hydroxytryptamine (5-HT)
- It plays a critical role in the regulation of many physiological processes mood, appetite, sleep, and sensory perception.
- It is also involved in neurohumoral transmission, particularly in the modulation of pain and mood.
- Serotonin binds to specific receptors on the target cells activate or inhibit various signaling pathways. Regulate many functions, including mood, emotion, cognition, and sensory perception.

Abnormalities in Serotonin function:
- In the brain, serotonin is particularly important for regulating mood and behavior.
- Abnormalities in serotonin function have been implicated in a variety of psychiatric disorders depression, anxiety, and schizophrenia.

Drugs modulating Serotonin function:
- Drugs that enhance serotonin function, such as selective serotonin reuptake inhibitors (SSRIs) are commonly used to treat these disorders.
- In the periphery the serotonin causes regulation of various physiological processes gastrointestinal function, blood clotting, and blood vessel tone.
- It is also involved in the regulation of pain perception particularly in the spinal cord and peripheral nervous system.
- Inhibiting the release of serotonin in these areas enhance pain sensitivity
- While enhancing serotonin release can reduce pain sensitivity.

ROLE OF DOPAMINE IN NEUROHUMORAL TRANSMISSION

- Dopamine is a neurotransmitter plays an important role in the regulation of neurohumoral transmission particularly in the reward and motivation pathways of the brain.
- Dopamine binds to specific receptors on the target cell which can activate or inhibit various signaling pathways.
- In the brain, dopamine is mainly found in neurons in the midbrain that project to various regions including the striatum, prefrontal cortex, and limbic system.

Abnormalities in Dopamine function:

- Abnormalities in dopamine function have been implicated in a variety of neurological and psychiatric disorders including Parkinson's disease, schizophrenia, addiction, and attention deficit hyperactivity disorder (ADHD).

Pleasurable effect of dopamine:

- When we experience something pleasurable or rewarding, such as food or social interaction dopamine is released reinforcing the behavior and motivating us to seek out similar experiences in the future.
- Dopamine is also involved in the regulation of movement particularly in the control of fine motor skills.

Dopamine and motor skills

- In Parkinson's disease, the degeneration of dopamine-producing neurons in the midbrain leads to a loss of motor control and other symptoms.

B. GENERAL & PREANESTHETIC

GENERAL ANESTHETICS

General Anesthetics are the drugs which produce reversible loss of consciousness and all types of sensations. The main features of general anesthesia involves loss of sensation (pain), Sleep and amnesia, immobility and muscle relaxation and also involves abolition of somatic and autonomic reflexes. Modern anesthetics acts very rapidly and combination of inhaled and i.v. drugs have been used to achieve proper anesthesia.

MECHANISM OF GENERAL ANAESTHESIA

The mechanism of action of General Anesthesia is not precisely known and it is basically related to the physicochemical properties of the drugs. Mayer and Overton (1901) gave a direct relation between lipid/water partition coefficient o the Gas and their potency. Minimal Alveolar Concentration (MAC) is the lowest concentration of anesthesia needed in pulmonary alveoli to produce immobility in response to any painful stimuli. It is valid mainly for the inhalational anesthetics. Anesthetics may be acting through different mechanism on molecular basis. The main region involved in causation of unconsciousness is in thalamus or reticular activating system. Also some findings claim that ligand gated ion channels are the main targets of the anesthetic actions. General anesthetics in contrast are reported to inhibit excitatory NMDA type glutamate receptors and they may act by depressing synaptic transmission while local anesthetics which act by blocking axonal conduction.

STAGES OF ANAESTHESIA

Gas cause irregular descending depression of CNS, i.e. the higher functions are lost first and progressively lower areas of brain.

The main four stages if anesthesia are:

1. Stage of analgesia: Starts from anesthetic inhalation and lasts upto the loss of consciousness. Pain is slowly decreased but patient remains conscious and amnesia appear at the end. Respiration is normal during this stage.
2. Stage of delirium: Consciousness during this stage is fully lost but patient may appear excited (muscle tone increases). Heart rate and BP may rise and pupils may dilate due to sympathetic stimulation.
3. Surgical Anaesthesia: Starts from regular respiration to cessation of breathing. It basically involves Roving eyeballs and fixed at end, loss of corneal reflexes, and pupil starts dilating (light reflex lost).

CLASSIFICATION OF GENERAL ANAESTHETICS:

1. Inhalational anesthesia:

a. Gas: Nitrous oxide
b. Volatile liquids: Ether, Halothane, Enflurane, Isoflurane, Desflurane, Sevoflurane
2. Intravenous anesthetics:
a. Inducing agents: Thiopentone Sodium, Methohexitone Sodium, Propofol, Etomidate
b. Slower acting drugs: Benzodiazepines- Diazepam, Lorazepam, Midazolam
c. Dissociative anesthesia- Ketamine Opioid analgesia- Fentanyl

INHALATIONAL ANAESTHETICS

These anesthetics diffuse across pulmonary and tissue barriers. The potency and partial pressure in brain decide the depth of anesthesia. The speed of induction of anesthetic effects depends upon:

1. Solubility: Large amount of anesthetics that are highly soluble in blood must be dissolved before PP is raised. The change in PP in blood leads to consequent induction and slow recovery. Drugs with low blood:gas partition coefficient (Nitrous oxide) induce quickly

2. Inspired Gas Partial Pressure: A higher partial pressure of the gas in lungs will result in more rapid achievement of anesthetic levels in blood. Thus, a quick induction can be made by administering the GA at high concentration at start

3. Ventilation rate: The greater the ventilation than there will be more rapid increase in alveolar and blood partial pressure of the anesthetic agent and more rapid will be onset of anesthesia.

4. Pulmonary blood flow: Higher the pulmonary blood flows, slower will be the rise in partial pressure of gas and thus onset of anesthesia is reduced. In contrast lower the blood flow rate, inset will be faster.

5. Cerebral Blood Flow: Gas is rapidly delivered to highly perfused organ (Brain). This can be hastened by inhalation of CO2 which causes vasodilation which further leads to acceleration of induction and recovery.

All the inhalational anesthetics are eliminated through lungs. The factors for both induction and recovery are similar. The rate of recovery from anesthesia using agents with low blood:gas partition coefficient is faster than that of anesthetics with high blood solubility. This is one of the important property which leads to discovery of newer inhalational anesthetics like Desflurane which have low blood solubility and are characterized by recovery times that are considerably shorter than other older agents. Halothane and Isoflurane show slow recovery due to their higher lipid solubility and large amount of anesthetics enter muscle and fat which is released slowly into blood.

PHARMACOLOGICAL ACTIONS O INHALED ANAESTHETICS

1. CNS: Inhaled anesthetics decrease brain metabolic rate. They generally reduce vascular resistance and increase cerebral blood flow and may increase intracranial pressure. High

concentration of Enflurane may cause spike and wave activity and muscle twitching, but this effect is limited to this drug only

2. Cardiovascular effects: Inhalational anesthetics decrease arterial blood pressure moderately. Enflurane and Halothane are myocardial depressants by reducing Ca2+ concentration while Isoflurane causes peripheral vasodilation. Nitrous oxide is less likely to lower blood pressure than are other inhalational anesthetics.

3. Respiratory effects: Rate of respiration may be increased but the tidal volume is decreased which may cause increase in arterial CO2 tension. Nitrous oxide may or may not effect respiration while Halothane and Isoflurane causes greater depression of respiration.

ADVERSE EFFECTS

- Prolonged exposure to nitrous oxide decreases methionine synthase activity and may lead to megaloblastic anaemia.
- Some Patients may develop malignant hyperthermia when exposed to halogenated anesthetics.
- Renal insufficiency may be one of the problem after using prolonged anesthesia.

INTRAVENOUS ANAESTHETICS

Several chemical classes of drugs are used as intravenous agents in anesthesia: for eg: **1. BARBITURATES:** Thiopental and methohexital have high lipid solubility which promotes rapid entry into the brain, results in anesthesia less than one minute. It is used for short surgical procedures.

2. KETAMINE: It produces dissociative anesthesia, patient remains conscious but has marked catatonia and amnesia. The drug is a cardiovascular stimulant and this action may lead to increase in intracranial pressure.

3. OPIOIDS: Morphine and fentanyl are used with other CNS depressants in anesthesia regimens and are valuable in high risk patients who might not survive a full general anesthetic. If administered iv may cause chest wall rigidity and can impair ventilation.

4. PROPOFOL: Produces anesthesia at a rate similar to intravenous barbiturates but recovery is rapid. It may show antiemetic action. Propofol can cause marked hypotension during induction of anesthesia. Total body clearance of Propofol is greater than hepatic blood flow.

5. BENZODIAZEPINES: Midazolam is widely used with inhaled anesthetics and iv opioids. The onset of its CNS effects is slower than that of Thiopental and has longer duration of action.

PREANESTHETIC MEDICATION

"It is the term applied to the administration of drugs prior to general anesthesia

• So as to make anesthesia safer for the patient" Ensures comfort to the patient & to minimize adverse effects of anesthesia

• Relief of anxiety & apprehension preoperatively & facilitate smooth induction Amnesia for pre- & post-operative events

• Potentiate action of anesthetics, so less dose is needed

• Antiemetic effect extending to post-operative period

• Decrease secretions & vagal stimulation caused by anesthetics

1. To decrease salivary & bronchial secretions (a and hence prevent reflex laryngospasm.)

2. To prevent cardiac arrest due to vagal stimulation.

• Decrease acidity & volume of gastric juice to prevent reflux & aspiration pneumonia

1. Anti-anxiety drugs: Provide relief from apprehension & anxiety - Postoperative amnesia e.g. Diazepam (5-10mg oral), Lorazepam (2mg i.m.) (avoided co-administration with morphine, pethidine)

2. Sedatives-hypnotics: e.g. Promethazine (25mg i.m.) has sedative, antiemetic & anticholinergic action - Causes negligible respiratory depression & suitable for children

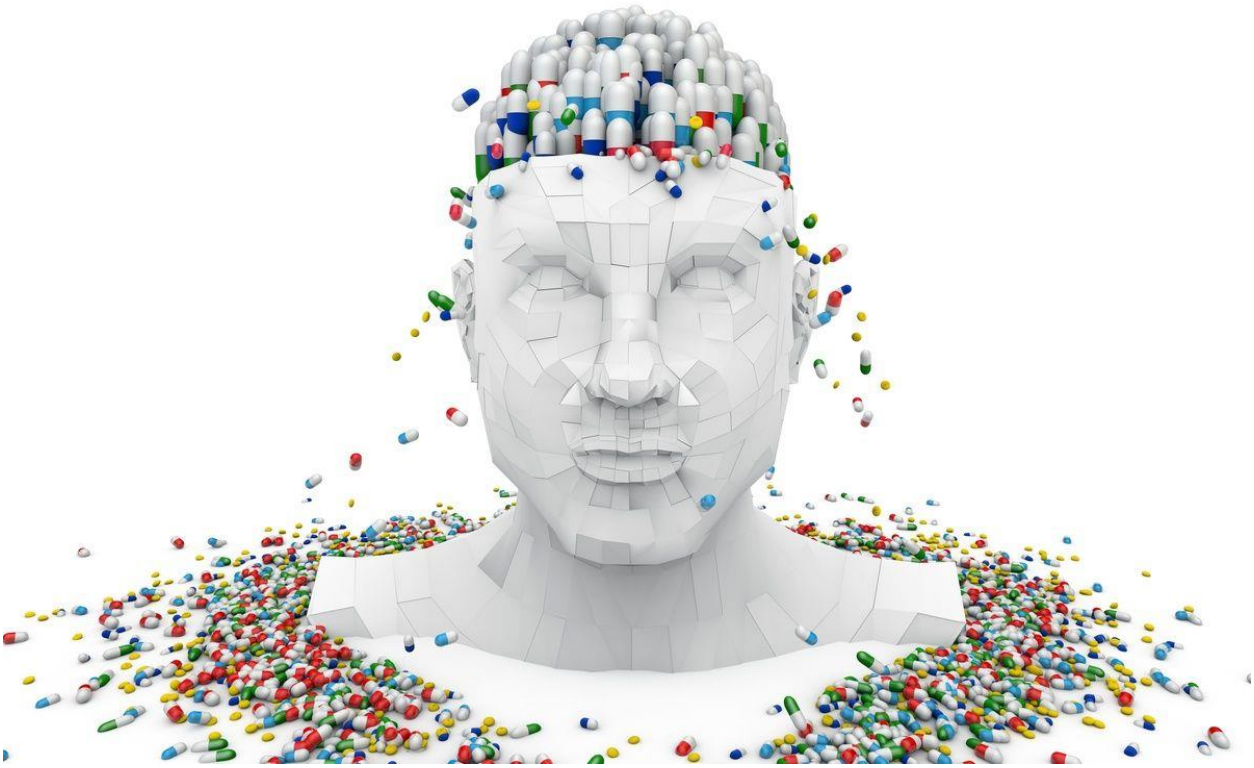
3. Opioid analgesics: Morphine (8-12mg i.m.) or Pethidine (50- 100mg i.m.) used one hour before surgery - Provide sedation, pre-& post-operative analgesia, reduction in anesthetic dose - Fentanyl (50-100µg i.m. or i.v.) preferred nowadays (just before induction of anesthesia)

4. Anticholinergics: Atropine (0.5mg i.m.) or Hyoscine (0.5mg i.m.) or Glycopyrrolate (0.1-0.3mg i.m.) one hour before surgery (not used nowadays) - Reduces salivary & bronchial secretions, vagal bradycardia, hypotension - Glycopyrrolate (selective peripheral action) acts rapidly, longer acting, potent antisecretory agent, prevents vagal bradycardia effectively

5. Antiemetics: Metoclopramide (10mg i.m.) used as antiemetic & as prokinetic gastric emptying agent prior to emergency surgery - Domperidone (10mg oral) more preferred (does not produce extrapyramidal side effects) - Ondansetron (4-8mg i.v.), a 5HT3 receptor antagonist, found effective in preventing post-anesthetic nausea & vomiting

6. Drugs reducing acid secretion: Ranitidine (150-300mg oral) or Famotidine (20-40mg oral) given night before & in morning along with Metoclopramide reduces risk of gastric regurgitation & aspiration pneumonia - Proton pump inhibitors like Omeprazole (20mg) with Domperidone (10mg) is preferred nowadays.

C. SEDATIVES & HYPNOTICS



SEDATIVE-HYPNOTICS

Sedative is a drug that reduces excitement and calms the subject without inducing sleep, though drowsiness may be produced; while Hypnotic is a drug that induces and/or maintains sleep, similar to normal arousable sleep.

The sedatives and hypnotics are more or less CNS depressants with somewhat differing timeaction and dose-action relationships. Hypnotics given in high doses can produce general anaesthesia. Thus, sedation—hypnosis—general anaesthesia may be regarded as increasing grades of CNS depression. Treatment of insomnia is the most important use of this class of drugs.

Sleep

The duration and pattern of sleep varies considerably among individuals. Age has an important effect on quantity and depth of sleep. It has been recognized that sleep is an architectured cyclic process. The different phases of sleep and their characteristics are—

Stage 0 (awake): From lying down to falling asleep and occasional nocturnal awakenings; constitutes 1–2% of sleep time. Eye movements are irregular or slowly rolling.

Stage 1 (dozing): Eye movements are reduced but there may be bursts of rolling. Neck muscles relax. Occupies 3–6% of sleep time.

Stage 2 (unequivocal sleep): little eye movement; subjects are easily arousable. This comprises 40–50% of sleep time.

Stage 3 (deep sleep transition): Eye movements are few; subjects are not easily arousable; comprises 5–8% of sleep time.

Stage 4 (cerebral sleep): Eyes are practically fixed; subjects are difficult to arouse. Night terror may occur at this time. It comprises 10–20% of sleep time. During stage 2, 3 and 4 heart rate, BP and respiration are steady and muscles are relaxed.

Stages 3 and 4 together are called slow wave sleep (SWS).

REM sleep (paradoxical sleep): There are marked, irregular and darting eye movements; dreams and nightmares occur, which may be recalled if the subject is aroused. Heart rate and BP fluctuate; respiration is irregular. Muscles are fully relaxed, but irregular body movements occur occasionally. About 20–30% of sleep time is spent in REM.

Normally stages 0 to 4 and REM occur in succession over a period of 80–100 min. Then stages 1–4–REM are repeated cyclically.

CLASSIFICATION

1. Barbiturates Long acting: Phenobarbitone Short acting: Butobarbitone, Pentobarbitone Ultra-short acting: Thiopentone, Methohexitone

2. Benzodiazepines Hypnotic: Diazepam, Flurazepam, Lorazepam, Temazepam, Nitrazepam, Alprazolam, Triazolam Antianxiety: Diazepam, Chlordiazepoxide, Oxazepam Lorazepam, Alprazolam. Anticonvulsant: Diazepam, Clonazepam, Clobazam

3. Newer non benzodiazepine hypnotics: Zopiclone Zolpidem Zaleplon Chloral hydrate, Triclophos, Paraldehyde, Glutethimide, Methyprylon, Methaqualone and Meprobamate are historical sedative-hypnotics no longer used.

BENZODIAZEPINES (BZDs)

Chlordiazepoxide was the first BZDs to be introduced into clinical medicine in 1961 and since then about 2000 BZDs have been synthesized, of which 35 are now in clinical use.

Pharmacological Actions

The most important actions of BZDs are on the CNS and include:

1. Sedation and hypnosis
2. Reduction in anxiety
3. Anaesthesia
4. Muscle relaxation
5. Anticonvulsant effects
6. Amnesia.

Hypnosis: BZDs hasten the onset of sleep. At slightly higher doses, they induce sleep (hypnosis) and increase the duration of sleep. The stage 2 NREM sleep is prolonged while the duration of REM sleep and stage 4 NREM is decreased. The suppression of REM sleep is very little with BZD. The quality of sleep resembles natural sleep more closely when compared to other older hypnotics. Tolerance develops to this effect gradually after about 1–2 weeks of use.

Sedation or anxiolytic effects: BZDs reduce anxiety and aggression and produce a calming effect. Alprazolam has additional antidepressant properties. Psychomotor and cognitive functions are also depressed.

Anaesthesia: BZDs produce CNS depression in a dose-dependent manner. Sedation, hypnosis, stupor, anaesthesia and coma are the different grades of CNS depression. BZDs in higher doses than that used for sedation produce general anaesthesia which can reach up to stage III of anaesthesia. Midazolam is used as an IV anaesthetic. BZDs including diazepam, lorazepam and midazolam can be used as adjuvants to general anaesthetics, but they carry the risk of prolonging

respiratory depression which could be due to their longer half-lives. These effects can be reversed by flumazenil.

Muscle relaxant action: BZDs reduce muscle tone by a central action. They depress the spinal polysynaptic reflexes which maintain the muscle tone. Generally, anxiety is associated with an increased muscle tone and may be responsible for aches and pains in these patients. The muscle relaxation by BZDs adds to their beneficial effects in such patients. High doses also depress transmission at the NMJ.

Anticonvulsant effects: BZDs increase the seizure threshold and act as anticonvulsants. They suppress the development and spread of seizures. Several BZDs have somewhat selective anticonvulsant effects which is seen at doses that do not produce profound CNS depression. Diazepam is used intravenously for the treatment of status epilepticus and rectally in febrile convulsions. Other BZDs, like clonazepam, are used in the treatment of absence seizures and myoclonic seizures in children. Nitrazepam and lorazepam also have useful antiepileptic activity.

Amnesia: BZDs produce anterograde amnesia, i.e. loss of memory for the events happening after the administration of BZDs. This property is an advantage when BZDs are used in surgical procedures as the patient does not remember the unpleasant events. However, this may be a disadvantage when used for other indications particularly over a long time.

Other Actions

• Cardiovascular functions: In higher doses, BZDs decrease BP, increase heart rate and also depress respiration. In patients with impaired cardiac function, regular therapeutic doses of BZDs can cause significant

CV depression especially on parenteral administration. Toxic doses result in depressed myocardial contractility and vascular tone leading to cardiovascular collapse.

• Respiration: BZDs in higher doses can cause respiratory depression. It can be profound in patients with pre-existing respiratory disease.

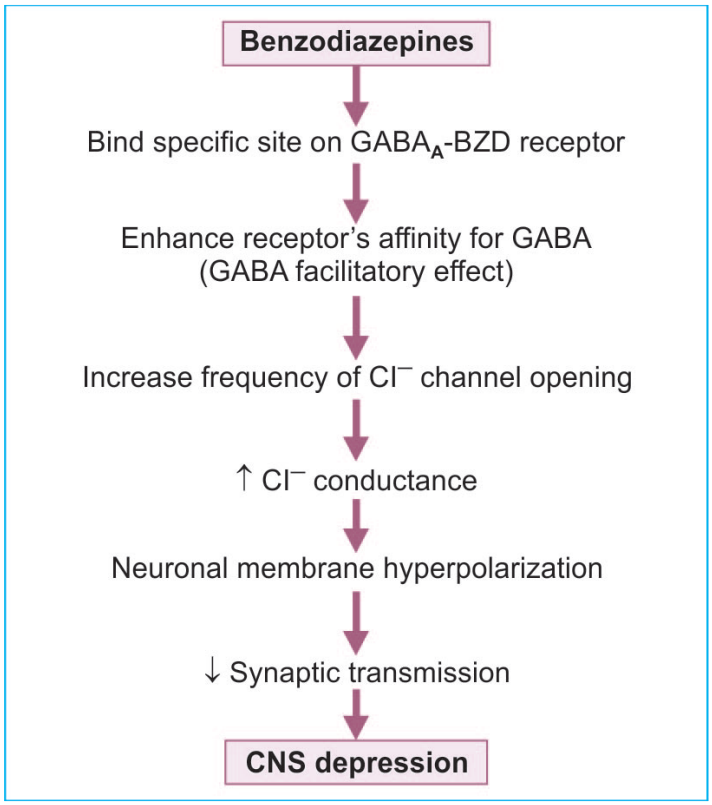
• Diazepam decreases nocturnal gastric acid secretion.

Mechanism of Action

GABA is the principle inhibitory neurotransmitter of the central nervous system and it acts through GABA receptors. BZDs bring about their effects through GABA, i.e. they modulate the response to GABA by acting on GABAA receptors. Benzodiazepines bind to the GABAA receptor present in the neurons of the CNS. They bind at a site which is different from the GABA-binding site and enhance the affinity of GABA for the receptor.

GABA enhances chloride ion conductance through this receptor and this effect is potentiated or intensified by BZDs. BZDs bind to the receptor (BZ1 subtype) and increase the frequency of chloride channel opening in response to GABA. This in turn leads to an increased flow of chloride

ions into the neurons, resulting in hyperpolarization of these neuronal membranes which in turn, results in decreased synaptic transmission



Drug Interactions

CNS depressants + BZD □□increased sedation

1. All other CNS depressants add to the effects of sedative hypnotics. For example: Alcohol, opioid analgesics,

antipsychotics, antiepileptics, antidepressants and sedative antihistamines given concurrently can cause significant CNS depression.

2. Microsomal enzyme inhibitors like ketoconazole, omeprazole, erythromycin and others prolong the t½ of BZDs.

3. Though BZDs are extensively bound to plasma proteins, displacement interactions are not clinically significant.

USES

Currently, BZDs are one of the most frequently prescribed drugs. They have also been combined with many other categories of drugs with a view to improve efficacy by relieving attendant anxiety.

1. As hypnotic: A hypnotic should not be casually prescribed for every case of insomnia. Understanding the pattern and cause of insomnia in the specific patient is important, and use of a variety of other measures can avoid unnecessary hypnotic medication. When indicated, BZDs or the newer non-BZDs like zolpidem, zaleplon are the hypnotic of choice.

2. Other uses

(a) As anxiolytic and for day-time sedation.

(b) As anticonvulsant, especially emergency control of status epilepticus, febrile convulsions, tetanus, etc.

(c) As centrally acting muscle relaxant.

(d) For preanaesthetic medication, i.v. anaesthesia and conscious sedation.

(e) Before ECT, electrical cardioversion of arrhythmias, cardiac catheterization, endoscopies, in obstetrics and many minor procedures—diazepam i.v. has gained popularity because of its calming-amnesicanalgesic and muscle relaxant properties and relative safety.

(f) Alcohol withdrawal in dependent subjects.

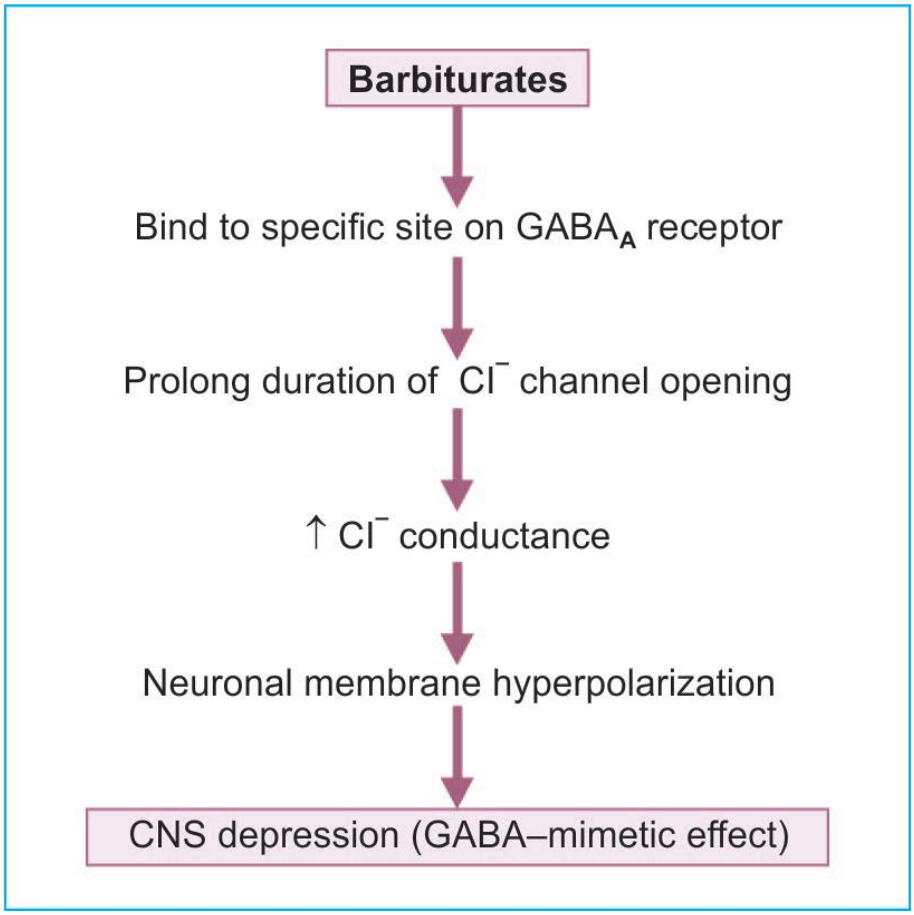
(g) Along with analgesics, NSAIDs, spasmolytics, antiulcer and as adjuvants to treat 'gas' or nonspecific dyspeptic symptoms.

BARBITURATES

Barbiturates are derivatives of barbituric acid and were the largest group of hypnotics in clinical use until the 1960s.

Mechanism of Action

Barbiturates bind to a specific site on theGABA receptor Cl– channel complex (which is different from the BZD binding site). They facilitate inhibitory neurotransmission by prolonging the duration of opening of the chloride ion channels by GABA and they hyperpolarise the neural membrane. At high concentrations, barbiturates directly enhance the chloride conductance, i.e. by a GABA mimetic effect.



Pharmacological Actions

CNS: Barbiturates cause depression of all excitable tissues of which CNS is the most sensitive.

Sedation and hypnosis: In hypnotic doses, barbiturates induce sleep and prolong the duration of sleep. The REM–NREM sleep cycle is altered with decreased duration of REM and prolonged NREM sleep. On waking up, there is some hangover with headache and residual sedation.

Barbiturates reduce anxiety, impair shor tterm memory and judgement. They can produce euphoria and are drugs of addiction while some people may experience dysphoria.

Barbiturates produce hyperalgesia (increased sensitivity to pain). Therefore, barbiturates, when given as hypnotics for a patient in pain may be more troublesome than being of any benefit.

Anaesthesia: In higher doses, barbiturates produce general anaesthesia. The ultra shortacting barbiturates like thiopentone are used intravenously for this effect.

Anticonvulsant effects: All barbiturates have anticonvulsant action. Phenobarbitone and mephobarbitone have specific anticonvulsant activity in subhypnotic doses and are used in the treatment of epilepsy.

Respiratory System: Barbiturates cause significant depression of respiration. High doses cause profound respiratory depression and also bring about a direct paralysis of the medullary respiratory centre. BZDs in higher doses can cause respiratory depression. It can be profound in patients with pre-existing respiratory disease.

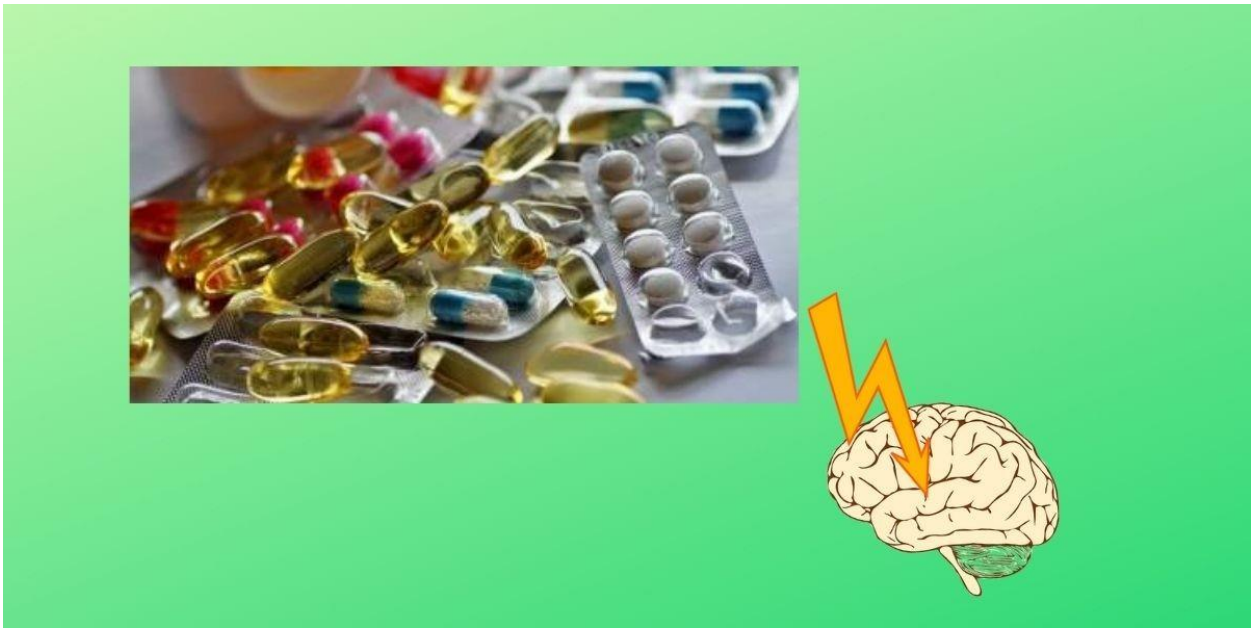
Cardiovascular System: Hypnotic doses of barbiturates produce a slight reduction in blood pressure and heart rate as seen during natural sleep. Toxic doses of barbiturates produce a significant fall in BP due to direct decrease in myocardial
contractility and vasomotor centre depression.

Uses of Barbiturates

Because of respiratory depression and abuse liability, barbiturates are generally not preferred.

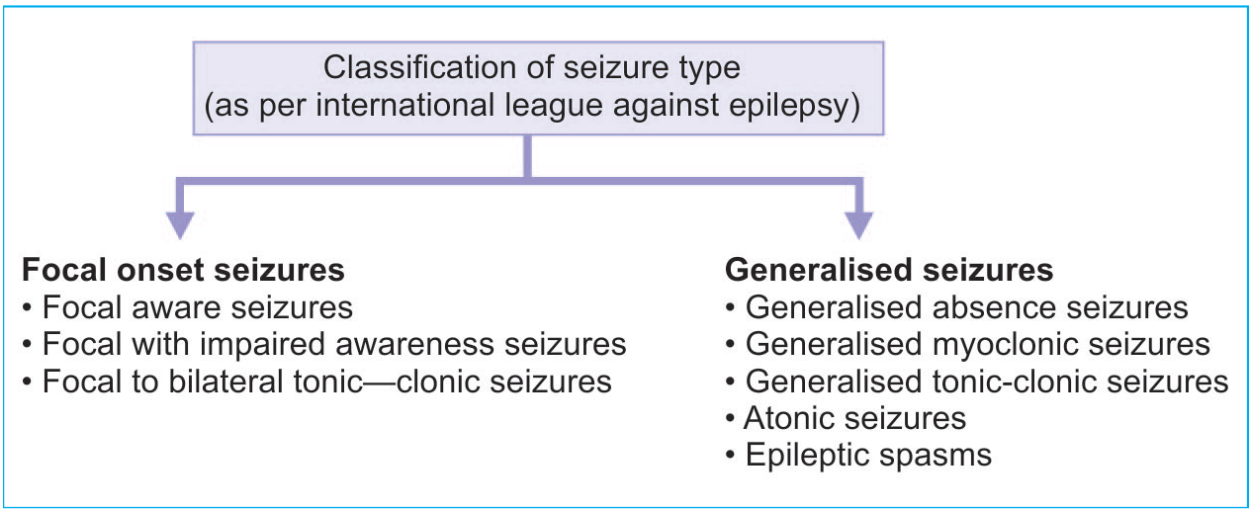
1. Anaesthesia: Thiopentone sodium is used IV for the induction of general anaesthesia.
2. Neonatal jaundice: Phenobarbitone is a microsomal enzyme inducer because of which it enhances the production of glucuronyl transferase—the enzyme required for metabolism and excretion of bilirubin. It, therefore, helps in the clearance of jaundice in the neonates.
3. Antiepileptic: Phenobarbitone is used as an antiepileptic
4. Sedation and hypnosis: Not preferred.
5. Preanesthetic medication: Not preferred.

D. ANTIEPILEPTICS



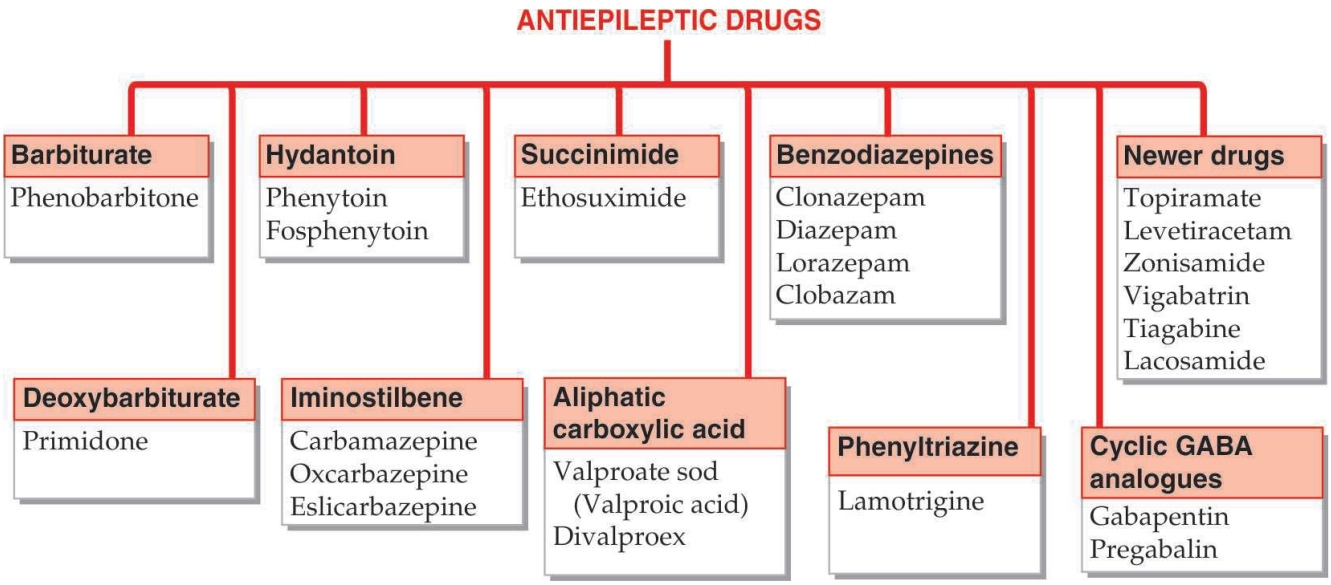
ANTIEPILEPTICS

Epilepsy is a common neurological abnormality that affects about 0.5–1% of the population worldwide. Epilepsy is a chronic disorder of brain function characterised by recurrent seizures often accompanied by Seizure indicates a transient alteration in behaviour because of disordered firing of groups of brain neurons. Such discharges may spread to other parts of the brain to different extents. In most of the cases, the cause is not known. It may be due to various reasons including trauma during birth process, head injury, childhood fevers,
brain tumours, meningitis or drug induced.



ANTIEPILEPTIC

Antiepileptics can be classified as follows:



Mechanism of Action of Antiepileptics

The strategies to treat epilepsy include enhancing GABA-mediated inhibition, reducing excitatory transmission or modifying the ionic conductances. Thus, anti-epileptics act by one or more of the following mechanisms

• Na+ channel blockers cause Na+ channel blockade and prolongation of their inactive state and delaying their recovery, e.g. phenytoin, carbamazepine, lamotrigine.

• Ca++ channel blockers (thalamic-T type) block low threshold Ca++ current in the thalamic neurons—control absence seizures, e.g. ethosuximide.

• Increasing GABA-mediated inhibition by:

– acting on GABA receptors, e.g. benzodiazepines, pregabalin, gabapentin

– inhibiting GABA metabolism—valproate

– blocking excitatory glutamate receptors— felbamate

– potentiating GABA—topiramate

PHENYTOIN

Phenytoin (diphenylhydantoin) was synthesized in 1908, but its anticonvulsant property was discovered only in 1938.

Mechanism of Action

Phenytoin causes blockade of the voltage dependent sodium channels and stabilizes the neuronal membrane. It inhibits the generation of repetitive action potentials.

Voltage-dependent Na+ channels enter an inactive stage after each action potential. Phenytoin blocks the Na+ channels which are in an inactivated state and delay the recovery of these channels from inactivation. It decreases the number of channels which are available for the generation of action potentials and inhibits

excitability of these voltage-dependent Na+ channels. Phenytoin preferentially blocks high frequency firing (neurons in normal state have low frequency firing while in seizures, high-frequency firing occurs)

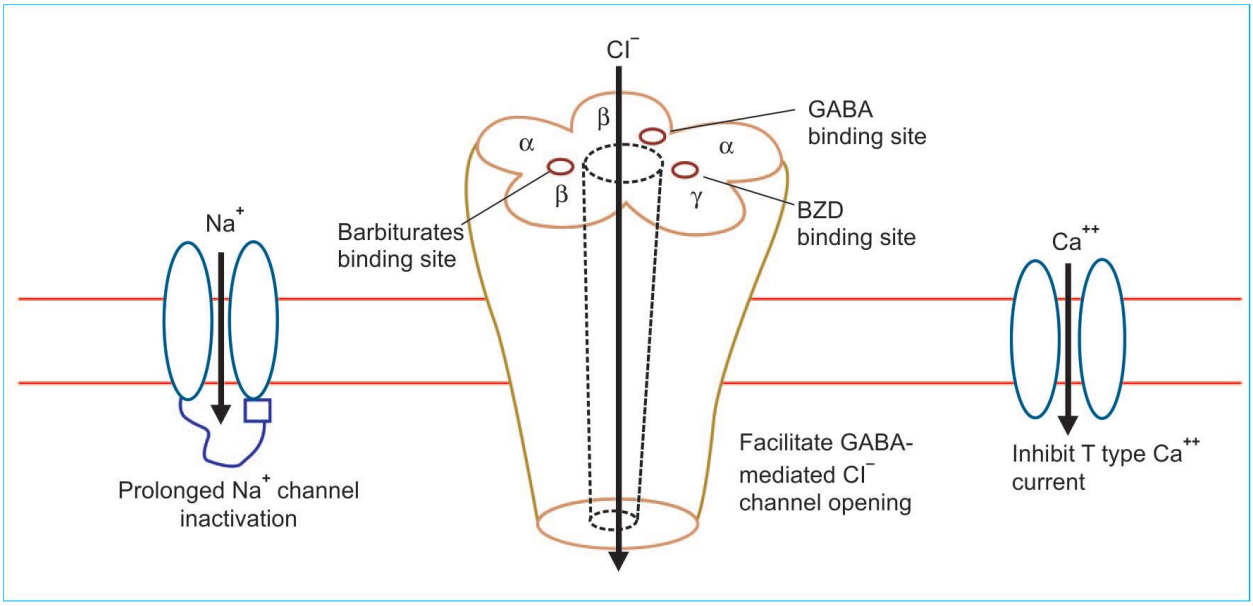
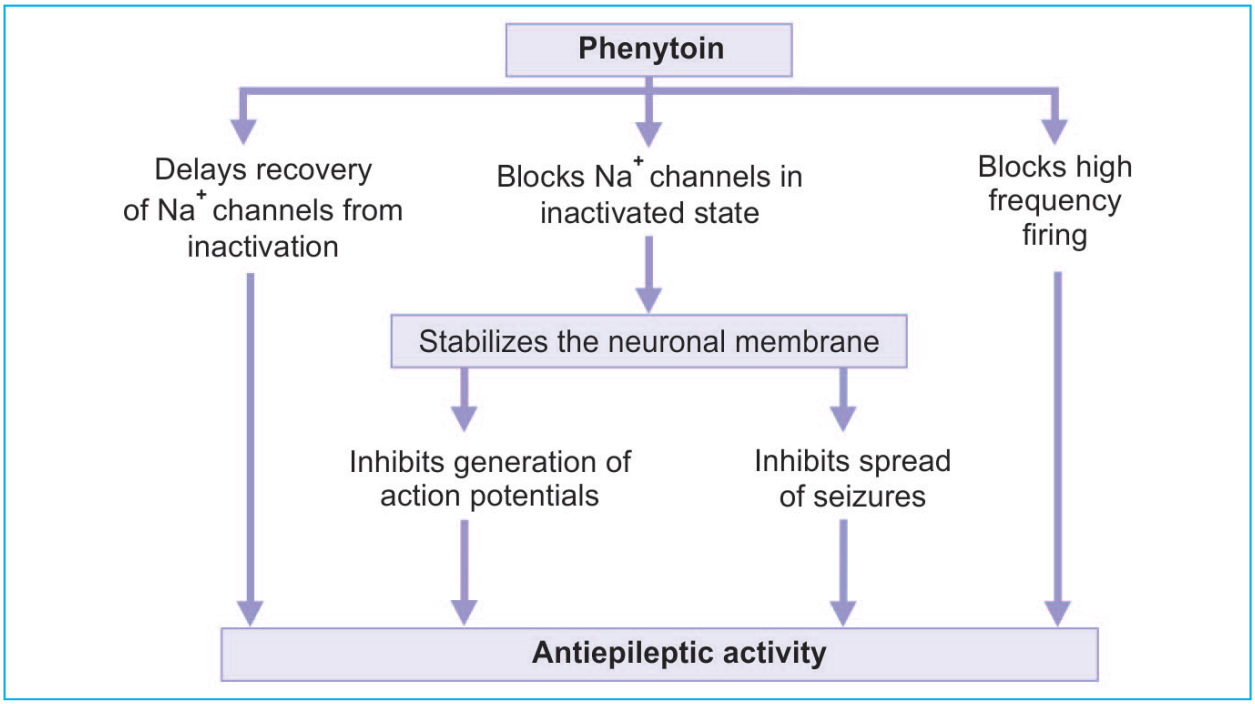


Fig. 15.1: Mechanisms of action of antiepileptics. Antiepileptics may act by blockade of Na+ channels, by facilitating GABA activity or by blockade of Ca++ current



Mechanism of action of phenytoin

Adverse Effects

Adverse effects depend on the dose, duration and route of administration.

1. Nausea, vomiting, epigastric pain, anorexia.
2. Nystagmus, diplopia, ataxia are common.
3. Gingival hyperplasia is more common in children on prolonged use. It could be because phenytoin inhibits the enzyme collaginase and alters collagen metabolism.

It also promotes angiogenesis in the gingival tissue through increased activity of growth factors. It is more common in children and good oral hygiene should be followed.

Uses

1. Generalised tonic-clonic seizures (GTCS) and focal onset seizures (not useful in absence seizures).
2. Status epilepticus—phenytoin is used by slow IV injection.
3. Trigeminal neuralgia—as an alternative to carbamazepine.
4. Cardiac arrhythmias—phenytoin is useful in digitalis-induced arrhythmias

VALPROIC ACID

Valproic acid (salt-sodium valproate) is a very effective antiepileptic drug useful in many types of epilepsies including absence seizures, focal onset and generalised tonic-clonic seizures.

Divalproex sodium is a combination of valproic acid and sodium valproate. The combination is said to have a better bioavailability and is better tolerated.

Mechanism of action: Valproic acid acts by multiple mechanisms.

1. It enhances the levels of GABA by:
   - Increasing the synthesis of GABA—by increased activity of GABA synthetase enzyme.
   - Decreasing the metabolism of GABA— by inhibiting GABA transaminase enzyme.
2. Like phenytoin, valproic acid blocks the sodium channels.
3. Like ethosuximide valproate decreases low threshold Ca++ current (T-currents) in the thalamus.

Pharmacokinetics: Valproate is well absorbed when given orally, but food may delay its absorption, 90% bound to plasma proteins and is metabolised in the liver. Clearance is dose dependent with half-life varying from 9 to 18 hr.

Adverse effects: Gastrointestinal symptoms, like nausea, vomiting, epigastric distress, occur initially. Weight gain is common. Tremors, sedation, ataxia, rashes and alopecia are rare. Sodium valproate can cause hepatotoxicity in children below 2 years of age which can be fatal.

E. ALCHOLS & DISULFIRAM

ALCOHOLS

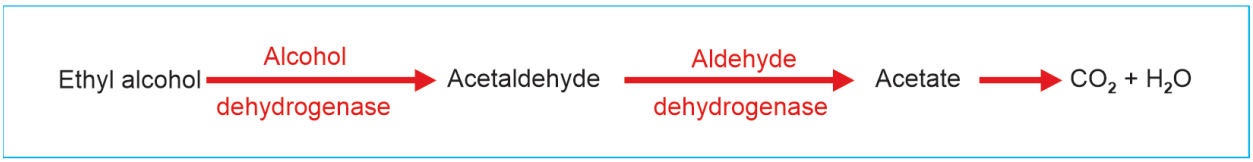
ETHYL ALCOHOL (ETHANOL)

Ethyl alcohol is a monohydroxy alcohol manufactured by fermentation of sugars. It is a colourless, volatile, inflammable liquid. The ethanol content of various alcoholic beverages ranges from 4 to 55%. For commercial use, alcohol is largely produced from molasses which is a by-product when sugar is manufactured from sugarcane.

Mechanism of Action

Ethanol acts by:

1. Inhibiting central neuronal nicotinic cholinergic receptors
2. Inhibiting excitatory NMDA and kainite receptor functions.
3. Promoting the function of 5-HT3 receptors.
4. Ethanol also influences many ion channels including K+ channels.



Actions

1. Local: On topical application, ethanol evaporates quickly and has a cooling effect. It is an astringent—precipitates surface proteins and hardens the skin. 40–50% alcohol is a rubefacient and counterirritant. Alcohol is also an antiseptic.

At 70%, it has maximum antiseptic properties, which decreases above that. It could be because presence of some water allows the alcohol to enter the bacterial cell and kill the bacteria. It is not effective against spores.

2. CNS: Alcohol is a CNS depressant. Small doses cause euphoria, relief of anxiety and loss of social inhibitions. Moderate doses, blunt the reflexes and impair muscular coordination and visual acuity making driving dangerous. With higher doses, mental clouding, impaired judgement, fine and precise movement, drowsiness and loss of self-control result. High doses cause stupor and coma. Death is due to respiratory depression. Alcohol may precipitate convulsions in epileptics. Tolerance develops on long term use.

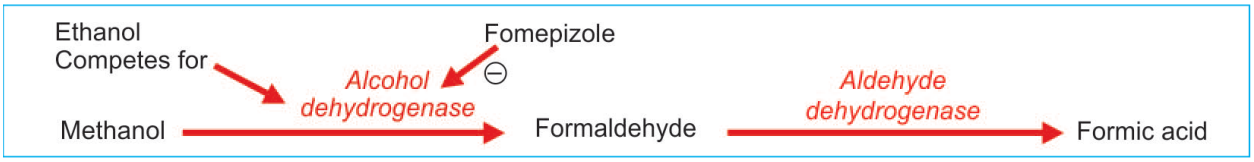
3. CVS: The actions are dose dependent. Small doses cause cutaneous vasodilation resulting in flushing and feeling of warmth. Large doses cause hypotension due to depression of myocardium and vasomotor centre. Arrhythmias may also be seen in heavy drinking or ‘binge drinking’. Chronic heavy drinking is associated with hypertension.

Chronic moderate drinking, however, has shown to prevent coronary heart disease and stroke. It could be because of raised HDL, raised tissue plasminogen activator and because it could also inhibit inflammatory processes in atherosclerosis.

4. GIT and liver: Alcohol is an irritant— increases gastric secretion and produces vasodilation and warmth. It is an appetizer. Chronic alcoholism results in chronic gastritis. Chronic consumption of moderate amounts of alcohol results in accumulation of fat in the liver, liver enlargement, followed by fatty degeneration and cirrhosis. Alcohol induces hepatic microsomal enzymes.

METHYL ALCOHOL (METHANOL, WOOD ALCOHOL)

Methanol is used to denature ethyl alcohol. It has no therapeutic value. Ingestion results in methanol poisoning. Methanol can also be absorbed through the skin. Methanol is converted to formaldehyde—catalysed by alcohol dehydrogenase; formaldehyde is converted to formic acid by the action of aldehyde dehydrogenase. Toxic effects are due to formic acid.



Metabolism of methanol

Manifestations of toxicity may take about 30 hr to appear as they are due to the metabolites and include vomiting, headache, visual distrubances, vertigo, severe abdominal pain, hypotension, delirium, acidosis and coma. Formic acid has affinity for optic nerve and causes retinal damage resulting in blindness. There are reports of even 15 ml of methanol causing blindness. Death is due to respiratory failure.

Treatment

1. Correction of acidosis: As acidosis hastens retinal damage, immediate correction of acidosis with IV sodium bicarbonate infusion helps in preventing blindness.

2. Protect eyes: Patient should be kept in a dark room to protect the eyes.

3. Gastric lavage: Should be given.

4. BP and ventilation: Must be maintained.

5. Ethyl alcohol: Should be given immediately.

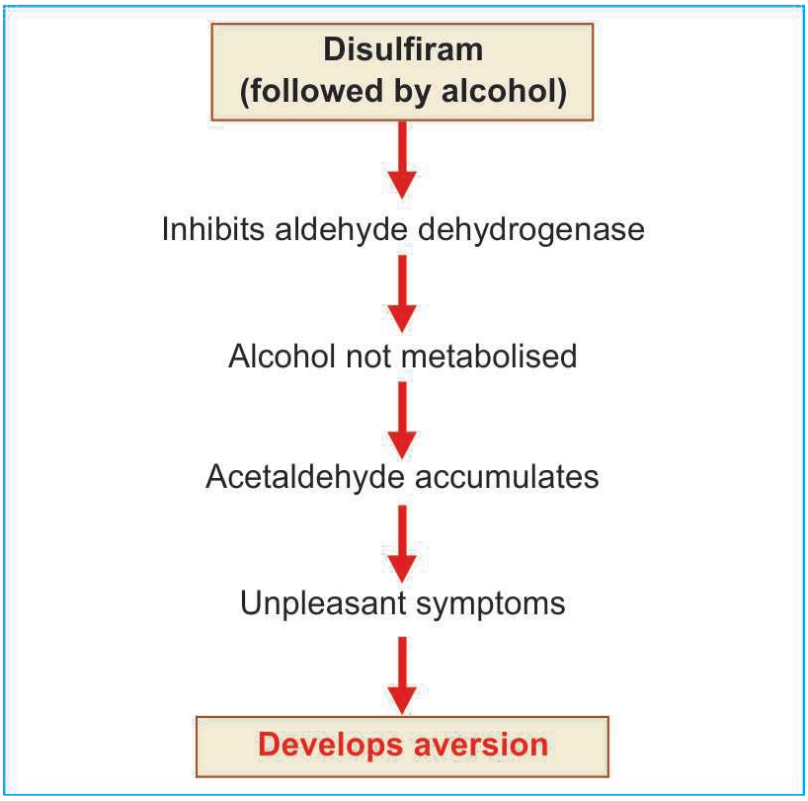
It competes with methanol for alcohol dehydrogenase because of its higher affinity for alcohol dehydrogenase.

It thus slows the metabolism of methanol and prevents the formation of toxic metabolites. A loading dose of 0.6 g/kg is followed by an infusion of 10 g/hour.

DISULFIRAM

Disulfiram is used to make alcohol consumption an unpleasant experience so that the person gives up drinking. Disulfiram inhibits the enzyme aldehyde dehydrogenase. If alcohol is consumed after taking disulfiram, acetaldehyde accumulates and within a few minutes it can produce flushing, throbbing headache, nausea, vomiting, sweating, hypotension and confusion—called the antabuse reaction, due to accumulation of acetaldehyde.

The effect lasts for 7–14 days after stopping disulfiram. Therefore, the person develops aversion to alcohol and often gives up the habit.



[Date]

PHARMACOLOGY OF DRUGS ACTING ON CNS

N.SUMANASRI

UNIT- 5

Pharmacology of drugs acting on central nervous system

a. Psychopharmacological agents: Antipsychotics, antidepressants, anti-anxiety agents, anti-manics and hallucinogens.

b. Drugs used in Parkinsons disease and Alzheimer's disease.

c. CNS stimulants and nootropics.

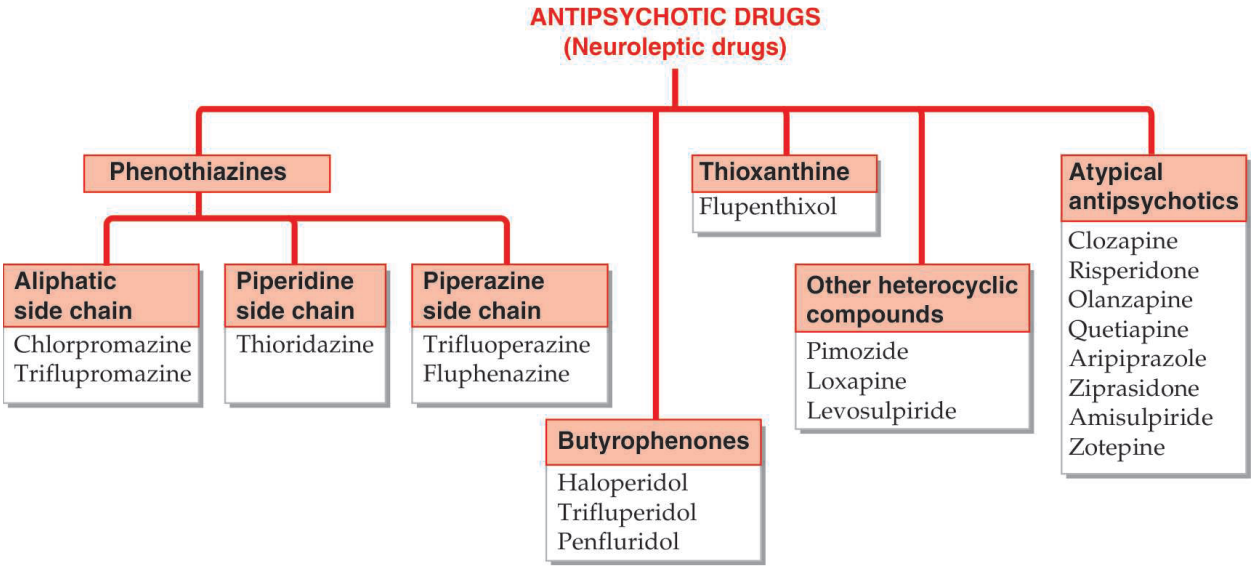
d. Opioid analgesics and antagonists.

e. Drug addiction, drug abuse, tolerance and dependence.

ANTIPSYCHOTIC DRUGS
(Neuroleptics)

- These are drugs having a salutary therapeutic effect in psychoses.
- Psychoses are the most severe forms and involve a marked impairment of behaviour, inability to think coherently, and to comprehend reality. Patients have no 'insight' into these abnormalities and have hallucinations and delusions. These include functional disorders where there is no organic cause like in schizophrenia, delusional disorders (paranoia) and affective (mood) disorders.

CLASSIFICATION

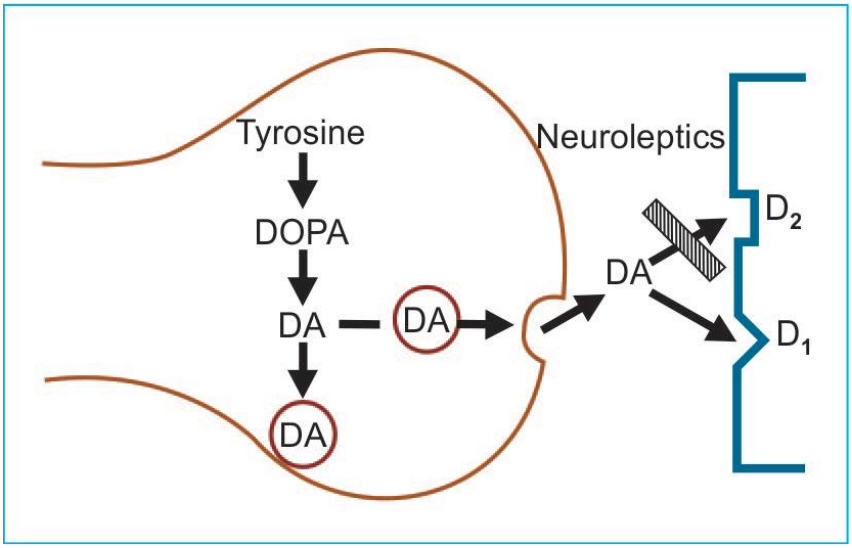


CHLORPROMAZINE (CPZ)

Delay and Deniker demonstrated the antipsychotic effect of chlorpromazine. It has a wide variety of actions (hence the brand name Largactil) because it blocks the actions of several neurotransmitters including adrenaline, dopamine, histamine, acetylcholine and serotonin.

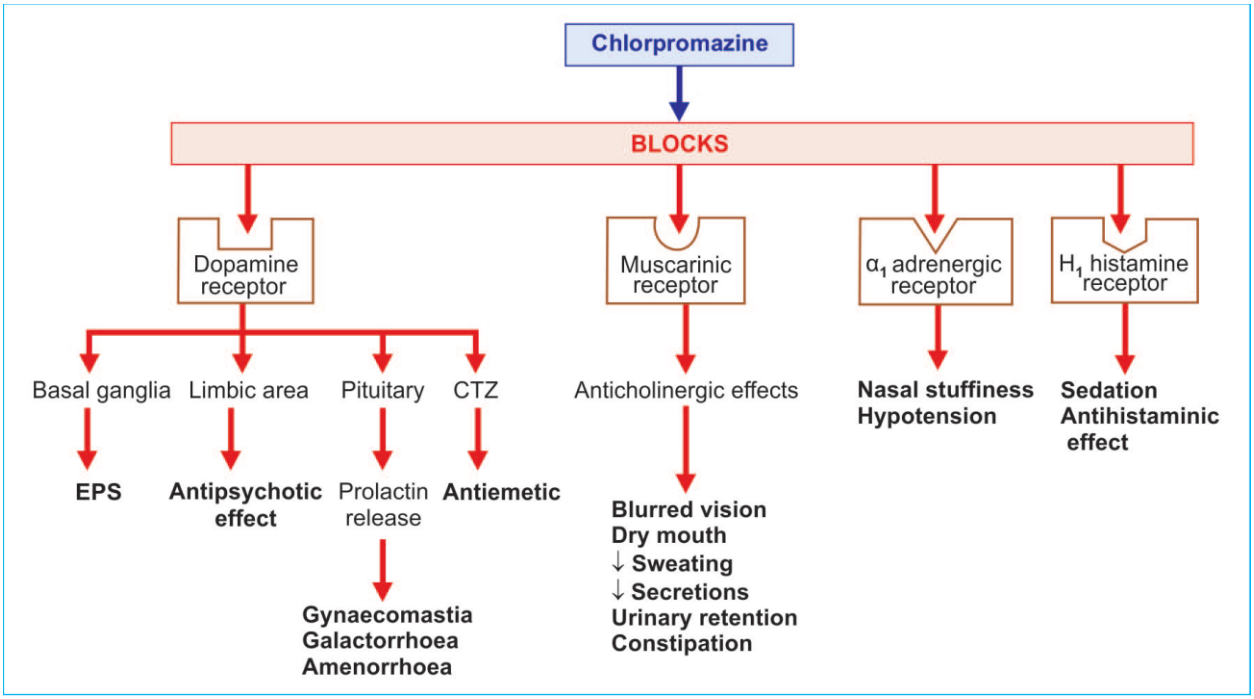
Mechanism of Action

Typical or first generation neuroleptics act by blocking the dopamine D2 receptors in the CNS. There are 5 subtypes of dopamine receptors—D1 to D5.



Mechanism of action of neuroleptics. Neuroleptics block the dopamine D2 receptors and act as antipsychotics

- They are all Gprotein-coupled receptors. As proposed in DA hypothesis, dopaminergic over activity mainly in the limbic area is thought to be responsible for schizophrenia, and typical antipsychotics block dopamine D2 receptors in the CNS particularly in the mesolimbic area. Some drugs like phenothiazines also block D1, D3 and D4 receptors. However, antipsychotic efficacy correlates with D2 blocking ability. Dopamine receptor blockade also is responsible for the classical side effects of these agents including extrapyramidal effects.



Chlorpromazine and other neuroleptics block dopamine, muscarinic, α1 adrenergic and H1 histamine receptors which is responsible for their wide range of actions and adverse effects.

Pharmacological Actions

CNS: Behavioural effects—in normal subjects, CPZ reduces motor activity, produces drowsiness and indifference to surroundings. In psychotic agitated patients, it induces neuroleptic syndrome, reduces aggression, initiative, impulsiveness and motor activity, relieves anxiety and brings about emotional quietening and drowsiness. Hallucinations, delusions and disordered thought gradually subside. In animal studies, neuroleptics selectively inhibit conditioned avoidance response. They induce sedation and normalise the sleep disturbances characteristic of psychoses.

Other CNS Actions

1. Cortex: CPZ lowers seizure threshold and can precipitate convulsions in untreated epileptics.
2. Hypothalamus: CPZ decreases gonadotrophin secretion and may result in amenorrhoea in women. It increases the secretion of prolactin resulting in galactorrhoea and gynaecomastia.
3. Basal ganglia: CPZ acts as a dopamine antagonist and, therefore, results in extrapyramidal motor symptoms (druginduced parkinsonism).
4. Brainstem: Vasomotor reflexes are depressed leading to a fall in BP.
5. CTZ: Neuroleptics block the dopamine (DA) receptors in the CTZ and thereby act as antiemetics.

Autonomic nervous system: The actions on the ANS are complex. CPZ is an alpha blocker. The alpha blocking potency varies with each neuroleptic. CPZ also has anticholinergic properties which leads to side effects. The degree of anticholinergic activity also varies with each drug.
CVS: Neuroleptics produce orthostatic hypotension due to alpha receptor blockade action and reflex tachycardia. CPZ also has a direct myocardiac depressant effect like quinidine.
Local anaesthetic: CPZ has local anaesthetic properties—but is not used for the purpose since it is an irritant.
Kidney: CPZ depresses ADH secretion and has weak diuretic effects.
Tolerance develops to the sedative and hypotensive actions while no tolerance is seen to the antipsychotic actions.

Pharmacokinetics

CPZ is incompletely absorbed following oral administration and also undergoes significant first pass metabolism (bioavailability is 30%). It is highly protein bound; has a t½ of 20 to 24 hr and is, therefore, given once a day.
Dose: 100–800 mg daily. LARGACTIL 10, 25, 50, 100 mg tab; 25 mg/5 ml syr; 50 mg/2 ml inj.

Adverse Reactions

- Blurred vision,
- Dry mouth,
- Reduced sweating,
- Decreased gastric motility,
- Constipation and urinary retention result
- Ocular toxicity
- Hypersensitivity reactions: Jaundice, agranulocytosis and skin rashes.

Drug Interactions

Neuroleptics enhance the sedative effects of CNS depressants, alpha blockers and of anticholinergic drugs. When combined with these groups of drugs, the effects may be additive. Neuroleptics inhibit the actions of dopamine agonists and L-dopa.

Uses

Neuroleptics are given orally (chlorpromazine 100–800 mg). In acute psychosis, they may be given intramuscularly and the response is seen in 24 hr while in chronic psychosis it takes 2–3 weeks of treatment to demonstrate the beginning of obvious response.
1. Psychiatric conditions: Psychoses including **schizophrenia** and organic brain syndromes like delirium and dementia all respond to antipsychotics. The manic phase of bipolar mood disorder responds to antipsychotics and generally atypical antipsychotics are used.

2. Other neuropsychiatric syndromes: Neuroleptics are useful in the treatment of several syndromes with psychiatric features like psychoses associated with chronic alcoholism, Huntington's disease and Gilles de La Tourette's syndrome.
3. Hiccough: CPZ can control intractable hiccough though the mechanism of action is not known.
4. Nausea, vomiting: Prochlorperazine is a good antiemetic as it blocks the DA receptors in the CTZ and in the stomach. It is used in vomiting due to radiation sickness and drug-induced vomiting.
5. Pruritus: Promethazine also blocks—H1 receptors and is useful in pruritus.
6. Neuroleptanalgesia: Droperidol is used with fentanyl for neuroleptanalgesia.

Atypical or Second Generation Antipsychotics

The newer atypical antipsychotics are second generation agents with weak D2 blocking properties but prominent 5-HT2 antagonistic actions. They have the following advantages over first generation agents:
1. Extrapyramidal side effects are absent or of much lower intensity.
2. Low endocrine side effects—particularly no raised prolactin levels, hence no galactorrhoea and no gynaecomastia.
3. Effective in suppressing both positive and negative symptoms of schizophrenia
4. Effective in resistant cases of psychosis. Atypical antipsychotics are used as **firstline** drugs in newly diagnosed patients (because of lower incidence of EPS) and in patients having troublesome EPS with conventional antipsychotics. However, their efficacy is not superior to conventional antipsychotics.

Clozapine is an effective antipsychotic. It blocks the dopamine D1 and D4 receptors but has low affinity for D2 receptors, hence very low incidence of EPS. Clozapine also blocks 5-HT2A, alpha adrenergic, muscarinic and H1 histamine receptors. Clozapine is metabolized by microsomal enzymes mainly CYP 3A4 in the liver.

Adverse effects:

- Agranulocytosis
- Fatal
- sedation,
- weight gain,
- hyperglycaemia,
- urinary incontinence,
- hypotension and
- tachycardia.

Olanzapine is similar to clozapine in actions and has the added advantage that it does not cause agranulocytosis. It blocks D2, 5-HT2, alpha adrenergic, muscarinic and H1 histamine receptors. It is well absorbed on oral administration. It has a t½ of 24–30 hr—given once daily; effective against

both positive and negative symptoms of schizophrenia. The incidence of EPS is negligible. No rise in prolactin levels and sexual dysfunction. However, **anticholinergic side effects**, **weight gain, hyperglycaemia** and hypertriglyceridaemia can occur. These side effects are particularly of concern in diabetics. It is used in mania, schizoaffective disorders and in Tourette's syndrome.
Dose: 2.5–10 mg daily. OLANDUS 2.5, 5, 7.5, 10 mg tab. OLZAP 5, 10 mg tab.

Quetiapine is an effective antipsychotic, similar in actions to clozapine. Blocks 5-HT1A, 5-HT2, D2, alpha 1, alpha 2, M1 and H1 receptors. Since it is a weak D2 blocker, EPS and hyperprolactinaemia are less marked; weight gain, hypotension and drowsiness are moderate. Quetiapine is completely absorbed on oral use, has a short t½ of 6 hr—hence given twice daily. The initial dose is 25 mg BD gradually increased over 4–6 days to 300–400 mg per day.
SEROQUIN, SOCALM 25, 100, 200 mg tab. QUITIPIN 25, 50, 100, 200, 300 mg tab.

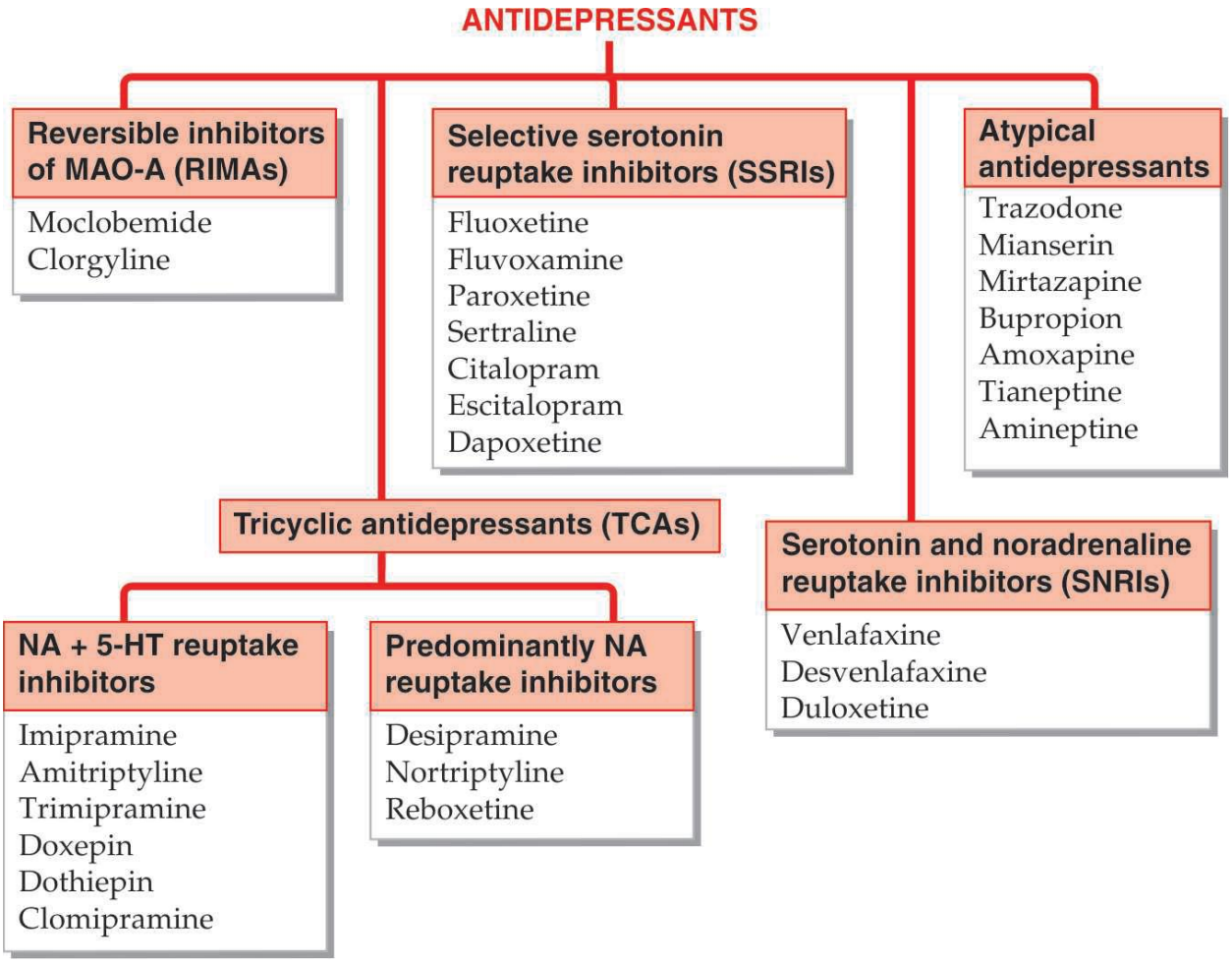
NEWER DRUGS

Brexpiprazole is an atypical antipsychotic. It is similar to aripiprazole with lower risk of agitation and restlessness compared to aripiprazole.
Cariprazine is a new class of antipsychotic. It acts at multiple receptors:
i. It is selective D3 partial agonist—may have beneficial effects in negative symptoms
ii. D2 antagonist
iii. 5-HT2 antagonist.
Cariprazine is indicated in schizophrenia and bipolar disorder.

ANTIDEPRESSANTS

- These are drugs which can elevate mood in depressive illness. Practically all antidepressants affect monoaminergic transmission in the brain in one way or the other, and many of them have other associated properties. Over the past three decades, a large number of antidepressants with an assortment of effects on reuptake/metabolism of biogenic amines, and on pre/post junctional aminergic/cholinergic receptors have become available so that a cogent classification is difficult.

CLASSIFICATION

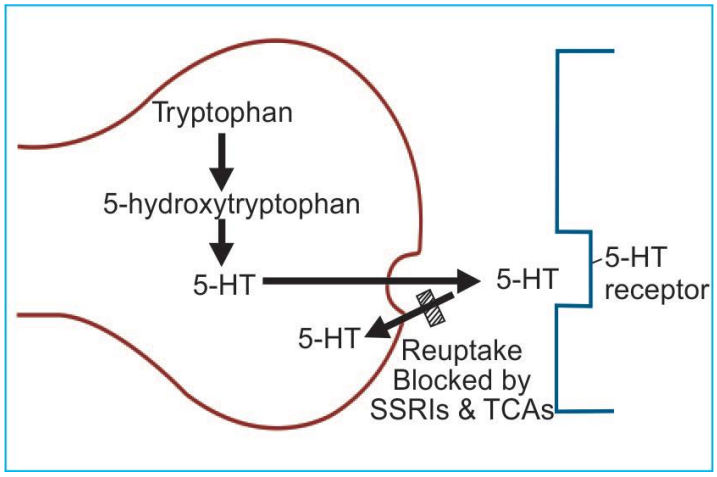


SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs)

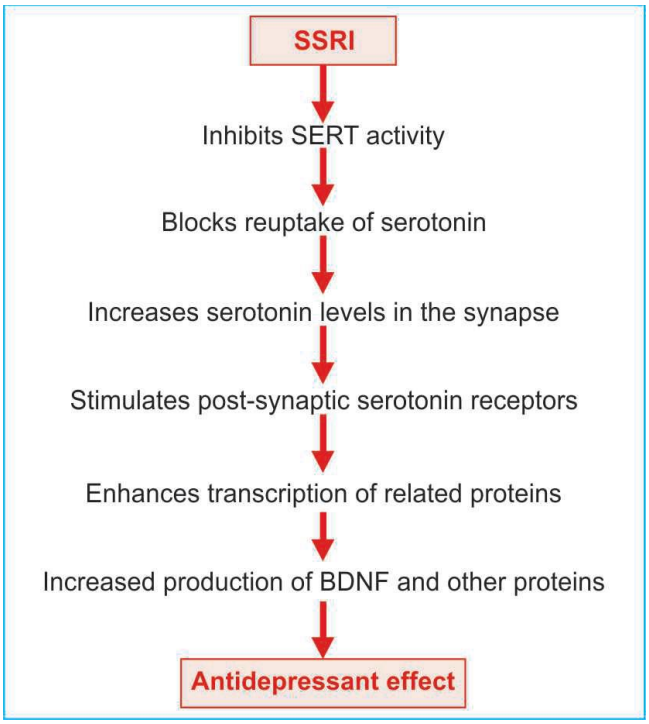
SSRIs include fluoxetine, fluvoxamine, paroxetine, citalopram, sertraline and escitalopram. They are now considered the first-line drugs in depression.

Mechanism of Action

SSRIs block the reuptake of serotonin from the synapse into the serotonergic nerve endings by inhibiting the **serotonin transporter (**SERT). About 80% reuptake is inhibited and more serotonin is available at the synapse which in turn results in transcription of certain proteins leading to the production of related proteins like BDNF responsible for the effects of SSRIs. Hence, they enhance serotonin levels in these synapses. TCAs were the first-line drugs and were widely used till the advent of SSRIs. Presently, SSRIs have taken over the place to a large extent because of several advantages over TCAs.



Mechanism of action of SSRIs. They block the reuptake of serotonin and improve serotonergic transmission



Mechanism of action

Pharmacokinetics: SSRIs are well absorbed when given orally, most are bound to plasma proteins. SSRIs are microsomal enzyme inhibitors— though each of them inhibit different isoforms. Fluoxetine is converted to an active metabolite norfluoxetine—prolonging the action to 7–10 days. Escitalopram is 1000 times more potent than citalopram. Moreover, unlike with other SSRIs, drug interactions are uncommon with escitalopram

Adverse effects:

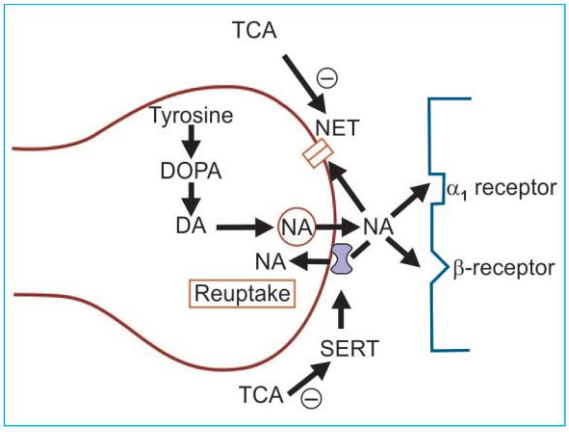
- Nausea,
- Vomiting,
- Insomnia,
- Headache,
- Restlessness,
- Anxiety and
- Sexual dysfunction
- Serotonin syndrome

TRICYCLIC ANTIDEPRESSANTS

Tricyclic antidepressants (TCAs) like imipramine have been extensively used in the treatment of depression for a few decades. TCAs are less expensive than SSRIs and are, therefore, still in use.

Mechanism of action:

TCAs block the reuptake of both NA and serotonin into the presynaptic terminals by binding to the transporters, viz. serotonin transporter (SERT) and norepinephrine transporter (NET). The synaptic levels of these monoamines increase and thereby prolong their action on the receptors. Thus TCAs potentiate amine neurotransmission in the CNS. The extent of binding and selectivity for SERT and NET varies with each TCA.



Mechanism of action of tricyclic antidepressants. 80% of noradrenaline and serotonin released into the synaptic cleft enters into the synaptic neuron by reuptake through SERT and NET. This reuptake is blocked by TCA

Pharmacological Actions

1. CNS: In normal subjects, TCAs cause dizziness, drowsiness, confusion and difficulty in thinking. In depressed patients, after 2–3 weeks of treatment, elevation of mood occurs; the patient shows more interest in the surroundings and the sleep pattern becomes normal.
2. CVS: Postural hypotension and tachycardia (due to blockade of □1-adrenergic and muscarinic receptors) can be severe in over dosage.
3. ANS: TCAs have anticholinergic properties and cause dry mouth, blurred vision, constipation and urinary retention.

Pharmacokinetics

TCAs are rapidly absorbed, extensively protein bound and metabolised in the liver. Microsomal enzymes are involved in the metabolism of TCAs and can result in drug interactions. TCAs are converted to active metabolites and thereby have a longer action. They have a long t½ and can be

given once daily—at night to avoid daytime sedation. On prolonged administration, accumulation can occur resulting in cumulative toxicity.

Adverse Effects

- Sedation,
- Confusion,
- Postural hypotension,
- Tachycardia
- Sweating.
- Dry mouth,
- Constipation,
- Blurred vision and
- Urinary retention
- Weight gain
- Cardiac arrhythmias.

Drug Interactions

1. Tricyclics potentiate sympathomimetics— even small amounts of adrenaline used with local anaesthetics can cause serious hypertension.
2. Highly protein bound drugs like phenytoin, aspirin and phenylbutazone displace TCAs from binding sites resulting in toxicity.
3. TCAs potentiate the effects of alcohol and other CNS depressants.
4. TCAs have anticholinergic effects and this effect gets added up with other drugs.

SEROTONIN NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIs)

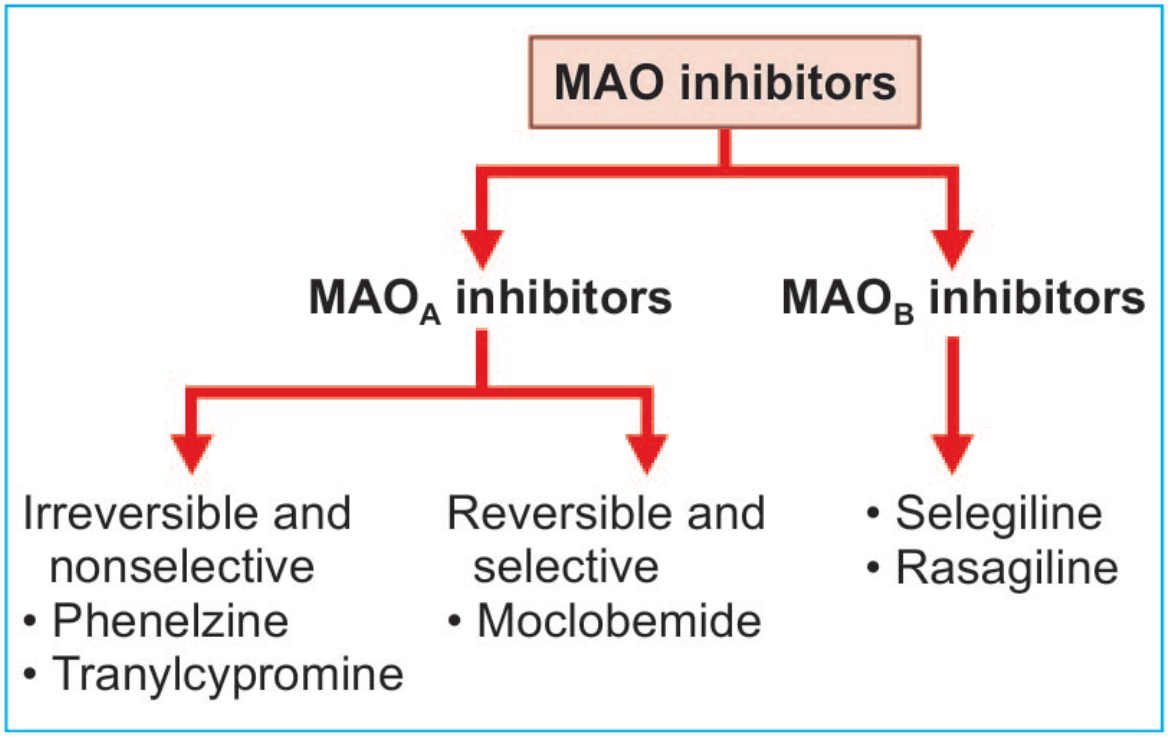
Venlafaxine, desvenlafaxine, duloxetine, milnacipran inhibit the reuptake of both serotonin and norepinephrine at the presynaptic neurons by binding to SERT and NET like TCA. Unlike TCA, they do not have anticholinergic, α-blocking or antihistaminic effects— hence fewer side effects. SNRIs are also useful in chronic pain.

Venlafaxine is thought to be faster acting and may be useful in patients not responding to other antidepressants.Venlafaxine has a short t½ (~5 hr) and needs to be given twice daily; it is safe in overdosage. If abruptly stopped or if doses are missed, withdrawal symptoms are common. Venlafaxine is better tolerated than the TCAs because it does not block alpha adrenergic, muscarinic and histamine H1 receptors and, therefore, is devoid of the related adverse effects.
Dose: 75–150 mg/day. VENLA, VENAXIN 25, 37.5, 75 mg tab, 150 mg SR- cap.

Desvenlafaxine is a metabolite of venlafaxine.
Milnacipran is similar to other SNRIs.
Duloxetine is similar to venlafaxine, is well absorbed and metabolised by microsomal enzymes.
Dose: 30–80 mg/day. DULIFE, DELOK 20, 30 mg cap.

MAO INHIBITORS

Monoamine oxidase (MAO) is an enzyme which metabolizes NA, 5-HT and DA. Drugs which inhibit this enzyme, enhance the neuronal levels of monoamines like NA, DA and 5-HT. MAO exists as two isoezymes— MAOA and MAOB. MAOA is selective for 5-HT.



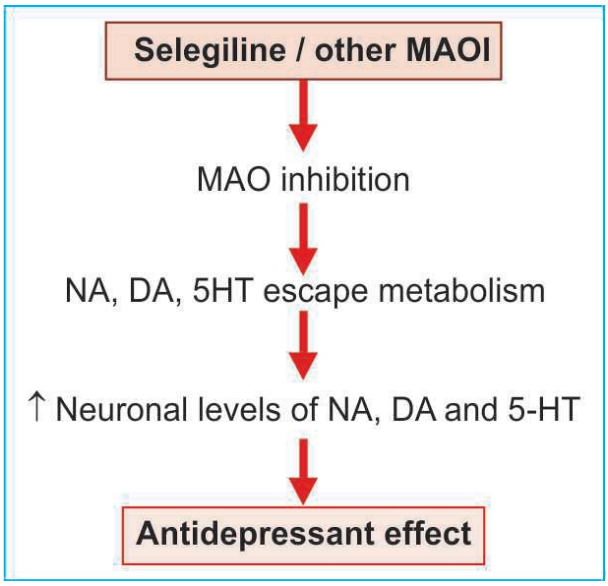
MAO inhibitors include:

Nonselective and irreversible MAO inhibitors have the following features:

• Irreversibly inhibit the enzyme MAO and enhance neuronal levels of noradrenaline, dopamine and 5-HT.

• Antidepressant actions develop slowly over weeks of treatment and MAO activity recovers over 1–2 weeks on stopping the drug.

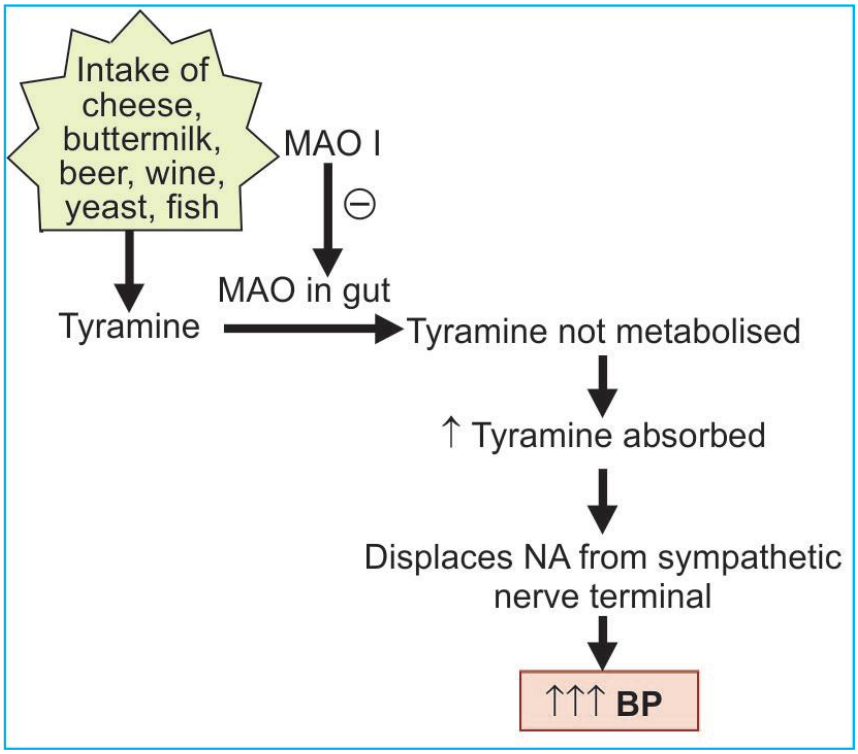
• Side effects are orthostatic hypotension, weight gain, restlessness, insomnia (due to CNS stimulation), anticholinergic effects and, rarely, liver dysfunction.



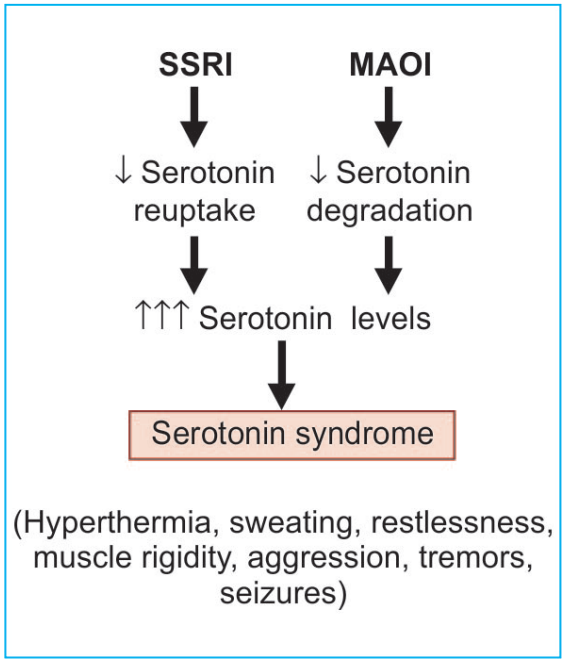
• Abrupt stopping can result in **withdrawal syndrome** with confusion, excitement and even psychosis.

• They interact with many drugs and food. Patients on MAO inhibitors taking tyramine containing food like cheese, beer, wines, yeast, buttermilk and fish—develop severe hypertension and is known as ***'cheese reaction.'*** Tyramine is normally metabolised by MAO in the gut wall. On inhibition of MAO by drugs, tyramine escapes metabolism and displaces NA from nerve endings leading to hypertension.

Cheese reaction due to MAO inhibitors



Serotonin syndrome: When an SSRI and an MAO inhibitor are administered concurrently, there could be a significant increase in serotonin levels in the synapses—this is because of both reduced reuptake and inhibition of metabolism. Raised serotonin levels can result in hyperthermia, restlessness, sweating, muscle rigidity, aggressive behaviour, tremors, seizures and coma. It can be fatal. This pharmacodynamics interaction can also occur when there is a potentiation of serotonergic activity with drugs like amphetamines, cocaine (5-HT release) tryptophan (5-HT synthesis), buspirone, and sumatriptan (5-HTagonist). Hence such combinations should be avoided. Because of the side effects and drug interactions, MAO inhibitors are not the preferred antidepressants.

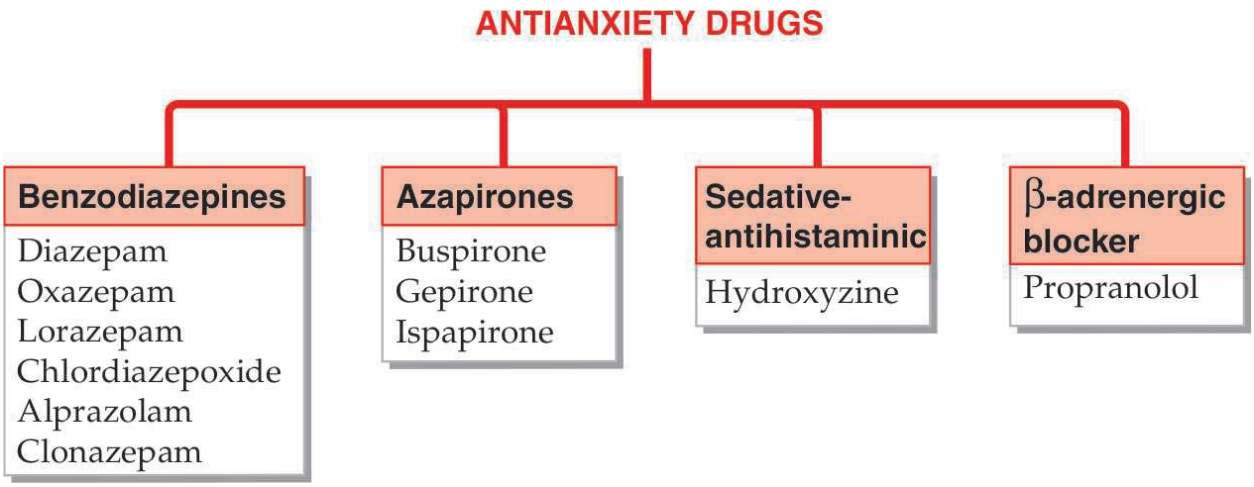


ANTIANXIETY DRUGS

These are an ill-defined group of drugs, mostly mild CNS depressants, which are aimed to control the symptoms of anxiety, produce a restful state of mind without interfering with normal mental or physical functions. The anxiolytic-sedative drugs differ markedly from antipsychotics, and more closely resemble sedative-hypnotics. They:

1. Have no therapeutic effect to control thought disorder of schizophrenia.
2. Do not produce extrapyramidal side effects.
3. Have anticonvulsant property.
4. Produce physical dependence and carry abuse liability.

CLASSIFICATION



BENZODIAZEPINES

Some members have a slow and prolonged action, relieve anxiety at low doses without producing significant CNS depression. They have a selective taming effect on aggressive animals and suppress induced aggression. They also suppress the performance impairing effect of punishment. In contrast to barbiturates, they are more selective for the limbic system and have proven clinically better in both quality and quantity of improvement in anxiety and stress-related symptoms. At antianxiety doses, cardiovascular and respiratory depression is minor.

Because anxiety is a common complaint and is a part of most physical and mental illness, and because the BZDs—

• have little effect on other body systems
• have lower dependence producing liability than barbiturates and other sedatives; withdrawal syndrome is milder and delayed due to their long half lives
• are relatively safe even in gross overdosage,
Benzodiazepines are presently one of the most widely used class of drugs. Potent BZDs like lorazepam and clonazepam injected i.m. have adjuvant role in the management of acutely psychotic and manic patients.

1. Chlordiazepoxide : It was the first BZD to be used clinically. Oral absorption is slow. A smooth long lasting effect is produced. It is preferred in chronic anxiety states. Chlordiazepoxide is often combined with other drugs in psychosomatic disorders, and has been the commonest BZD used to cover alcohol withdrawal. Its t½ is 6–12 hours, but active metabolites are produced which extend the duration of action. Its anticonvulsant action is weak.
Daily dose: 25–100 mg; LIBRIUM 10, 25 mg tabs; EQUILIBRIUM 10 mg tab.

2. Diazepam It is quickly absorbed; produces a brief initial phase of strong action followed by prolonged milder effect due to a two phase plasma concentration decay curve (distributive phase t½ 1 hr, elimination phase t½ 20–30 hours). The biological effect t½ is still longer due to production of active metabolites. It is preferred in acute panic states and anxiety associated with organic disease.
Daily dose: 5–20 mg; VALIUM, PLACIDOX 2, 5, 10 mg tabs; CALMPOSE 5, 10 mg tab, 2 mg/5 ml Syr.

3. Lorazepam Has slow oral absorption. Being less lipid-soluble than diazepam, its rate of entry in brain is slower. The plasma t½ is shorter (10–20 hours); no active metabolite is produced, since it is directly conjugated with glucuronic acid, and is suitable for older patients. However, it is quite sedative and capable of producing marked amnesia when injected i.v. Injection site complications are minor. Therefore, it is the only BZD recommended for i.m. use. Lorazepam has been preferred for short lasting anxiety states, panic, OCD and tension syndromes, as well as for psychosomatic diseases and for i.v. use in status epilepticus.
Daily dose: 1–6 mg; LARPOSE, ATIVAN 1, 2 mg tab. CALMESE 1, 2 mg tabs, 4 mg/2 ml inj.

4. Alprazolam A high potency anxiolytic BZD which in addition has some mood elevating action in mild depression. As such, it is particularly useful in anxiety associated with depression. Good response has been obtained in panic disorders with severe anxiety and autonomic symptoms. Its plasma t½ is about 12 hours, but an active metabolite is produced. Alprazolam is also used as hypnotic. When administered daily as anxiolytic, some patients experience anxiety in between doses, which may be obviated by employing sustained release tablet. Withdrawal symptoms may be more marked on discontinuation than with other BZDs.

Dose: 0.25–1.0 mg TDS; upto 6 mg/day in panic disorder; ALPRAX 0.25, 0.5, 1.0 mg tabs., 0.5, 1.0, 1.5 mg SR tabs; ALZOLAM 0.25, 0.5, 1.0 mg tabs; 1.5 mg SR tab, ALPROCONTIN 0.5, 1.0, 1.5 mg CR tabs. RESTYL 0.25, 0.5, 1.0 mg tabs, RESTYL-SR 0.5, 1.0, 1.5 mg SR tabs.

Buspirone

Buspirone is an azapirone with good anxiolytic properties. It differs from BZDs in many aspects. It is a selective 5-HT1A partial agonist. 5-HT1A receptors are inhibitory autoreceptors and binding of buspirone inhibits the release of 5-HT. Buspirone is also a weak D2 antagonist. It is useful in mild to moderate anxiety. Antianxiety effect develops slowly over 2 weeks. Unlike diazepam, it is not a muscle relaxant, not an anticonvulsant, does not produce significant sedation, tolerance or dependence and is not much useful in panic attacks. Buspirone is rapidly absorbed and metabolized in the liver, undergoes extensive first pass metabolism. Microsomal enzyme inducers like rifampicin shorten the t½ while enzyme inhibitors like erythromycin prolong its t½.

Dose: 5–15 mg OD or TDS. BUSPIN, BUSCALM 5, 10 mg tab

Adverse effects

- Headache,
- Dizziness,
- Nausea,
- Tachycardia,
- Nervousness,
- Paraesthesias
- Rarely,
- Restlessness.

Uses

Buspirone is used in mild to moderate anxiety and is particularly beneficial when sedation is to be avoided. **Ipsapirone** and **gepirone** are similar to buspirone.

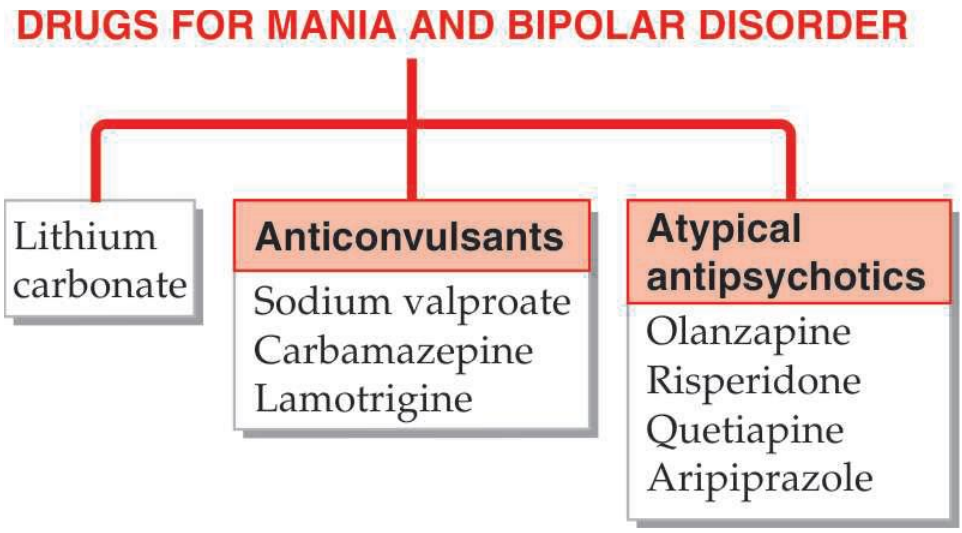
ANTI-MANICS

Mood disorders, also called affective disorders, are a group of psychoses associated with changes of mood, i.e. depression and mania.
It is a bipolar disorder.

Bipolar Depression

Bipolar depression is characterised by alternate episodes or periods of mania and depression. It was earlier called manic depressive psychosis (MDP) or manic depressive illness (MDI). The patient has cyclical mood swings. It is less common and is associated with a hereditary tendency. Mania can be considered opposite of depression with elation, overenthusiasm, over-confidence, often associated with irritation and aggression.

CLASSIFICATION



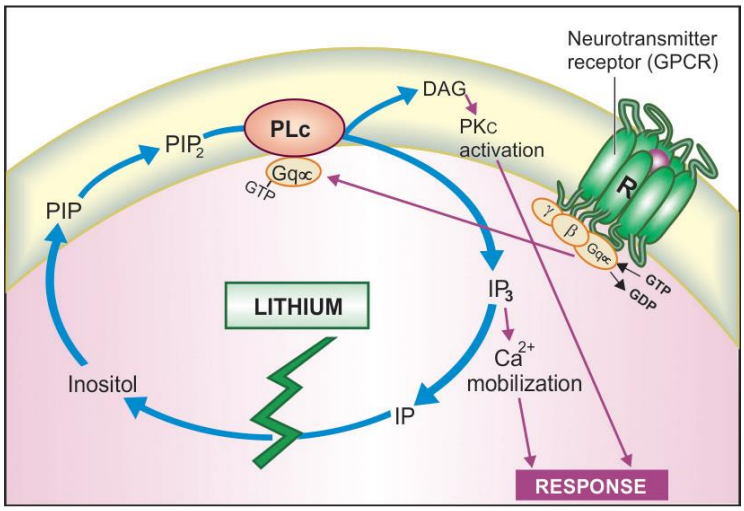
LITHIUM CARBONATE

- Lithium is a small monovalent cation. In 1949, it was found to be sedative in animals and to exert beneficial effects in manic patients. In the 1960s and 1970s the importance of maintaining a narrow range of serum lithium. Concentration was realized and unequivocal evidence of its clinical efficacy was obtained.
- Lithium is a drug of its own kind to suppress mania and to exert a prophylactic effect in bipolar (manic) disorder doses which have no overt CNS effects. Lithium is established as the standard antimanic and mood stabilizing drug. However, over the past 2–3 decades, several anticonvulsants and atypical antipsychotics have emerged as equally effective and more manageable alternatives to lithium.

MECHANISM OF ACTION

Mechanism of action of lithium is **complex** and not fully understood. It is thought that lithium acts by the following mechanisms.

1. **Inositol pathway:** Lithium interferes with the regeneration of inositol. It inhibits inositol monophosphatase and other enzymes and thereby inhibits the conversion of IP3 to inositol, leading to a depletion of phosphatidyl inositol biphosphate (PIP2). This results in a reduction in the formation of the second messengers. IP3 and DAG leading to a reduction in the receptor activity. Lithium selectively inhibits signal transduction in the hyperfunctioning neurons as seen in mania. Lithium inhibits monophosphatases that convert IP to inositol.



PIP—Phosphatidyl inositol phosphate; PIP2—Phosphatidyl inositol bisphosphate; IP3—Inositol trisphosphate; IP— Inositol-1-phosphate; PLc—Phospholipase C; DAG—Diacylglycerol; PKc—Protein Kinase C; Gq—Coupling Gq protein; R—Neurotransmitter receptor

2. **Effect on electrolytes:** Lithium can compete with and replace sodium at many sites including neurons. It may alter neuronal functions resulting in its mood stabilizing effects.

3. **G-proteins:** Lithium inhibits the receptor mediated activation of G-proteins in the CNS, i.e. they could uncouple receptors from their G-proteins. This action could also contribute to its mood stabilizing action.

4. **Neurotransmitters:** Lithium inhibits the release of noradrenaline and dopamine from the nerve terminals. Lithium also prevents the super sensitivity of the receptors induced by dopamine antagonists (antipsychotics).

Pharmacokinetics

Lithium is a small ion and mimics the role of sodium in excitable tissues. Given orally it is well-absorbed. It is filtered at the glomerulus but reabsorbed like sodium. Steady state concentration is reached in 5–6 days. Lithium is secreted in sweat, saliva and breast milk. Since safety margin is narrow, **plasma lithium concentration needs to be monitored** (0.5–1 mEq is the therapeutic plasma concentration) 3–5 mEq can cause fatal toxicity.

Adverse Effects

- Nausea,
- Vomiting,
- Mild diarrhoea,
- Oedema,
- Thirst and
- Polyuria
- Tremors
- Hypothyroidism
- Nephrogenic diabetes insipidus
- Weight gain
- Tremors,
- Drowsiness,
- Giddiness,
- Confusion,
- Ataxia,
- Blurred vision and nystagmus

Drug Interactions

1. Diuretics enhance Na+ loss and lithium absorption from the kidney. This increases plasma lithium levels resulting in toxicity.

Lithium + Diuretics

Diuretic ⟶ Na+ loss ⟶ Li+ reabsorption

(in place of Na+)

↓

Toxicity ⟶ plasma Li+

2. NSAIDs decrease lithium elimination and increase toxicity.

Carbamazepine is found to be effective in preventing the relapses of bi polor mood disorder and in the treatment of acute mania. It can be combined with lithium for better therapeutic effects but lithium can enhance the toxicity of carbamazepine. Mechanism of action is not understood. Carbamazepine may be used alone in mild cases as a mood stabilizer.

Dose: Started with 200 mg twice daily and may be increased if required.

Sodium valproate can be tried alone in mild to moderate cases or along with lithium in refractory cases. It is now known that sodium valproate has antimanic effects and is presently the first-line mood stabilizer. It has several advantages.

- It is almost as effective as lithium.
- It may be effective in patients not responding to lithium.
- Safer
- Better tolerated
- Dose can be rapidly titrated upwards.

• It is well tolerated and adverse effects are milder as compared to lithium. Nausea may be experienced in some patients.
• It can be combined with other antipsychotics and the combination is well tolerated.
• Valproic acid is now considered the first line drug in the initial treatment of mania.
Dose: Started with 750 mg/day—may be increased to 1500–2000 mg/day.

Other antiepileptics: Lamotrigine, gabapentin topiramate and other newer antiepileptics are being tried in the prophylaxis of bipolar mood disorder as alternatives to lithium.

Other drugs: Antipsychotics like risperidone, olanzapine, quetiapine and aripiprazole are also being tried.

Riluzole, a neuroprotective agent used in amyotrophic lateral sclerosis, is also being tried in mood dosorders.

HALLUCINOGENS

DEFINITION

These are drugs which alter mood, behaviour, thought and perception in a manner similar to that seen in psychosis.

• Many natural products having hallucinogenic property have been discovered and used by man since prehistoric times.

• A number of synthetic compounds have also been produced.

CLASSIFICATION

INDOLE AMINES

1. Lysergic acid diethylamide (LSD)
   – Synthesized by Hofmann (1938) who was working on chemistry of ergot alkaloids, and himself experienced its hallucinogenic effect.
   – It is the most potent psychedelic, 25–50 μg produces all the effects.
   – In addition to the mental effects, it produces pronounced central sympathetic stimulation.
   – Its action appears to involve serotonergic neuronal systems in brain.
2. Lysergic acid amide – A close relative of LSD but 10 times less potent; found in morning glory (Ipomoea violace) seeds.

PHENYLALKYL AMINES

1. Mescaline – From Mexican 'Peyote cactus' Lophophora williamsi. – It is a low potency hallucinogen used by natives during rituals. – It is a phenylalkylamine but does not have marked sympathomimetic effects.
2. Ecstasy – Methylene dioxy methamphetamine (MDMA, or tenamphetamine) is an amphetamine-like synthetic compound with stimulant and hallucinogenic properties, that has been abused as a recreational and euphoriant drug, especially by college students under the name 'Ecstasy'. Fear of neurotoxicity has reduced its popularity.
3. Yaba
   • This is a combination of methamphetamine with another stimulant methylhexanamine or caffeine.
   • Popular as a 'street drug' in Thailand and Myanmar, it has spread to many countries including India, as a 'party drug' among the youth.
   • Users claim it to be an aphrodisiac and produces a 'high'. The risk of neurotoxicity is similar to amphetamine.
   • Other synthetic phenylalkylamines with hallucinogenic property are Dimethoxymethyl amphetamine (DOM) and Methylene dioxyamphetamine (MDA).
   • High doses and repeated use of amphetamine can also cause psychosis.

3. ARYLCYCLOHEXYL AMINES

Phencyclidine

– It is an anticholinergic, which activates σ receptors in brain causing disorientation, distortion of body image, hallucinations and an anaesthetic like state.

– Ketamine is a closely related compound with lower hallucinogenic potential and is used in anaesthesia.

– Mixed with drinks, ketamine has been abused as a ‘rape drug’, because of its fast and strong depressant-amnesic action.

4. CANNABINOIDS

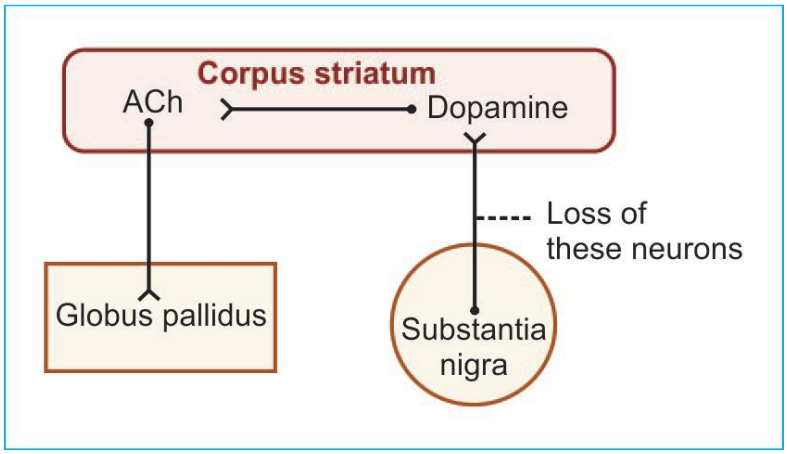
• 9Δ Tetrahydrocannabinol (9Δ THC) It is the active principle of Cannabis indica (Marijuana), which has been the most popular recreational and ritualistic intoxicant used for millennia. Its use has spread worldwide.

B. DRUGS USED IN PARKINSONS DISEASE AND ALZHEIMER'S DISEASE.

PARKINSONS DISEASE

DEFINITION

- **Parkinsonism** is a chronic, progressive, motor disorder characterised by rigidity, tremors and bradykinesia. Other symptoms include excessive salivation, abnormalities of posture and gait, seborrhoea and mood changes. It was described by James Parkinson in 1817 and is, therefore, named after him.
- In idiopathic parkinsonism, there is degeneration of nigrostriatal neurons in the basal ganglia resulting in dopamine deficiency. The balance between inhibitory dopaminergic neurons and excitatory cholinergic neurons is disturbed. Dopamine synthesized in the dopaminergic nerve terminals acts on dopamine receptors. Of the 5 subtypes (D1–D5) of the DA receptors, all types are present in different parts of the brain, but striatum is rich in D1 and D2 subtypes and are important in the pathophysiology of parkinsonism.
- Anti parkinsonian drugs can only help to alleviate the symptoms and improve the quality of life. The two strategies in the treatment are:
  i. To enhance dopamine activity
  ii. To depress cholinergic overactivity.



Pathophysiology of parkinsonism: Nigrostriatal neurons degenerate resulting in □DA content in these neurons

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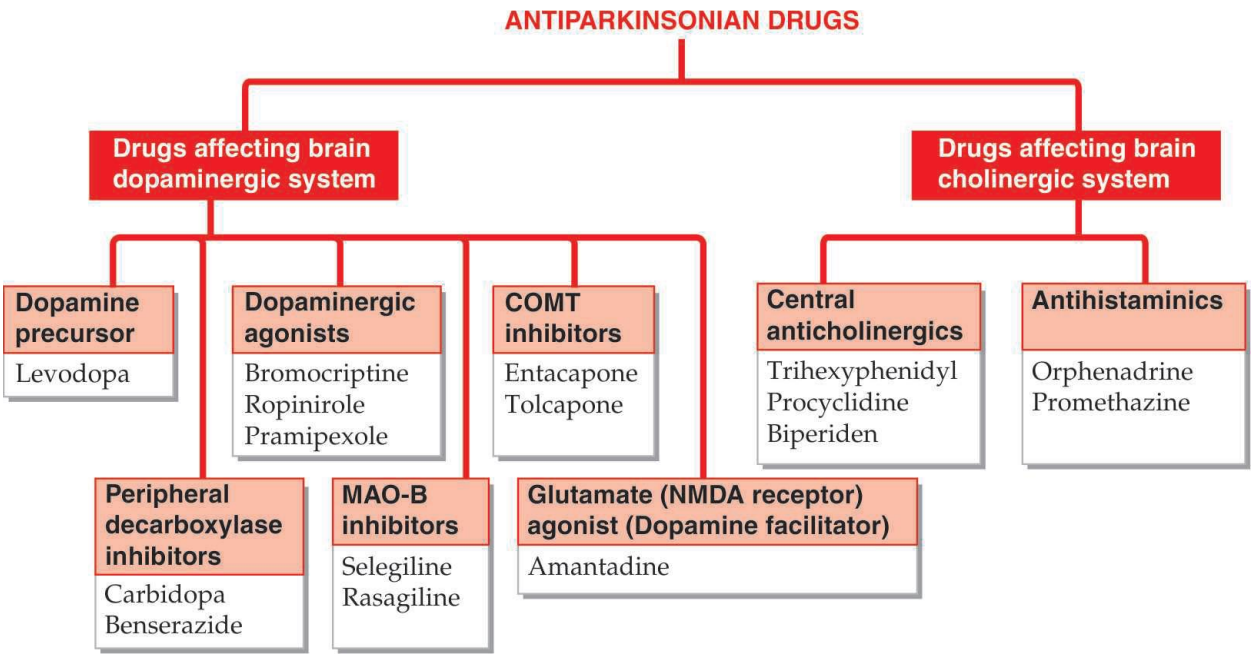


DOPAMINE PRECURSOR

Levodopa

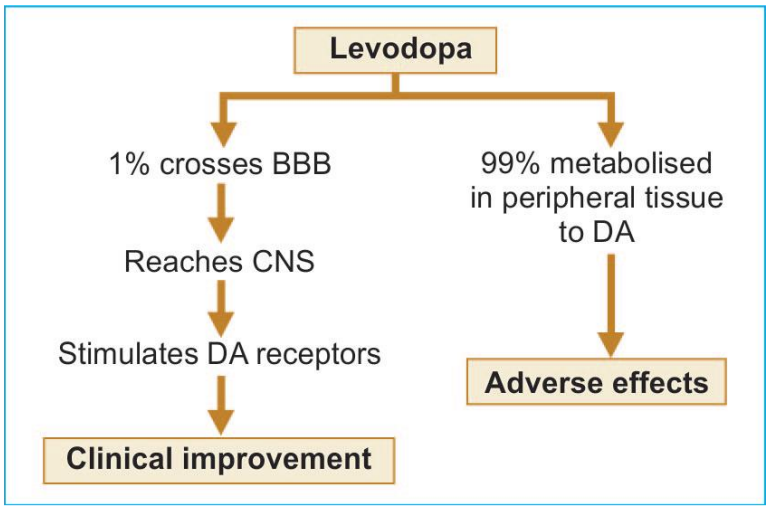
Though parkinsonism is due to dopamine deficiency, dopamine is of no therapeutic value because it does not cross the blood–brain barrier. Levodopa is a prodrug which is converted to dopamine in the body. Levodopa crosses the BBB and is taken up by the surviving nigrostriatal neurons. It is converted to DA in the dopaminergic neurons of the striatum.

$$\text{Levodopa} \xrightarrow{\textit{Dopa decarboxylase}} \text{Dopamine}$$

MECHANISM OF ACTION

- On administration of levodopa, there is an overall improvement in the patient as all the symptoms subside.
- Bradykinesia, rigidity and tremors respond. There is an improvement in sialorrhoea, seborrhoea, mood changes and general motor performance. The patient shows more

interest in the surroundings. However, some studies have shown that levodopa may generate oxidative stress damaging the dopaminergic neurons on long term use.



Other Actions

Large amounts of levodopa are converted to dopamine in the periphery which brings about other actions.

- CTZ: Dopamine stimulates the CTZ to induce vomiting.
- CVS: It causes postural hypotension, tachycardia and arrhythmias. Dopamine is a catecholamine.
- Endocrine: Dopamine suppresses the prolactin secretion.

Pharmacokinetics

- Levodopa is rapidly absorbed from the small Intestine. An active transport process that is meant for amino acids is responsible for absorption and transport of levodopa into the brain across the BBB. Therefore, some amino acids in food compete with levodopa for both absorption and transport into the brain.
- Presence of food delays its absorption. If gastric emptying is delayed, bioavailabilty is reduced due to higher first pass metabolism. It undergoes first pass metabolism in the gut and the liver. Its t½ is 1–2 hours. 1–2% of an oral dose reaches the brain.

Adverse Reactions

- Nausea,
- Vomiting,
- Anorexia,
- Postural hypotension,
- Palpitation
- Anxiety,

- Depression,
- Hallucinations,
- Mania,
- Trauma,
- Confusion

Drug Interactions

1. Pyridoxine enhances peripheral decarboxylation of levodopa and thus reduces its availability to the CNS.
2. Phenothiazines and metoclopramide are DA antagonists. They reverse the effects of levodopa.
3. Non-selective MAO inhibitors prolong the action of levodopa and may result in hypertensive crisis.

COMT Inhibitors

Tolcapone and entacapone inhibit the peripheral metabolism of levodopa by inhibiting the enzyme COMT—thereby they increase the bioavailability of levodopa. Tolcapone crosses the BBB and enhances the availability of levodopa in the brain. The duration of action of levodopa is prolonged and the response is smoother with reduced on-off periods. Both are rapidly absorbed; entacapone has peripheral effects, whereas tolcapone has both central and peripheral effects.

Adverse effects:

- Nausea,
- Diarrhoea orthostatic hypotension,
- Dyskinesias,
- Sleep disturbances,
- Confusion and
- Hallucinations

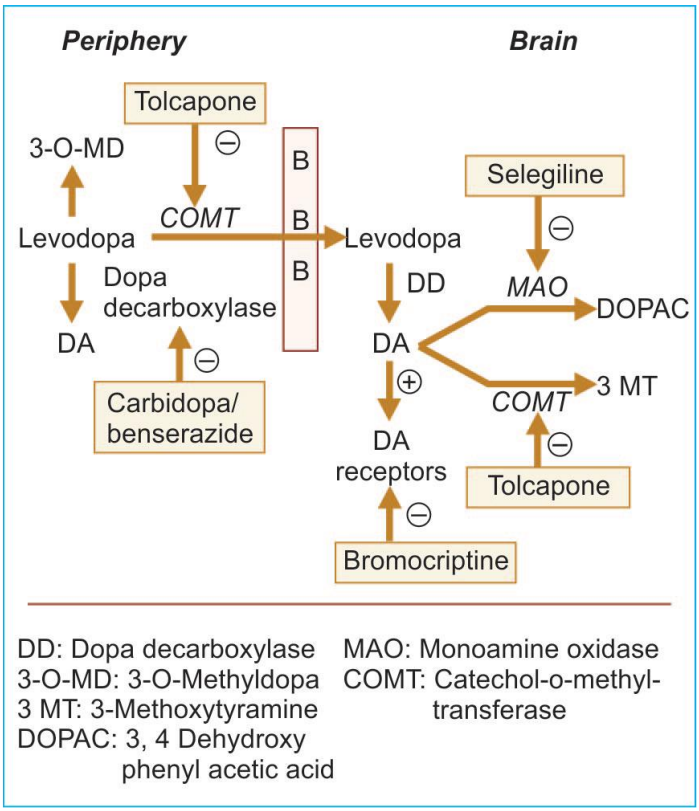
ENTACAPONE Dose: 200 mg 1 tab with every dose of LEVODOPA. COMTAN, EMTACOM 200, 400 mg tab.

DOPAMINE RECEPTOR AGONISTS

- Dopaminergic agonists have the advantages of **directly stimulating the DA receptors** and do not depend on the enzymes for convertion to active metabolites (unlike levodopa). They are less likely to generate free radicals which could damage the dopaminergic neurons. They are longer acting than levodopa and are the first-line drugs in Parkinson's disease.

- **Bromocriptine and pergolide,** the older agents, are ergot derivatives. Bromocriptine is an agonist at D2 and a partial agonist at D1 while pergolide is an agonist at both D1 and D2 receptors. The newer agents **ropinirole** and **pramipexole** are non-ergot derivatives, are selective D2 and D3 agonists, are better tolerated than older agents and quickly attain therapeutic levels (hence dose titration can be done faster). Their adverse effects are milder except that they may cause some sleep disorders. Being longer-acting, they are less likely to cause dyskinesia and 'on-off' phenomenon. DA agonists are well absorbed given orally.

Dopamine agonists are all longer acting because of which they are useful in the treatment of 'on-off' phenomenon.



Sites of action of drugs in parkinsonism

Adverse effects

- Nausea,
- Vomiting,
- Anorexia,
- Dyspepsia and
- Skin eruptions

ALZHEIMER'S DISEASE

- Alzheimer's disease (AD) is a neurodegenerative disorder, characterized by progressive impairment of memory and cognitive functions.
- Pathological features include atrophy of the cerebral cortex and loss of neurons—mainly cholinergic neurons with multiple senile (amyloid) plaques and neurofibrillary tangles in the brain. Since there is loss of cholinergic neurons, drugs that enhance cholinergic function have been tried. Many other drugs have also been used to improve cognitive functions with variable results.

CLASSIFICATION

1. **Cholinesterase inhibitors**
    - Tacrine, rivastigmine, donepezil, galantamine
2. **Nootropic agents (cognition enhancers)**
    - Piracetam, aniracetam, cerebrolysin
3. **NMDA receptor antagonist**
    - Memantine
4. **Others**
    - Piribedil, ginkgo biloba

Tacrine

It is a centrally acting cholinesterase inhibitor. It enhances cholinergic transmission in the brain. But it is short acting and also causes various side effects including nausea, vomiting, abdominal cramps, diarrhoea and hepatotoxicity. The newer agents rivastigmine, donepezil and galantamine are better tolerated with fewer side effects. They are selective central anticholinesterases—hence do not cause the GI side effects which are due to peripheral cholinergic activity. They increase acetylcholine levels in the surviving neurons and have produced good response— cognitive function improves and the symptom score shows benefit. They are not hepatotoxic and are longer acting. All are started at low doses which are gradually increased.

Donepezil has the advantage of longer action and once a day administration.

Preparations

Rivastigmine 1.5–6 mg BD. RIVAMER 1.5, 3, 4.5 and 6 mg cap.

Donepezil: 5 mg HS. DONECEPT 5, 10 mg cap.

Galantamine: 4 mg BD. GALAMER 4, 8, 12 mg tab.

Nootropic agents have not shown consistent results in Alzheimer's disease.

Memantine is an NMDA receptor antagonist found to be useful in patients with moderate to severe AD. The benefit is thought to be due to blockade of glutamate-induced excitotoxicity Memantine is well tolerated as the adverse effects are mild and reversible—may cause dizziness and headache. It is used in moderate to severe AD. Started with 5 mg OD and increased to 10 mg BD.

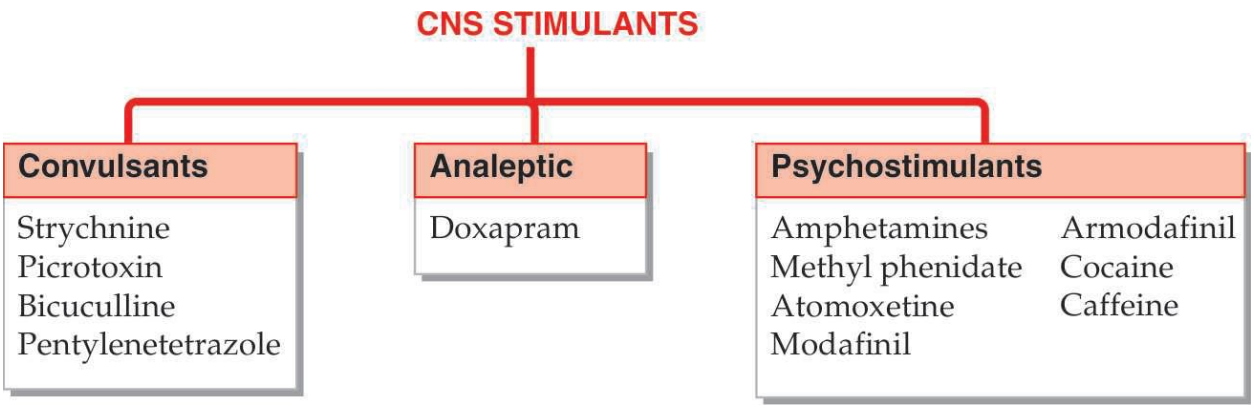
Ginkgo biloba: An extract of the chinese plant contains ginkgoflavon glycosides. It is thought to act as a PAF antagonist and decreases the production of TXA2 and inhibits platelet aggregation. It has been used as a cognition enhancer—but the benefits have yet to be proved.
GINKOCER, GINKOBA 40 mg tab.

C. CNS STIMULANTS AND NOOTROPICS.

CNS STIMULANTS

These are drugs whose primary action is to stimulate the CNS globally or to improve specific brain functions.

CLASSIFICATION



I. CONVULSANTS

1. Strychnine It is an alkaloid from the seeds of *Strychnos nux-vomica*, that is a potent convulsant. The convulsions are reflex, tonic-clonic and symmetrical. Strychnine acts by blocking *post-synaptic* inhibition produced by the inhibitory transmitter glycine. One of the sites that has been clearly demonstrated is the Renshaw cell-motoneurone junction in the spinal cord through which inhibition of antagonistic muscles is achieved. Accidental strychnine poisoning may occur, especially in children. Treatment of poisoning is similar to that of status epilepticus.

2. Picrotoxin It is obtained from 'fish berries' of East Indies *Anamirta cocculus.* Picrotoxin is a potent convulsant— convulsions are clonic, spontaneous and asymmetrical. The convulsions are accompanied by vomiting, respiratory and vasomotor stimulation. Picrotoxin acts by blocking *presynaptic* inhibition mediated through GABA. However, it is not a competitive antagonist; does not act on GABA receptor itself, but on an allosteric site and prevents Cl^- channel opening. Diazepam, which facilitates GABAergic transmission, is the drug of choice to treat picrotoxin poisoning.

3. Bicuculline This synthetic convulsant has picrotoxinlike actions. It is a competitive GABAA receptor (intrinsic Cl^- channel receptor) antagonist. It is only a research tool.

II. ANALEPTICS (Respiratory stimulants)

These are drugs which stimulate respiration and were believed to have resuscitative value in coma or fainting. They do stimulate respiration in subconvulsive doses, but margin of safety is narrow. *Doxapram* and some other analeptics injected i.v. were used in the past as an expedient measure in fainting, barbiturate poisoning, suffocation, drowning, ventilatory failure in COPD, but are outmoded now.

III. PSYCHOSTIMULANTS

These drugs have predominant cortical action; their psychic effects are more prominent than those on medullary vital centres.

Methylphenidate It is chemically and pharmacologically similar to amphetamine. Both act primarily by releasing NA and DA in the brain. Both produce increase in mental activity at doses which have little action on other central and peripheral functions. Methylphenidate is considered superior to amphetamine for attention deficit hyperkinetic disorder (ADHD) in children, because it causes lesser tachycardia and growth retardation. Behaviour and learning ability are improved in 3 out of 4 treated children.

Methylphenidate can also be used for concentration and attention defect in adults, and for narcolepsy, but should not be employed to treat depression, dementia, obesity or to keep awake. Methylphenidate is well absorbed orally, metabolized and excreted in urine, plasma t½ is 4–6 hours, but central effects last much longer. Twice daily dosing (morning and afternoon) is enough.

Side effects

- Anorexia,
- Insomnia,
- Growth retardation,
- Abdominal discomfort and
- Bowel upset.

Dose: Adults 5–10 mg BD; children 0.25 mg/kg/day initially, increased up to 1 mg/kg/day if needed. RETALIN 5, 10, 20, 30 mg tab.

Atomoxetine This is a selective NA reuptake inhibitor, unrelated to amphetamine as well as to imipramine, which does not enhance DA release in the brain, and is neither a CNS stimulant nor an antidepressant. However, it has been found to improve attention span and behavior in ADHD. It is indicated in children >6 years and in adults with concentration and attention problems.

COGNITION ENHANCERS (Cerebroactive drugs)

These are a heterogenous group of drugs developed for use in dementia and other cerebral disorders. They do elicit pharmacological effects, but widely different mechanisms of action are claimed. Therapeutic benefits are limited, and at the best, short-lasting.

Dementia Refers to acquired global impairment of intellect, memory, ability to comprehend and recognize people, loss of orientation and other cognitive functions, in the absence of gross clouding of consciousness or motor dysfunction. Memory, capacity to solve problems of day to day living, performance of learned motor skills, social skills and control of emotions are primarily affected.

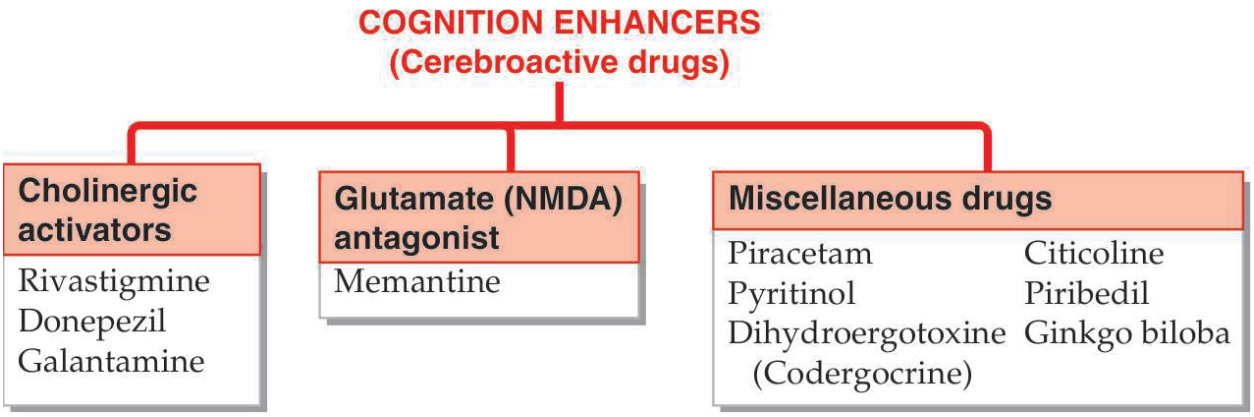
Alzheimer's disease (AD) A progressive neurodegenerative disorder which affects older individuals and is the most common cause of dementia. It may progress to a totally vegitative state. Atrophy of cortical and subcortical areas is associated with deposition of β-*amyloid protein* in the form of extracellular senile (amyloid) plaques and formation of intracellular neurofibrillary tangles made up of 'tau' protein. These abnormal proteins accumulate mostly due to reduced clearance, but in some cases, due to overproduction, and cause neuronal damage followed by neuron loss. There is marked cholinergic deficiency in the brain, though other neurotransmitter systems, especially glutamate and neuropeptide, are also affected.

The indications of cognition enhancers include:

1. Alzheimer's disease (AD) and multi-infarct dementia (MID).
2. Mild cognitive impairment (MCI) or 'common symptoms' of the elderly; dizziness and episodic memory lapses.
3. Mental retardation in children, learning defects, attention deficit disorder.
4. Transient ischaemic attacks (TIAs), cerebrovascular accidents, stroke.
5. Organic psychosyndromes and sequelae of head injury, ECT, brain surgery.

Apart from some cholinergic activators and glutamate antagonist introduced over the past 2–3 decades, the above therapeutic field is barren and commercially highly profitable. A variety of drugs have been briskly promoted by manufacturers and wishfully prescribed by physicians. The mechanism by which they are believed to act are:

- Increasing global/regional cerebral blood flow (CBF)
- Direct support of neuronal metabolism.
- Enhancement of neurotransmission.
- Improvement of descrete cerebral functions, e.g. memory.



Rivastigmine This carbamate derivative of physostigmine inhibits both AChE and BuChE, but is more selective for the G1 isoform of AChE that predominates in certain areas of the brain. Rivastigmine is highly lipid-soluble—enters brain easily. Greater augmentation of cholinergic transmission in the brain is obtained with mild peripheral effect. The carbamyl residue introduced by rivastigmine into AChE molecule dissociates slowly resulting in inhibition of cerebral AChE for upto 10 hours despite the 2 hr plasma t½ of the drug.

In clinical trials an average of 3.8 point improvement in Alzheimer's Disease Assessment Scale (ADAS-cog) has been obtained compared to placebo. Other symptoms like apathy, delusions, hallucinations and agitation also improve, but to a lesser extent. Disease progression is not affected. Peripheral cholinergic side effects are mild. It has not produced liver damage. Rivastigmine is indicated in mild-to-moderate cases of AD, but not in advanced disease.

Dose: Initially 1.5 mg BD, increase every 2 weeks by 1.5 mg/ day upto 6 mg/BD.

EXELON, RIVAMER 1.5, 3, 4.5, 6.0 mg caps. Transdermal patches delivering 4.6 mg, 9.5 mg or 13.3 mg rivastigmine per 24 hours have also been produced.

Donepezil This cerebroselective and reversible anti-AChE produces measurable improvement in several cognitive as well as non-cognitive (activities of daily living) scores in AD, which is maintained upto 2 years. The benefit is ascribed to elevation of ACh level in the cortex, especially in the surviving neurones that project from basal forebrain to cerebral cortex and hippocampus. Therapeutic doses produce only weak peripheral AChE inhibition: cholinergic side effects are mild. Because of long t½ (~70 hr), donepezil is administered once daily at bed time; a distinct advantage over rivastigmine and galantamine which need twice daily dosing. Moreover, it can be used even in relatively severe case of AD. Donepezil is generally well tolerated and is not hepatotoxic.

Dose: 5 mg OD HS (max 10 mg OD); DONECEPT, DOPEZIL, DORENT 5, 10 mg tabs.

Memantine This newer NMDA receptor antagonist, related to amantadine (that is also a NMDA antagonist), has been found to slow the functional decline in moderate-to-severe AD, but benefit in milder disease is unclear.

Symptom relief is similar to or lesser than anti-AChEs. It appears to block excite toxicity of the transmitter glutamate in a noncompetitive and use-dependent manner. Beneficial effects have also been noted in parkinsonism. used in AD. Side effects are constipation, tiredness, headache, dizziness, and drowsiness. It is indicated in moderate-to-severe AD, either to replace anti-AChEs or to supplement them. Memantine can be used for other types of dementia as well.

Dose: Initially 5 mg OD, increase gradually upto 10 mg BD; stop if no clinical benefit in 6 months. ADMENTA, MENTADEM 5, 10 mg tabs, ALMANTIN 5 mg tab.

Piracetam This cyclic GABA derivative has no GABA like activity and has been called 'nootropic' meaning a drug that selectively improves efficiency of higher telencephalic integrative activities. Piracetam is not a vasodilator, does not affect total/ regional CBF, but may reduce blood viscosity. In India and some other countries it has long been promoted for cognitive impairment and dementia in the elderly as well as for mental

retardation in children. However, a Cochrane Database review (2004) has concluded that published data does not support such use. In the UK, it is approved for adjunctive treatment of cortical myoclonus, but it is not approved in the USA.

Side effects are minor: gastric discomfort, nervousness, excitement, insomnia, dizziness and skin rash.

Dose*:* 0.8–1.6 g TDS oral; children 20 mg/kg BD–TDS; 1–3 g i.m. 6 hourly in stroke/head injury; 7.2 g/day in divided doses for myoclonus.

NORMABRAIN, NEUROCETAM, NOOTROPIL 0.4 g, 0.8 g, 1.2 g. caps, 500 mg/5 ml syr., 300 mg/ml inj.

Opioid analgesics and antagonists.

Algesia (pain) is an unpleasant bodily sensation perceived as suffering, usually evoked by an external or internal noxious stimulus.

Analgesic A drug that selectively relieves pain by acting in the CNS or on peripheral pain mechanisms, without significantly altering consciousness.

OPIOID ANALGESICS

Opium A dark brown, resinous material obtained from poppy (Papaver somniferum) capsule.

It contains two types of alkaloids.

- **Phenanthrene derivatives**

Morphine (10% in opium)

Codeine (0.5% in opium)

Thebaine (0.2% in opium), (Nonanalgesic)

- **Benzoisoquinoline derivative**

Papaverine (1%)

Noscapine (6%)

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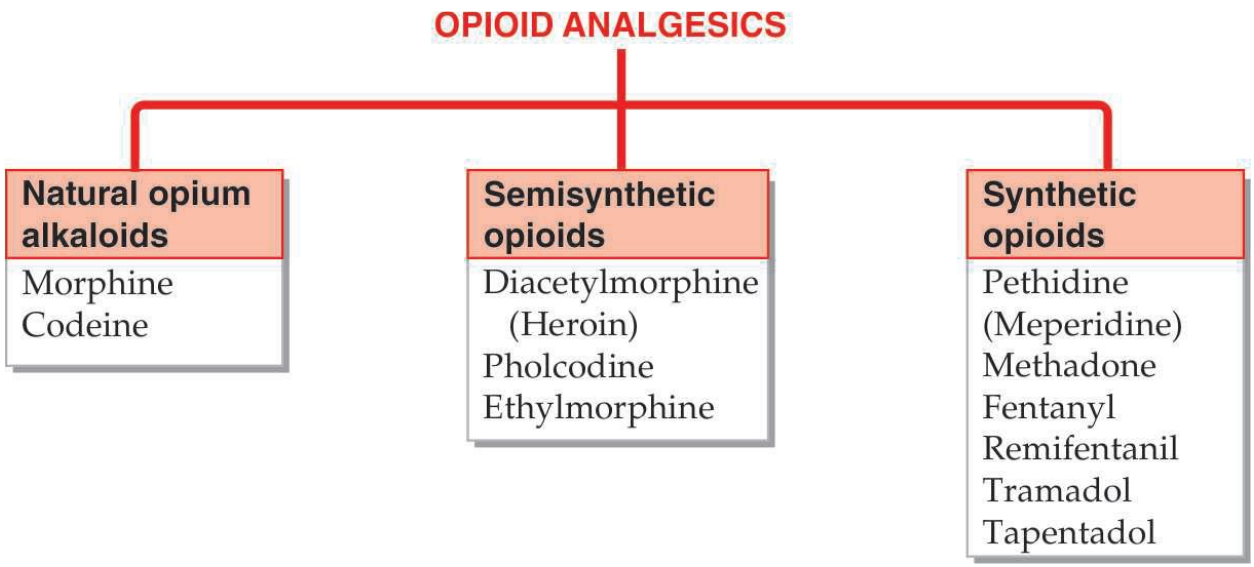


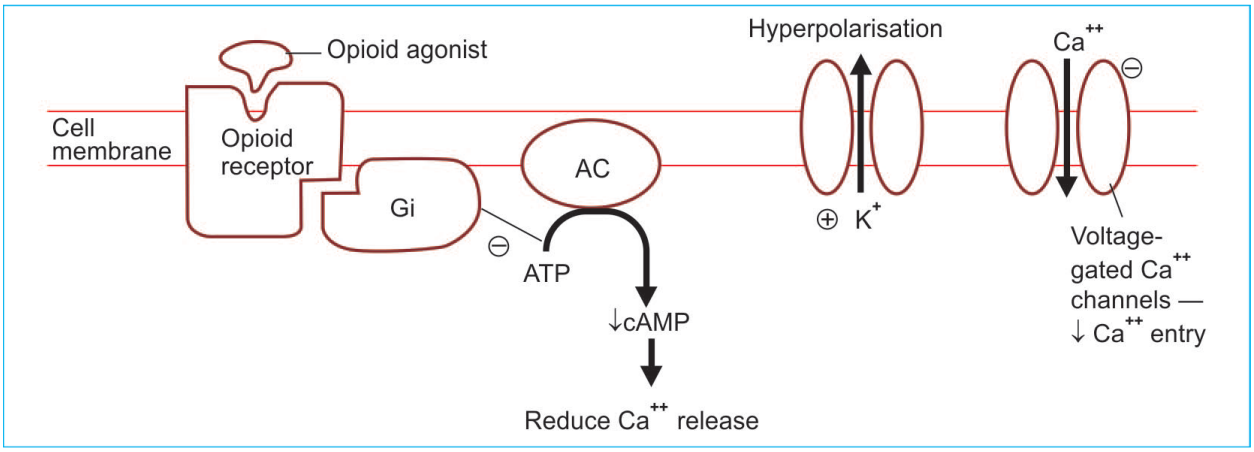
MORPHINE

Morphine is the most important alkaloid of opium. Though many new opioids with actions similar to morphine have been synthesized, none of them are superior to morphine as an analgesic. Morphine is discussed as the prototype of the group.

Mechanism of Action

1. Morphine and other opioids produce their effects by acting on specific **opioid receptors**. These receptors are abundant in the CNS and other tissues. The opioid receptors are mu, kappa and delta receptors. All opioid receptors are G-protein-coupled receptors. Stimulation of these receptors inhibits adenylate cyclase resulting in decreased intracellular cAMP formation.
2. They also facilitate the opening of K+ channels leading to hyperpolarisation.
3. In addition to this, they inhibit the opening of calcium channels. All these result in a decrease in the intracellular calcium which, in turn, decrease the release of neurotransmitters. Various neurotransmitters including dopamine, glutamate, GABA, NA, 5-HT and substance P are involved in the transmission of pain impulses.

- Opioids also directly inhibit the transmission in the dorsal horn ascending pathway.
- Opioids stimulate the descending pain control pathway—from the midbrain and brainstem to the dorsal horn of the spinal cord. Opioid receptors are abundant in these areas including the periaqueductal grey (PAG) area, substantia gelatinosa and the spinal cord.



Mechanisms of action of opioids. Opioid receptors are G-protein-coupled receptors. Stimulation of these receptors ↓ cAMP formation, ↓ K+ efflux causing hyperpolarisation and also inhibit Ca++ entry through voltage-gated Ca++ channels. AC=Adenylyl cyclase; cAMP=cyclic-AMP

Pharmacological Actions

I. Central Nervous System

1. **Analgesia:** Morphine is a potent analgesic and relieves pain without loss of consciousness. Dull aching visceral pain is relieved better than sharp pricking pain. In higher doses, it relieves even the severe pain as
that of biliary colic. Morphine alters both the perception and reaction to pain. It raises the pain threshold and thus increases the capacity to tolerate pain. Further, it alters the emotional reaction to pain. Euphoria and sedation also contribute to its analgesic effects.

2. **Euphoria, sedation and hypnosis:**
Morphine produces a feeling of well-being termed euphoria. It is this effect which makes it an important drug of abuse. Rapid intravenous injection of morphine produces a warm flushing of the skin and the lower abdomen lasting for about45 seconds which is known as 'high', 'rush' or 'kick'. The person loses rational thinking and is lost in colourful day dreams. It also produces drowsiness, a calming effect, inability to concentrate, feeling of detachment and indifference to surroundings. The effects of morphine may not be pleasurable in all. A person has to learn to perceive its pleasurable effects. It may produce dysphoria in some.

3. Pupils: Morphine produces miosis resulting in a characteristic pinpoint pupil in high doses. This is due to stimulation of (EW) nucleus of the third cranial nerve. Thus, by a central effect, it produces miosis. Hence, morphine used as eye drops does not produce miosis.

4. **Vagus:** Morphine stimulates vagal centre causing bradycardia.

5. **Heat regulation:** Opioids shift the equilibrium point of heat-regulating centre so that body temperature falls slightly.

II. Peripheral Actions

1. **Cardiovascular system:** In therapeutic doses, morphine produces hypotension by:

- Direct peripheral vasodilatation
- Inhibition of baroreceptor reflexes

In higher doses, it causes depression of the vasomotor centre and provokes histamine release—both contributing to a fall in BP. Postural hypotension and fainting may occur.

2. **GIT:** Opioids decrease the motility of the gut.

- Stomach: Gastric motility is decreased resulting in increased gastric emptying time. Oesophageal reflux may increase. Gastric acid secretion is reduced. Opioids increase the tone of the antrum and first part of the duodenum which almost 12 hr and this can retard the absorption of orally given drugs.
- Intestines: Morphine diminishes all intestinal secretions, delays digestion of food in the small intestine; resting tone is increased. There can be spasms of the intestine. The tone of the sphincters is increased leading to spasm. The intestinal motility (propulsive) is markedly diminished. The resulting delay in the passage of the intestinal contents in the large intestine, together with reduced secretions and inattention to the sensory stimuli for defaecation reflex— all contribute to produce

marked constipation. The effects of morphine on the gut are by stimulation of the □ and □ receptors in the gut.

3. **Other smooth muscles:**

• Biliary tract: Morphine causes spasm of the sphincter of Oddi. Intrabiliary pressure rises and may cause biliary colic. Atropine partly antagonises this while opioid antagonists relieve it.

Pharmacokinetics

Given orally, absorption of morphine is slow and incomplete. Morphine undergoes extensive first pass metabolism. Bioavailability is 20 to 40%. Given subcutaneously, onset of action is in 15–20 min, peak effect in 1 hr, t½ 2–3 hr and duration of action is 3–5 hr. Morphine is metabolized in the liver by glucuronide conjugation. The active metabolite morphine-6-glucuronide is more potent than morphine and is excreted through the kidneys. Morphine undergoes enterohepatic circulation. Dose: 10–50 mg oral, 10–15 mg SC/IM inj, 2–6 mg IV; 2–3 mg epidural. MORCONTIN CONTINUS—10, 30, 40, 100 mg continuous release tablets.

Adverse Effects

- Nausea,
- Vomiting,
- Drowsiness,
- Dizziness,
- Sedation,
- Mental clouding
- Respiratory depression,
- Constipation,
- Dysphoria,
- Urinary retention and
- Hypotension.

Pethidine (Meperidine)

Pethidine is a phenylpiperidine derivative of morphine. Though chemically it is very much different from morphine, many of its actions resemble that of morphine. It was accidentally found to have opioid effects when efforts were made to obtain anticholinergic drugs. When compared to morphine:

• Pethidine is 1/10th as potent as morphine (100 mg pethidine = 10 mg morphine). However, efficacy as an analgesic is equal to morphine.

• The onset of action is more rapid and duration of action is shorter.

• It produces corneal anaesthesia.

• It is not a good antitussive.

• It is less constipating, causes less urinary retention

• In some patients, it may cause dysphoria.

• It also has anticholinergic effects which can cause dry mouth, tachycardia and blurring of vision.
• Release of histamine is milder.
• May produce a negative inotropic effect.
• In toxic doses, pethidine sometimes produces CNS stimulation with tremors, restlessness and convulsions instead of sedation. This is because of the toxic metabolite—norpethidine.

Preparations dose: 25–100 mg IM/SC, PETHIDINE HCl 100 mg/2 ml inj 50, 100 mg tab.

Methadone

Methadone, a synthetic opioid, has actions similar to morphine. Its outstanding features are:
• It is an effective analgesic.
• It is effective by many routes including oral, rectal, SC, IV and spinal routes.
• It is effective in certain types of neuropathic and cancer pain which are not relieved by morphine. Methadone is therefore, now a preferred analgesic.
• It has a long duration of action (t½ 24–36 hours) and, therefore, effectively suppresses withdrawal symptoms in addicts.

Mechanism of Action

1. Methadone is a μ receptor agonist.
2. Methadone also blocks NMDA receptors.
3. Blocks mono aminergic receptor uptake transporters.

The latter two actions may be responsible for its better efficacy as an analgesic in certain types of pain. Methadone is about 90% bound to plasma proteins; it is also firmly bound to proteins in various tissues, including brain. After repeated administration, it gradually accumulates in tissues. When administration is discontinued, the drug is slowly released from the binding sites. Methadone is metabolized by microsomal enzymes like CYP3A4 in the liver. Hence, microsomal enzyme inhibition by drugs and hepatic failure can enhance blood levels of methadone. This probably accounts for its milder withdrawal symptoms.

As euphoric effects are less intense, abuse potential is less. Tolerance develops more slowly. In addicts, withdrawal symptoms are gradual in onset, less intense, but prolonged.

Dose: 10 mg oral or IM PHYSEPTONE 10 mg inj, 2 mg/5 ml Linctus.

OPIOID ANTAGONISTS

Three opioid antagonists are in use:
Naloxone
Naltrexone
Nalmefene

Naloxone acts as a competitive antagonist to all types of opioid receptors. It is a pure antagonist. In normal individuals, it does not produce any significant actions. But in opium addicts, given IV, it promptly antagonises all the actions of morphine including respiratory depression and sedation and precipitates withdrawal syndrome. It also blocks the action of endogenous opioid peptides—endorphins, enkephalins and dynorphins. It blocks the analgesia produced by placebo and acupuncture. This suggests that endogenous opioid peptides are responsible for analgesia by these techniques.

Given orally it undergoes high first pass metabolism and is metabolised by the liver.

Hence, it is given intravenously. Duration of action is 1–2 hours . It is metabolised by glucuronide conjugation.

Dose: 0.4 mg IV. NARCOTAN 0.4 mg/ml and 0.04 mg/ml Ampoules.

Uses

1. Naloxone is the drug of choice for morphine overdosage. 0.1–0.4 mg is injected intravenously. The dose should be repeated after every 1–2 hr as naloxone is short acting and respiratory depression may recur again. Constant monitoring is, therefore, required till the patient fully recovers from opioid overdosage.
2. It is also used to reverse neonatal asphyxia due to opioids used in labour.

Dose: 5–10 □g/kg repeated, if required.

3. Naloxone can also be used for the diagnosis of opioid dependence—it precipitates withdrawal symptoms.
4. Hypotension seen during shock could be due to endogenous opioids released during such stress. Naloxone has been found to be beneficial in reversing hypotension.

Naltrexone is another pure opioid antagonist.

It is:

- More potent than naloxone
- Orally effective
- Has a longer duration of action of 1–2 days.
- Naltrexone is well absorbed when given orally but undergoes first pass metabolism.

Dose 50–100 mg/day. NALTIMA 50 mg tab.

Uses

1. Naltrexone is used for ‘opioid blockade’ therapy in post-addicts is found to be effective (50–100 mg/day orally single dose or on alternate days) so that even if the addicts take an opioid, they do not experience the pleasurable effects and, therefore, lose the craving.

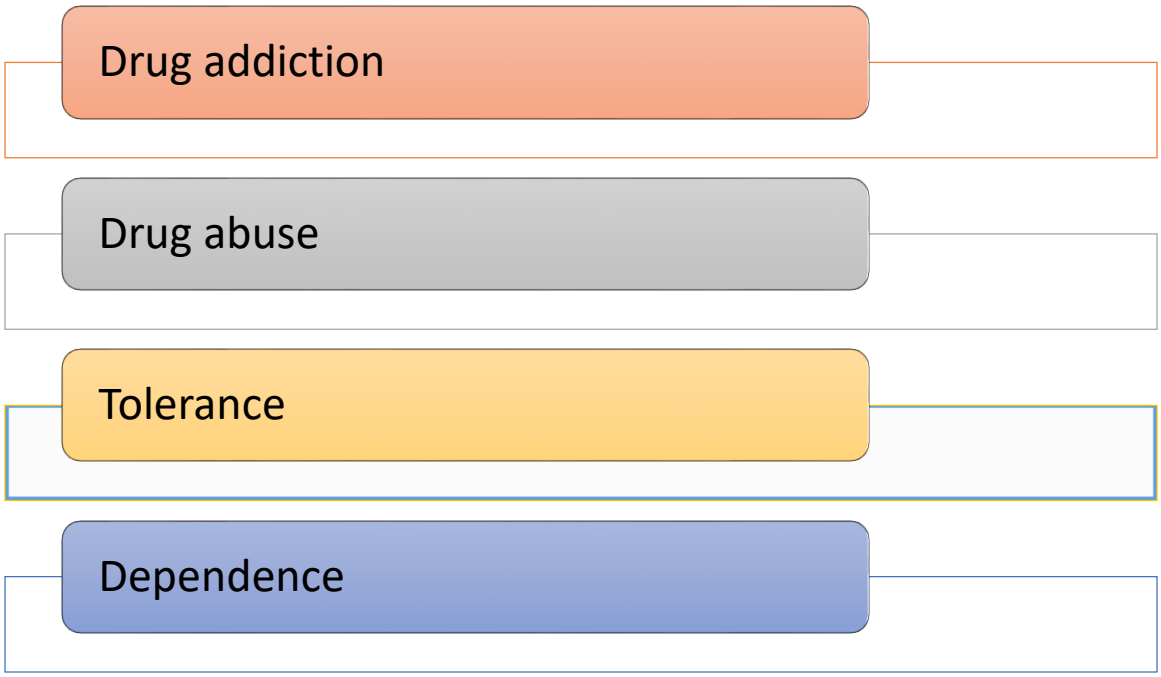
2. Alcohol craving is also reduced by naltrexone and is used to prevent relapse of heavy drinking.

Nalmefene

Nalmefene is a derivative of naltrexone. It is orally effective (but only an IV preparation is available) and longer acting. It has better bioavailability and is not hepatotoxic. It is used in opioid overdosage.

Peripheral Opioid Antagonists

1. **Methylnaltrexone and Naloxegol** are mu opioid antagonists acting peripherally and they reverse the opioid induced constipation in patients receiving long-term treatment with opioids for chronic cancer pain (0.25 mg
in the morning).
2. **Alvimopan** blocks the □ receptors in the gut and does not significantly penetrate CNS. It is used in the treatment of postoperative ileus following bowel resection.
3. **Diprenorphine, naloxonazine, naltrindole and naloxone benzoyl-hydrazone** are other opioid antagonists.


Drug addiction
Drug abuse
Tolerance
Dependence

DRUG ADDICTION: Refer in unit -1

TOLERANCE: Refer in unit -1

DEPENDENCE: Refer in unit-1

DRUG ABUSE: Drug abuse refers to the misuse or excessive use of drugs, whether they are legal or illegal substances. This misuse can lead to harmful effects on a person's physical and mental health, as well as their overall well-being. Drug abuse can result in addiction, serious health problems, social issues, and even legal consequences. It is important to seek help and support if you or someone you know is struggling with drug abuse.