ANS (Cholinergics & Anticholinergics) or Parasympathomimetics, Parasympatholytics

Autonomic Nervous System (Cholinergic)

Autonomic Nervous System consists of main 3 divisions

- Parasympathetic Nervous System (or Cholinergic)
-Sympathetic Nervous System (or Adrenergic)
- Enteric Nervous System

Parasympathetic Nervous System

Acetylcholine is the neurotransmitter at all autonomic ganglionic synapse

Hypothalamus is the major controlling centre for the parasympathetic system

Acetylcholine Receptors are Muscarinic and Nictotinic receptors

Muscarinic Receptors

The receptors are located at the para symp neuroeffector junction at all smooth muscles & glands

These are primarily divided into 5 subtypes (M_1, M_2, M_3 are most important)

M_1 Receptors (Neuronal & Gastric)

Location: Ganglia (autonomic & enteric), Gastric, Paracrine cells, CNS (cortex & hippocampus)

Function: gastric acid secretion, GI motility, CNS excitation

MOA: ↑ IP_3, ↑ DAG, Cytoplasmic Ca^{+2}, Depolarization

M_2 Receptors (Cardiac)

Location: SA node, AV node, Atrium, Ventricle, Presynaptic terminals

Function: SA node: ↓rate of impulse generation; AV node: ↓velocity of conduction, ↓contractility, vagal bradycardia

MOA: Inhibition of adenylate cyclase (↓cAMP) & opening of K^+ channels; Inhibits neuronal Ca^{+2} channels (Presynaptic inhibition of Ach release)

M_3 Receptors (Glandular)

Location: Exocrine glands, smooth muscles, vascular endothelium

Function: ↑exocrine secretions, smooth muscle contraction

MOA: ↑ IP_3, ↑ DAG, Cytoplasmic Ca^{+2}, Depolarization

Nicotinic Receptors

- These receptors are located in neuromuscular junctions & at all autonomic ganglia
- They play a facilitatory role in the release of other transmitters like Dopamine & Glutamate
- They are classified as Muscle type (N_M), Neuronal type (N_N) & Central nicotinic receptors

"Cholinomimetics" means the drugs which imitate or mimic the actions of Ach at the neuroeffector junction and also called as ***"Parasympathomimetics"***

Acetylcholine

- ACh is of no therapeutic value à due to its ultra short action (very rapidly hydrolyzed by the enzyme acetylcholinesterase present in the synaptic cleft) & secondly because of it widespread activity at all cholinergic sites throughout the body

Biosynthesis:

- ACh is synthesized in the axon terminal from Choline & Acetylcoenzyme-A by the cytosolic enzyme choline acetyltransferase

Metabolism

- ACh is hydrolyzed by an enzyme called Acetylcholinesterase to Choline & Acetic acid.
- Choline is again utilized for the biosynthesis of ACh

Acetylcholinesterase enzyme is of two types

1.*True ACh Esterase:* it is a membrane bound enzyme present in the cholinergic synaptic cleft

o It is very highly specific in hydrolyzing ACh & other acetylesters

o It is mainly localized in neuronal membrane, cholinergic synaptic cleft & to a small extent in RBS & placenta

2.*Plasma Choline Esterase (pseudo choline esterase or butyryl choline esterase):* it is synthesized in liver & found predominantly in plasma & in intestine.

o Its actions are non-specific as it hydrolyses succinyl choline, benzoylcholine & butyrylcholine esters more easily than ACh

ACTIONS

Eye

-Circular muscle of iris, ciliary muscle & lacrimal glands posses M_3 receptors

- Radial muscle of iris & eylid smooth muscles have no para symp supply
- ACh causes contraction of circular muscle of iris & ciliary muscle
- Contraction of circular muscle of iris à causes Miosis à also opens the pores of the canal of Schlemm (aided by stretching of pupil due to miosis) à which facilitates drainage of aqueous humor à better drainage reduces IOP
- Contraction of ciliary muscle à makes the suspensory ligaments of the lens loose à makes the lens more convex (by reducing its focal length) à eye's focus is accommodated for near vision
- Stimulation of M_3 receptors at lacrimal glands à produces lacrimation (due to vasodilatation)

Salivary Glands

- Salivary glands à M_3 à stimulation produces watery saliva à due to vasodilatation resulting from the release of bradykinin

Lungs

- Smooth muscle of bronchi à M_3 à stimulation causes bronchoconstriction & mucous glands à M_3 à stimulation causes more bronchial secretions

Gastro Intestinal Tract

- GIT smooth muscle à M_3 à stimulation causes increase in the motility & increase tone of the GUT smooth muscle
- Sphincters à M_3 à stimulation causes relaxation of sphincters
- Gastric glands à M_3 à stimulation causes increased secretions
- Gastric parietal cells à M_1 à stimulation promotes gastric acid secretions

Heart

- Para symp supply is only up to SA node, Atria & AV node but not below
- Ventricular myocardium has Muscarinic receptors but no innervation à can exhibit a decrease in contractile strength (only to exogenously administered ACh)
- SA node à M_2 à stimulation causes a decrease in the heart rate (negative chronotropy) & decrease in the contractile strength (negative inotropy)

- AV node à M_2 à stimulation causes a decrease in the conduction velocity & increase in the refractory period

Blood Vessels

-Arteries have no para symp innervation, but have M_3 à exogeneous cholinomimeitc cause fall in BP due to vasodilatation

- The endothelium of most blood vessels release EDRF (endothelium relaxing factors like NO & other cotransmitters) à causes vasodilatation due to M_3 activation by exogenous cholinomimetics.
- Systemic veins have neither para symp innervation nor M-receptors

Urinary Bladder

- Detrusor muscle à M_3 à stimulation causes contraction
- Sphincter à M_3 à stimulation causes relaxations
- Both these actions lead to voiding of urinary bladder

Pancreas

- Acni cells à M_3 à stimulation causes increased secretion of pancreatic juice

Male Sex Organs

- Vascular bed of erectile tissue is dilated while venous sphincters are closed leading to erection of penis (might be due to stimulation of M_3)

Sweat Glands

- Sweat glands à M_3 à stimulation causes increased sweating

Central Nervous System

- Tremors & Convulsions à due to Muscarinic effects
- Ataxia, behavioural disturbances & restlessness à due to Nicotinic effects

Classification (Parasymapathomimetics or Cholinomimetics)

Directly Acting

1.Acetylcholine

2.Synthetic Choline Esters

· Methacholine, Carbachol, Bethanechol

3.Natural Alkaloids

· Muscarine, Nicotine, Pilocarpine, Arecoline

4.Misc

· Tremorine, Oxotremorine

Indirectly Acting (Anticholinesterases)

Reversible (short to intermediate duration of action)

1.Natural Alkaloids : Physostigmine

2.Quaternary Compounds: Edrophonium, Neostigmine, Pyridostigmine, Ambenonium, Demecarium, Rivastigmine

Irreversible (long duration of action)

1.Organophosphates : Isoflurophate (DFP), Ecothiophate, Paraoxon, Parathion, Malathion, Diazinon

2.Carbamates: Propoxur

Muscarine

- It is obtained from poisonous mushrooms *Amantia muscaria*
- It crosses BBB very little because it is quaternary compound
- **Symptoms** of Mushrooms poisoning are Miosis, Sweating, Salivation, Diarrhea, increased micturation, decrease in HR (all the actions of ACh on Muscarinic receptors)

- Treatment: Parenteral administration of Atropine 1-2 mg i.m. every 30 min till symptoms subside with adequate supportive measures for respiration, circulation & pulmonary oedema
- Mushroom poisoning is also called as ***Mycetism***

Pilocarpine

- It is the chief alkaloid obtained from the leaves of the shrub *Pilocarpus jaborandi*
- It is a tertiary amine so it rapidly crosses BBB
- It has main M_3 action and mild N_N actions
- Pilocarpine is too toxic for systemic use as it produces usual effects of choline esters and pulmonary oedema
- Main therapeutic uses include
- Ophthalmic Use:

a) For the initial treatment of open angle glaucoma where it is instilled into eye as 0.5% - 0.4% solution

· Reduction in IOP occurs within few mins & lasts for 4 – 8 hrs

b) To counteract the mydriasis produced by Atropine

c)To break adhesions between the iris and the lens (as in Iridocyclitis) where it is instilled alternatively with homatropine (a mydriatic)

- As Sialagogue: Rarely, Pilocarpine (5 – 10 mg orally) is used to stimulate salivary secretions in patients after laryngeal surgery

The Pharmacological basis for the use of Pilocarpine in Glaucoma

Ans: Pilocarpine has main M_3 action à reduces IOP

- Circular muscle of iris, ciliary muscle & lacrimal glands posses M_3 receptors
- ACh causes contraction of circular muscle of iris & ciliary muscle
- Contraction of circular muscle of iris à causes Miosis à also opens the pores of the canal of Schlemm (aided by stretching of pupil due to miosis) à which facilitates drainage of aqueous humor à better drainage reduces IOP
- Contraction of ciliary muscle à makes the suspensory ligaments of the lens loose à makes the lens more convex (by reducing its focal length) à eye's focus is accommodated for near vision
- Stimulation of M_3 receptors at lacrimal glands à produces lacrimation (due to vasodilatation)

- For the initial treatment of open angle glaucoma where it is instilled into eye as 0.5% - 0.4% solution
· Reduction in IOP occurs within few mins & lasts for 4 – 8 hrs

Anticholinesterases or AChE inhibitors or Indirectly acting Parasymapthomimetics

- These drugs inhibit acetylcholinesterase (AChE) enzyme, which is present in synaptic cleft & responsible for rapid hydrolysis of ACh à so these drugs prolong the action and increase the availability of ACh at the Muscarinic and/or nicotinic receptors after its release from postganglionic parasympathetic neurons.

Reversible (Competitive) Inhibitors of AChE

- Includes: **Physostigmine, Neostigmine, Pyridostigmine, Edrphonium, Ambenonium, Demecarium & Rivastigmine**
- The reversible anticholinesterase drugs bear a structural resemblance to AChE à they combine with the anionic & esteratic sites of AChE à this complex is less readily hydrolysed than AChE-ACh complex à it results in a temporary inhibition of the enzyme (because AChE regeneration takes longer time) à prolongs the duration of action of ACh released in synaptic cleft
- Among these Edrophonium has a shorter duration of action (10min) à because, Edrophonium forms complex only at the anionic site à thereby reversibly preventing the binding of ACh with AChE
- Physostigmine is a tertiary amine à more lipid soluble à can cross BBB easily à centrally acting
- Remaing drugs are quaternary amines à less lipid soluble à can't cross BBB easily à peripheral actions

Physotigmine

- It's a tertiary amine
- It is highly lipid soluble & shows better absorption in all body components including CNS
- It acts on M_1, M_2, M_3
- It also stimulates ganglia
- Being highly toxic à only limited use

Therapeutic Uses

-Ophthalmic use

a) To counteract the effects of mydriatics after refraction testing

b) To prevent adhesions between iris & the lens or iris & cornea resulting due to irutis, iridocyclitis & corneal ulcer

c) For the treatment of Glaucoma

- In the treatment of Atropine poisoning (Belladona poisoning): Physostigmine is a specific antidote for atropine poisoning or for poisoning by any other anticholinergic drug

· Being a tertiary amine it can cross BBB easily & can antagonize central as well as peripheral toxicity

· Initially, the diagnosis is made by giving smaller doses of Physostigmine (0.5 to 1.0 mg i.m.) à if normal parasympathomimetic effects of Physostigmine (flushing, sweating, salivation, lacrimation) are not observed à it could be a case of atropine poisoning

· Treatment: Physostigmine 2mg i.v. or i.m. initially or additional doses thereafter if necessary

Myasthenia Gravis

- It is an acquired autoimmune disorder causing skeletal muscle fatiguability & weakness

-It is associated with the production of IgG antibody that binds to ACh receptors (N_M) at the post-junctional motor end plate

-The reduction in the number of receptors (N_M) results in the reduction of the amplitude of the end plate potential which in turn fails to trigger an action potential

Symptoms: weakness of the muscle & fatigue which worsens after the exercise but goes off after the rest, ptosis, diplopia, slurring of speech, difficulty in swallowing & weakness if extremities

Treatment: Treatment is started with any reversible anti AChE agent of intermediate duration of action; the main drugs which are available (any one from the following)

Neostigmine 15 – 30 mg 6 hrly orally;

Pyridostigmine 60 – 120 mg, 4 – 6 hrly orally; or

Ambenonium 5 – 25 mg 6 hrly orally

- Pyridostigmine 60 -120 mg 4 – 6 hrly orally & Prednisolone 10 mg OD or an alternate day, to be increased slowly to a maximum of 100 mg OD or alternate day

Basis: These drugs inhibit acetylcholinesterase (AChE) enzyme, which is present in synaptic cleft & responsible for rapid hydrolysis of ACh à so these drugs prolong the action and increase the availability of ACh at nicotinic receptors after its release from postganglionic parasympathetic neurons à more availability of N_M receptor

Paralytic Ileus

- ileus resulting from failure of peristalsis
- obstruction of the bowel ; specifically : a condition that is commonly marked by a painful distended abdomen, vomiting of dark or fecal matter, toxemia, and dehydration and that results when the intestinal contents back up because peristalsis fails although the lumen is not occluded
- a twisting of the intestine upon itself that causes obstruction
- **Treatment:** Neostigmine 0.5 – 1mg s.c.
- Basis: The reversible anticholinesterase drug bear a structural resemblance to AChE à it combines with the anionic & esteratic sites of AChE à this complex is less readily hydrolysed than AChE-ACh complex à it results in a temporary inhibition of the enzyme (because AChE regeneration takes longer time) à prolongs the duration of action of ACh released in synaptic cleft
- Due to the prolongation of ACh action, acts on M_3 receptors in GIT
-GIT smooth muscle à M_3 à stimulation causes increase in the motility & increase tone of the GUT smooth muscle
- Sphincters à M_3 à stimulation causes relaxation of sphincters

Urinary Bladder

- Loss of tone in urinary bladder
- Treatment: Neostigmine 0.5 – 1 mg s.c.
- Basis: The reversible anticholinesterase drug bear a structural resemblance to AChE à it combines with the anionic & esteratic sites of AChE à this complex is less readily hydrolysed than AChE-ACh complex à it results in a temporary inhibition of the enzyme (because AChE regeneration takes longer time) à prolongs the duration of action of ACh released in synaptic cleft
- Due to prolongation of duration of action of ACh causes the following actions

- Detrusor muscle à M_3 à stimulation causes contraction
- Sphincter à M_3 à stimulation causes relaxations
- Both these actions lead to voiding of urinary bladder

Post-operative Decurarization (Treatment of curare poisoning)

- Treatment: Neostigmine (0.5 - 1 mg i.v.) or Edrophonium (10 mg i.v.) along with Atropine à rapidly reverses muscle paralysis induced by d-tubocurarine given during anesthesia or by poisoning due to snake venom neurotoxin
- Prior atropinisation is more beneficial because it not only counteracts Muscarinic side effects of Neostigmine and also avoids the transient summation of bradycardia by these two drugs (atropine by blocking Presynaptic M_1 receptors on postganglionic parasymapathetic vagal nerve endings causes initial bradycardia)

Alzheimer's Disease

- Alzheimer's disease (AD) is the most prevalent form of dementia
- Marked decrease in choline acetyltransferase & loss of cholinergic neurons in brain à which account for much of the learning & memory deficit in AD
- Other neurotransmitter loss includes that of brain glutamate, dopamine, 5-HT & somatostatin
- Cholinesterase inhibitors like Rivastigmine, Tacrine, Donepezil, Galantamine are used in the treatment of AD
- These drugs block the degeneration of ACh & increase the availability of ACh in synaptic clefts
- Tacrine, a longer acting reversible anticholinesterase, can be used for palliative treatment of mild to moderate form of AD
- It is orally active & provides improvements inmemory, cognition
- Tacrine facilitates the release of ACh from cholinergic nerve endings
- Rivastigmine, Donepezil, Galantamine are newer anticholinesterases having better penetration into CNS
- These are less toxic and better tolerated

Irreversible inhibitors of AChE

- Organophosphorus compounds: **Diflos (DFP), Ecothiophate, Parathion, Malathion, Diazinon**
- Carbamate derivatives: **Proposure, Carbaryl**
- These drugs are pentavalent containing a labile fluoride group or a labile organic group
- These drugs are irreversible blockers because they phosphorylate the esteratic site of AChE irreversible by forming a covalent bond à during this, the labile group is released leaving the remaining part of the drug molecule attached covalently with the esteratic site of AChE through its phosphorus atom à AChE becomes inactive & complex becomes very stable (resistant to hydrolysis) due to covalent bonding)
- The phosphorylated AChE enzyme undergo a rapid process of "ageing"
- Ageing means that within a period of 1 – 2 hrs, AChE – drug complex undergoes molecular rearrangement & becomes completely resistant to hydrolysis (i.e. no reactivation of AChE)
- The ageing is due to the loss of one alkyl or one alkoxy group, leaving a much more stable monoalkyl or monoalkoxyl-phosphoryl-AChE complex

Pharmacological Effects (Symptoms of poisoning)

- These drugs are volatile non-polar substances of very high lipid solubility à they are rapidly absorbed through mucous membranes & unbroken skin
- Symptoms are manifested as combination of Muscarinic, Nicotinic and CNS side effects

1. ***Muscarinic toxic manifestations:*** Diarrhea, urination, miosis, bronchoconstriction, lacrimation, salivation, sweating, bradycardia & hypotension

2. ***Nicotinic toxic manifestations:*** Fasciculations of skeletal muscles leading to paralysis

3. ***CNS toxic manifestations:*** Restlessness, tremors, convulsions, ataxia & respiratory arrest

Treatment of Organophosphorus Poisoning

- Decontamination measures such as thorough cleaning of skin, giving bath using copious amount of water & soap with special attention to hair, nail & eyes. Remove contaminated clothes
- Atropine sulfate 2 mg i.v is the mainstay of treatment. It is repeated every 15 min until full atropinization occurs i.e dilation of pupils take place & all the Muscarinic symptoms & signs are reversed

- Atropine is then given as maintenance dose at 12 hourly interval depending upon severity condition
- Pralidoxime (2 PAM) which is a cholinesterase reactivator should be given within 24 – 48 hr (if it is not given promptly aging of enzyme occurs & reactivation does not occur after poisoning
- The dose is 1 – 2 gm dissolved in 250 ml of 5% glucose solution & injected over 15 – 30 min
- It relieves the nicotinic effects (muscle weakness, twitching & respiratory depression & also Muscarinic effects of organophosphorus poisoning
- Pralidoxime is hazardous in poisoning by carbamate insecticides
- Other measures: keep the airway clear, start mechanically assisted pulmonary ventilation, give gastric lavage with activated charcoal
- Lastly observe the patient closely for at least 72 hrs with constant monitoring of cardiac & pulmonary functions

Manifestations of Ageing

- Delayed neurotoxicity in the form of severe polyneuritis, ataxia, reduced tendon reflex, weakness & ultimately flaccid paralysis
- No specific therapy is known
- Pralidoxime has most marked action at skeletal neuromuscular junction & almost insignificant effect in CNS & autonomic effector sites

Basis of Pralidoxime in Organophosphorus poisoning

1.Organophosphoruscompounds phosphorylate the esteratic site of AChE irreversible by forming a covalent bond à during this, the labile group is released leaving the remaining part of the drug molecule attached covalently with the esteratic site of AChE through its phosphorus atom à AChE becomes inactive & complex becomes very stable

2.Pralidoxime reactivates the enzyme AChE by attaching with the anionic site which lies vacant in the phosphorylated enzyme

3.Oxime group in the Pralidoxime is closer to phosphorylated esteratic site, attracts phosphate group (phosphate transfer to –NOH group of 2-PAM) à the oxime-phosphate complex diffuses out, leaving the regenerated AChE enzyme in an active form

- All oximes are ineffective as antidotes if poisoning has occurred due to carbamate group of anti-AChE drugs (e.g., Propoxur)
- Carbamates attach themselves with anionic site is not free for attachment to Pralidoxime which is prerequisite for their mode of action

Antimuscarinic Drugs or Anticholinergics

- Anticholinergic includes both Antimuscarinic and Antinicotinic drugs

Classification of Antimuscarinic Drugs

1. Natural alkaloids

- Atropine (dl-hyoscyamine)
- Scopolamine (l-hyoscine)

2. Semi synthetic derivatives: Homatropine, Atropine methionitrate, Hyoscine methylbromide, Anisotropine, Benatropine, Ipratropium bromide, Tiotropium bromide

3. Synthetic derivatives

a) Tertiary amines: Eucatropine, Cyclopentolate, Tropicamide, Dicyclomine, Flavoxate, Oxybutinin, Pirenzepine, Telenzepine, Trihexyphenidyl, Procyclidine, Biperiden

b) Quaternary amines: Propantheline, Methantheline, Oxyphenonium, Glycopyrrolate, Clidinium, Isopropamide, Pipenzolate methylbromide

4. Miscellaneous group of drugs possessing anti-muscarinic effects

- Antihistamines: Diphenhydramine, Promethazine, Orphenadrine
- Phenothiazine group of antipsychotics: Chlorpromazine, Thioridazine
- Butyrophenone group of anipsychotics: Haloperidol
- Tricyclic antidepressants: Amitriptyline, Imipramine

Pharmacokinetics

- Absorption: these drugs are well absorbed from the gut & across the conjuctival membrane
- Distribution: except quaternary compounds, rest of the drugs gets widely distributed in all body compartments. Scopolamine is rapidly & fully distributed in CNS & has greater effects
- Metabolism: 50% atropine & 80% of scopolamine is metabolized by liver as conjugates
- Excretion: 50% of atropine is excreted unchanged through urine, $t_{1/2}$ is 3 hrs

Pharmacological Actions

- Sensitiveness of different smooth muscles & glands toward atropine action

Sweat, Bronchial & Salivary glands >> Heart & Eye >> Bladder & GIT >> Gastric glands

<u>Central Nervous System</u>

- Scopolamine has the greater permeability through BBB
- Atropine has effect on CNS only in higher doses & toxic doses
- In higher doses à stimulates higher cerebral centres
- In toxic doses à central excitation & leading to restlessness, irritability, disorientation, hallucinations & delirium
- With still large doses, the stimulation followed by depression leading to circulatory collapse, paralysis, coma & respiratory failure leading to death
- Scopolamine in therapeutic doses produces drowsiness, amnesia, fatigue, dreamless sleep (with reduction in REM sleep) & depression of vomiting centre by suppressing vestibular excitation
- In toxic doses, it causes agitation, excitement & hallucinations
- Still higher dose à stimulation is followed by depression leading to coma & respiratory failure

<u>Eye</u>

- They block M_3 receptors in papillary constrictor muscle à produces mydriasis
- The normal papillary responses being blocked, the eyes become unresponsiveness to light (loss of light reflex)

- They also block M_3 receptors at the ciliary muscle of lens à the suspensory ligaments get tightened resulting in flattening of the lens (i.e. becomes less convex) à eye set for distant vision à this effect is termed as paralysis of accommodation or "Cycloplegia"
- Both mydriasis & cycloplegia à precipitates rise in IOP in elderly persons or in individuals with shallow anterior chambers or with narrow angle glaucoma à this effect is due to falling of iris back over the canal of Schlemm which obstructs the drainage of aqueous humor
- They also blocks M_3 receptors at lacrimal glands à decrease in lacrimation à dry or sandy eyes

Cardio Vascular System

- In clinical doses, Atropine causes a transient bradycardia initially à due to M_1 antagonism
- Further dose leads Tachycardia à due to M_2 antagonism on the SA node
- Higher doses of atropine à dilates cutaneous blood vessels especially in face

Respiratory System

- Atropine decreases the secretions of nose, mouth, pharynx & bronchi à dry the mucus membrane of respiratory tract
- Also reduce the laryngospasm during General Anesthesia
- Drying of mucus secretions & suppression of mucociliary clearance à leads to formation of mucus plugs in patients with airway diseases à obstruct the air flow à predispose the patient to infection
- Ipatropium antagonize bronchoconstriction induced by histamine, bradykinin & $PGF_2\alpha$ à they block the indirect effects of inflammatory mediators that are released during the attacks of asthma
- Besides, these drugs have lesser drying effects on sputum (no risk of forming mucus plugs) & don't inhibit mucociliary movements

Gastro Intestinal Tract

- These drugs reduce the basal secretions (fasting phase) than intestinal phase secretions (secretions stimulated due to food, nicotine or alcohol) [M_1 & M_3 antagonism]

- They reduce the tone & motility of the gut from stomach to colon à prolongation of gastric emptying time, closure of sphincters, decrease in tone, amplitude & frequency of peristaltic movements [M_3 antagonism]
- They also posses spasmolytic activity à hey relax the gut in absence as well as in the presence of cholinoceptor stimulants
- These drugs also relax the bile duct & gall bladder

Genitourinary Tract

- They relax the smooth muscles of ureters & urinary bladed wall à voiding is slowed (urinary retention)

Sweat glands

- They cause decrease in sweating à skin becomes dry and hot (rise in body temperature occurs only in higher doses) à Atropine fever

Therapeutic Uses

Motion Sickness

- Scopolamine (0.6mg – 1.0mg s.c.) is effective in motion sickness caused during landing & takeoff by an aero plane or while traveling on a ship or traveling high altitude

Basis: during landing & takeoff by an aero plane or while traveling on a ship or traveling high altitude à due to disparity between sensory inputs received from non-vestibular proprioceptors *(muscle spindle, Golgi tendon organs & deep connective tissue receptors)* & vision as well as sensory outputs from vestibular apparatus to cerebellum. à results in dizziness, loss of balance, nausea and vomiting

- Diphenhydramine, Cyclizine or Meclizine à prevention of Motion sickness & for treatment of vertigo due to labyrinth dysfunction
- Cinnarizine à antivertigo drug à also used for the prevention of Motion sickness à its antihistaminic, anticholinergic, antiserotonin & Ca^{+2} channel blocking à by inhibiting the influx of Ca^{+2} from endolymph into the vestibular apparatus à blocks labyrinthine reflexes

Parkinson's disease

- Tremors & rigidity associated with Parkinson's disease seem o result from the relative dominance of cholinergic activity in the basal ganglia
- The combination of Antimuscarinic drug with a dopaminergic drug provides more effective-
§ Muscarinic receptors antagonists are used to treat the extrapyramidal side effects
- The centrally acting anticholinergic drugs are
- Benzotropine (1-5 mg/day)
- Benzhexol (2-10mg/day)
- Procyclidine (5-15mf/day)

Diagnosis of Alzheimer's Disease

- Tropicamide is used to diagnosis the AD (it is instilled in the eyes of patient with suspected AD has been found to exhibit unexpectedly marked dilatation of the pupil à due to changes in receptor sensitivity associated with the disease)

Lie detector

- Hyoscine with morphine produces twilight sleep with amnesia during labour
- It was famous as lie detector agent during World War – II as it produces sedation with amnesia

As Mydriatic

- During the Ophthalmoscopic examination of the retina

To prevent the adhesions in inflammatory conditions

- They are used along with miotics to prevent adhesions between the iris & the anterior surface of the lens as in iridocyclitis, iritis or uveitis

Bronchial Asthma & COPD

- Chronic Obstructive Pulmonary Disease (COPD) à where cholinergic tone is more important contributory factor
- Ipatropium reduces bronchial secretions, least drying effect n sputum, do not interfere with mucociliary clearance & cause bronchodilatation à so they are preferred in COPD

- Ipatropium can be given with β2 agonist it the treatment of Asthma due to longer bronchodilator activity

Preanesthetic Medication

- To reduce bronchial secretions (which is contributory factor in producing laryngospasm) & to prevent excessive vagal effect on heart
- But now a days no body using these drugs
- Scopolamine has an advantage because of its CNS depressants effects (amnesia & tranquillisation)
- Glycopyrolate causes less tachycardia & reduces bronchial , salivary secretions à so it is preferred in preanesthetic medication

Peptic Ulcer

- Propranthelin & Glycopyrolate were more preferred because they don't cross the BBB & less side effects
- These drugs reduce the basal secretions (fasting phase) [M_1 & M_3 antagonism]
- These drugs are not useful in the management of gastric ulcers as they increase the gastric emptying time à prolong the exposure of the ulcer bed to gastric acid
- Pirenzepine & Telenzepine are selective M_1 antagonists
- They are used along with other drugs in the management of peptic ulcer

Antispasmodics

- Methylatropine, Hyoscine methylbromide, Dicyclomine, Propantheline are used in the conditions of hypermotiliy of the gut as in intestinal colic, traveler's diarrhea, irritable bowel syndrome, mild dysentery
- These drugs are also used for the treatment of Biliary colic

To reduce excessive salivation

- These are used to reduce the excessive salivation associated with heavy metal poisoning or parkinsonism

Therapeutic uses related with Genitourinary tract

- Dicyclomine & Oxybutinin are used in the treatment of renal colic & to relieve urethral smooth muscle spasm
- Oxybutinin improves the bladder capacity
- Flavoxate, a directly acting smooth muscle relaxant à which anticholinergic drug used in in urinary incontinence & for suprapubic pain in cystitis & urethritis

Miscellaneous Uses

- Treatment of Mushroom poisoning
- Treatment of Muscarinic side effects of neostigmine
- Treatment of Organophosphorus poisoning along with AChE reactivating drugs

Adverse Effects & Toxicity

Most common side effects are

o Dryness of mouth

o Blurred vision & photophobia

o Constipation

o Urinary retention

o Decreased sweating

o Precipitation of glaucoma

Toxicity occurs due to overdosing (above 80 mg orally)

Symptoms of poisoning (Atropine Poisoning)

o Dry skin (as dry as bone)

o Hyperpyrexia

o Flushing of face (as red as beet)

o Mydriasis

o Photophobia (as blind as bat)

o Dry mouth

o Slurred speech

o Difficulty in micturation

o Confusion, delirium

o Hallucinations (as mad as hen)

o Tachycardia

Treatment (Atropine Poisoning)

- The right antidote is Physostigmine (1 – 4 mg slowly i.v every 2 hourly) till satisfactory Muscarinic blockade produced by atropine is countered or overcome

- Basis: Physostigmine is a reversible anticholesterase & chemically a tertiary amine à crosses BBB & indirectly increase the concentration of ACh à it can competitively overcome the antagonistic effect of atropine at Muscarinic & nicotinic receptors all over the body including in CNS

- Other measures-§ Control of hyperpyrexia by cold sponging, artificial respiration, oxygen by facemask

- Removal of unabsorbed drug by gastric lavage & putting universal antidote in stomach

- To control excitement & convulsion, give diazepam 2 mg i.m.

ANS (Cholinergics & Anticholinergics) or Parasympathomimetics, Parasympatholytics

Autonomic Nervous System (Cholinergic)

Autonomic Nervous System consists of main 3 divisions

- Parasympathetic Nervous System (or Cholinergic)
-Sympathetic Nervous System (or Adrenergic)
- Enteric Nervous System

Parasympathetic Nervous System

Acetylcholine is the neurotransmitter at all autonomic ganglionic synapse

Hypothalamus is the major controlling centre for the parasympathetic system

Acetylcholine Receptors are Muscarinic and Nictotinic receptors

Muscarinic Receptors

The receptors are located at the para symp neuroeffector junction at all smooth muscles & glands

These are primarily divided into 5 subtypes (M_1, M_2, M_3 are most important)

M_1 Receptors (Neuronal & Gastric)

Location: Ganglia (autonomic & enteric), Gastric, Paracrine cells, CNS (cortex & hippocampus)

Function: gastric acid secretion, GI motility, CNS excitation

MOA: ↑ IP_3, ↑ DAG, Cytoplasmic Ca^{+2}, Depolarization

M_2 Receptors (Cardiac)

Location: SA node, AV node, Atrium, Ventricle, Presynaptic terminals

Function: SA node: ↓rate of impulse generation; AV node: ↓velocity of conduction, ↓contractility, vagal bradycardia

MOA: Inhibition of adenylate cyclase (↓cAMP) & opening of K^+ channels; Inhibits neuronal Ca^{+2} channels (Presynaptic inhibition of Ach release)

M_3 Receptors (Glandular)

Location: Exocrine glands, smooth muscles, vascular endothelium

Function: ↑exocrine secretions, smooth muscle contraction

MOA: ↑ IP_3, ↑ DAG, Cytoplasmic Ca^{+2}, Depolarization

Nicotinic Receptors

- These receptors are located in neuromuscular junctions & at all autonomic ganglia
- They play a facilitatory role in the release of other transmitters like Dopamine & Glutamate
- They are classified as Muscle type (N_M), Neuronal type (N_N) & Central nicotinic receptors

"Cholinomimetics" means the drugs which imitate or mimic the actions of Ach at the neuroeffector junction and also called as ***"Parasympathomimetics"***

Acetylcholine

- ACh is of no therapeutic value à due to its ultra short action (very rapidly hydrolyzed by the enzyme acetylcholinesterase present in the synaptic cleft) & secondly because of it widespread activity at all cholinergic sites throughout the body

Biosynthesis:

- ACh is synthesized in the axon terminal from Choline & Acetylcoenzyme-A by the cytosolic enzyme choline acetyltransferase

Metabolism

- ACh is hydrolyzed by an enzyme called Acetylcholinesterase to Choline & Acetic acid.
- Choline is again utilized for the biosynthesis of ACh

Acetylcholinesterase enzyme is of two types

1.*True ACh Esterase:* it is a membrane bound enzyme present in the cholinergic synaptic cleft

o It is very highly specific in hydrolyzing ACh & other acetylesters

o It is mainly localized in neuronal membrane, cholinergic synaptic cleft & to a small extent in RBS & placenta

2.*Plasma Choline Esterase (pseudo choline esterase or butyryl choline esterase):* it is synthesized in liver & found predominantly in plasma & in intestine.

o Its actions are non-specific as it hydrolyses succinyl choline, benzoylcholine & butyrylcholine esters more easily than ACh

ACTIONS

Eye

-Circular muscle of iris, ciliary muscle & lacrimal glands posses M_3 receptors

- Radial muscle of iris & eylid smooth muscles have no para symp supply
- ACh causes contraction of circular muscle of iris & ciliary muscle
- Contraction of circular muscle of iris à causes Miosis à also opens the pores of the canal of Schlemm (aided by stretching of pupil due to miosis) à which facilitates drainage of aqueous humor à better drainage reduces IOP
- Contraction of ciliary muscle à makes the suspensory ligaments of the lens loose à makes the lens more convex (by reducing its focal length) à eye's focus is accommodated for near vision
- Stimulation of M_3 receptors at lacrimal glands à produces lacrimation (due to vasodilatation)

Salivary Glands

- Salivary glands à M_3 à stimulation produces watery saliva à due to vasodilatation resulting from the release of bradykinin

Lungs

- Smooth muscle of bronchi à M_3 à stimulation causes bronchoconstriction & mucous glands à M_3 à stimulation causes more bronchial secretions

Gastro Intestinal Tract

- GIT smooth muscle à M_3 à stimulation causes increase in the motility & increase tone of the GUT smooth muscle
- Sphincters à M_3 à stimulation causes relaxation of sphincters
- Gastric glands à M_3 à stimulation causes increased secretions
- Gastric parietal cells à M_1 à stimulation promotes gastric acid secretions

Heart

- Para symp supply is only up to SA node, Atria & AV node but not below
- Ventricular myocardium has Muscarinic receptors but no innervation à can exhibit a decrease in contractile strength (only to exogenously administered ACh)
- SA node à M_2 à stimulation causes a decrease in the heart rate (negative chronotropy) & decrease in the contractile strength (negative inotropy)

- AV node à M_2 à stimulation causes a decrease in the conduction velocity & increase in the refractory period

Blood Vessels

-Arteries have no para symp innervation, but have M_3 à exogeneous cholinomimeitc cause fall in BP due to vasodilatation

- The endothelium of most blood vessels release EDRF (endothelium relaxing factors like NO & other cotransmitters) à causes vasodilatation due to M_3 activation by exogenous cholinomimetics.
- Systemic veins have neither para symp innervation nor M-receptors

Urinary Bladder

- Detrusor muscle à M_3 à stimulation causes contraction
- Sphincter à M_3 à stimulation causes relaxations
- Both these actions lead to voiding of urinary bladder

Pancreas

- Acni cells à M_3 à stimulation causes increased secretion of pancreatic juice

Male Sex Organs

- Vascular bed of erectile tissue is dilated while venous sphincters are closed leading to erection of penis (might be due to stimulation of M_3)

Sweat Glands

- Sweat glands à M_3 à stimulation causes increased sweating

Central Nervous System

- Tremors & Convulsions à due to Muscarinic effects
- Ataxia, behavioural disturbances & restlessness à due to Nicotinic effects

Classification (Parasymapathomimetics or Cholinomimetics)

Directly Acting

1.Acetylcholine

2.Synthetic Choline Esters

· Methacholine, Carbachol, Bethanechol

3.Natural Alkaloids

· Muscarine, Nicotine, Pilocarpine, Arecoline

4.Misc

· Tremorine, Oxotremorine

Indirectly Acting (Anticholinesterases)

Reversible (short to intermediate duration of action)

1.Natural Alkaloids : Physostigmine

2.Quaternary Compounds: Edrophonium, Neostigmine, Pyridostigmine, Ambenonium, Demecarium, Rivastigmine

Irreversible (long duration of action)

1.Organophosphates : Isoflurophate (DFP), Ecothiophate, Paraoxon, Parathion, Malathion, Diazinon

2.Carbamates: Propoxur

Muscarine

- It is obtained from poisonous mushrooms *Amantia muscaria*
- It crosses BBB very little because it is quaternary compound
- **Symptoms** of Mushrooms poisoning are Miosis, Sweating, Salivation, Diarrhea, increased micturation, decrease in HR (all the actions of ACh on Muscarinic receptors)

- Treatment: Parenteral administration of Atropine 1-2 mg i.m. every 30 min till symptoms subside with adequate supportive measures for respiration, circulation & pulmonary oedema
- Mushroom poisoning is also called as ***Mycetism***

Pilocarpine

- It is the chief alkaloid obtained from the leaves of the shrub *Pilocarpus jaborandi*
- It is a tertiary amine so it rapidly crosses BBB
- It has main M_3 action and mild N_N actions
- Pilocarpine is too toxic for systemic use as it produces usual effects of choline esters and pulmonary oedema
- Main therapeutic uses include
- Ophthalmic Use:

a) For the initial treatment of open angle glaucoma where it is instilled into eye as 0.5% - 0.4% solution

· Reduction in IOP occurs within few mins & lasts for 4 – 8 hrs

b) To counteract the mydriasis produced by Atropine

c)To break adhesions between the iris and the lens (as in Iridocyclitis) where it is instilled alternatively with homatropine (a mydriatic)

- As Sialagogue: Rarely, Pilocarpine (5 – 10 mg orally) is used to stimulate salivary secretions in patients after laryngeal surgery

The Pharmacological basis for the use of Pilocarpine in Glaucoma

Ans: Pilocarpine has main M_3 action à reduces IOP

- Circular muscle of iris, ciliary muscle & lacrimal glands posses M_3 receptors
- ACh causes contraction of circular muscle of iris & ciliary muscle
- Contraction of circular muscle of iris à causes Miosis à also opens the pores of the canal of Schlemm (aided by stretching of pupil due to miosis) à which facilitates drainage of aqueous humor à better drainage reduces IOP
- Contraction of ciliary muscle à makes the suspensory ligaments of the lens loose à makes the lens more convex (by reducing its focal length) à eye's focus is accommodated for near vision
- Stimulation of M_3 receptors at lacrimal glands à produces lacrimation (due to vasodilatation)

- For the initial treatment of open angle glaucoma where it is instilled into eye as 0.5% - 0.4% solution
· Reduction in IOP occurs within few mins & lasts for 4 – 8 hrs

Anticholinesterases or AChE inhibitors or Indirectly acting Parasymapthomimetics

- These drugs inhibit acetylcholinesterase (AChE) enzyme, which is present in synaptic cleft & responsible for rapid hydrolysis of ACh à so these drugs prolong the action and increase the availability of ACh at the Muscarinic and/or nicotinic receptors after its release from postganglionic parasympathetic neurons.

Reversible (Competitive) Inhibitors of AChE

- Includes: **Physostigmine, Neostigmine, Pyridostigmine, Edrphonium, Ambenonium, Demecarium & Rivastigmine**
- The reversible anticholinesterase drugs bear a structural resemblance to AChE à they combine with the anionic & esteratic sites of AChE à this complex is less readily hydrolysed than AChE-ACh complex à it results in a temporary inhibition of the enzyme (because AChE regeneration takes longer time) à prolongs the duration of action of ACh released in synaptic cleft
- Among these Edrophonium has a shorter duration of action (10min) à because, Edrophonium forms complex only at the anionic site à thereby reversibly preventing the binding of ACh with AChE
- Physostigmine is a tertiary amine à more lipid soluble à can cross BBB easily à centrally acting
- Remaing drugs are quaternary amines à less lipid soluble à can't cross BBB easily à peripheral actions

Physotigmine

- It's a tertiary amine
- It is highly lipid soluble & shows better absorption in all body components including CNS
- It acts on M_1, M_2, M_3
- It also stimulates ganglia
- Being highly toxic à only limited use

Therapeutic Uses

-Ophthalmic use

a) To counteract the effects of mydriatics after refraction testing

b) To prevent adhesions between iris & the lens or iris & cornea resulting due to irutis, iridocyclitis & corneal ulcer

c) For the treatment of Glaucoma

- In the treatment of Atropine poisoning (Belladona poisoning): Physostigmine is a specific antidote for atropine poisoning or for poisoning by any other anticholinergic drug

· Being a tertiary amine it can cross BBB easily & can antagonize central as well as peripheral toxicity

· Initially, the diagnosis is made by giving smaller doses of Physostigmine (0.5 to 1.0 mg i.m.) à if normal parasympathomimetic effects of Physostigmine (flushing, sweating, salivation, lacrimation) are not observed à it could be a case of atropine poisoning

· Treatment: Physostigmine 2mg i.v. or i.m. initially or additional doses thereafter if necessary

Myasthenia Gravis

- It is an acquired autoimmune disorder causing skeletal muscle fatiguability & weakness

-It is associated with the production of IgG antibody that binds to ACh receptors (N_M) at the post-junctional motor end plate

-The reduction in the number of receptors (N_M) results in the reduction of the amplitude of the end plate potential which in turn fails to trigger an action potential

Symptoms: weakness of the muscle & fatigue which worsens after the exercise but goes off after the rest, ptosis, diplopia, slurring of speech, difficulty in swallowing & weakness if extremities

Treatment: Treatment is started with any reversible anti AChE agent of intermediate duration of action; the main drugs which are available (any one from the following)

Neostigmine 15 – 30 mg 6 hrly orally;

Pyridostigmine 60 – 120 mg, 4 – 6 hrly orally; or

Ambenonium 5 – 25 mg 6 hrly orally

- Pyridostigmine 60 -120 mg 4 – 6 hrly orally & Prednisolone 10 mg OD or an alternate day, to be increased slowly to a maximum of 100 mg OD or alternate day

Basis: These drugs inhibit acetylcholinesterase (AChE) enzyme, which is present in synaptic cleft & responsible for rapid hydrolysis of ACh à so these drugs prolong the action and increase the availability of ACh at nicotinic receptors after its release from postganglionic parasympathetic neurons à more availability of N_M receptor

Paralytic Ileus

- ileus resulting from failure of peristalsis
- obstruction of the bowel ; specifically : a condition that is commonly marked by a painful distended abdomen, vomiting of dark or fecal matter, toxemia, and dehydration and that results when the intestinal contents back up because peristalsis fails although the lumen is not occluded
- a twisting of the intestine upon itself that causes obstruction
- **Treatment:** Neostigmine 0.5 – 1mg s.c.
- Basis: The reversible anticholinesterase drug bear a structural resemblance to AChE à it combines with the anionic & esteratic sites of AChE à this complex is less readily hydrolysed than AChE-ACh complex à it results in a temporary inhibition of the enzyme (because AChE regeneration takes longer time) à prolongs the duration of action of ACh released in synaptic cleft
- Due to the prolongation of ACh action, acts on M_3 receptors in GIT
-GIT smooth muscle à M_3 à stimulation causes increase in the motility & increase tone of the GUT smooth muscle
- Sphincters à M_3 à stimulation causes relaxation of sphincters

Urinary Bladder

- Loss of tone in urinary bladder
- Treatment: Neostigmine 0.5 – 1 mg s.c.
- Basis: The reversible anticholinesterase drug bear a structural resemblance to AChE à it combines with the anionic & esteratic sites of AChE à this complex is less readily hydrolysed than AChE-ACh complex à it results in a temporary inhibition of the enzyme (because AChE regeneration takes longer time) à prolongs the duration of action of ACh released in synaptic cleft
- Due to prolongation of duration of action of ACh causes the following actions

- Detrusor muscle à M_3 à stimulation causes contraction
- Sphincter à M_3 à stimulation causes relaxations
- Both these actions lead to voiding of urinary bladder

Post-operative Decurarization (Treatment of curare poisoning)

- Treatment: Neostigmine (0.5 - 1 mg i.v.) or Edrophonium (10 mg i.v.) along with Atropine à rapidly reverses muscle paralysis induced by d-tubocurarine given during anesthesia or by poisoning due to snake venom neurotoxin
- Prior atropinisation is more beneficial because it not only counteracts Muscarinic side effects of Neostigmine and also avoids the transient summation of bradycardia by these two drugs (atropine by blocking Presynaptic M_1 receptors on postganglionic parasymapathetic vagal nerve endings causes initial bradycardia)

Alzheimer's Disease

- Alzheimer's disease (AD) is the most prevalent form of dementia
- Marked decrease in choline acetyltransferase & loss of cholinergic neurons in brain à which account for much of the learning & memory deficit in AD
- Other neurotransmitter loss includes that of brain glutamate, dopamine, 5-HT & somatostatin
- Cholinesterase inhibitors like Rivastigmine, Tacrine, Donepezil, Galantamine are used in the treatment of AD
- These drugs block the degeneration of ACh & increase the availability of ACh in synaptic clefts
- Tacrine, a longer acting reversible anticholinesterase, can be used for palliative treatment of mild to moderate form of AD
- It is orally active & provides improvements inmemory, cognition
- Tacrine facilitates the release of ACh from cholinergic nerve endings
- Rivastigmine, Donepezil, Galantamine are newer anticholinesterases having better penetration into CNS
- These are less toxic and better tolerated

Irreversible inhibitors of AChE

- Organophosphorus compounds: **Diflos (DFP), Ecothiophate, Parathion, Malathion, Diazinon**
- Carbamate derivatives: **Proposure, Carbaryl**
- These drugs are pentavalent containing a labile fluoride group or a labile organic group
- These drugs are irreversible blockers because they phosphorylate the esteratic site of AChE irreversible by forming a covalent bond à during this, the labile group is released leaving the remaining part of the drug molecule attached covalently with the esteratic site of AChE through its phosphorus atom à AChE becomes inactive & complex becomes very stable (resistant to hydrolysis) due to covalent bonding)
- The phosphorylated AChE enzyme undergo a rapid process of "ageing"
- Ageing means that within a period of 1 – 2 hrs, AChE – drug complex undergoes molecular rearrangement & becomes completely resistant to hydrolysis (i.e. no reactivation of AChE)
- The ageing is due to the loss of one alkyl or one alkoxy group, leaving a much more stable monoalkyl or monoalkoxyl-phosphoryl-AChE complex

Pharmacological Effects (Symptoms of poisoning)

- These drugs are volatile non-polar substances of very high lipid solubility à they are rapidly absorbed through mucous membranes & unbroken skin
- Symptoms are manifested as combination of Muscarinic, Nicotinic and CNS side effects

1. ***Muscarinic toxic manifestations:*** Diarrhea, urination, miosis, bronchoconstriction, lacrimation, salivation, sweating, bradycardia & hypotension

2. ***Nicotinic toxic manifestations:*** Fasciculations of skeletal muscles leading to paralysis

3. ***CNS toxic manifestations:*** Restlessness, tremors, convulsions, ataxia & respiratory arrest

Treatment of Organophosphorus Poisoning

- Decontamination measures such as thorough cleaning of skin, giving bath using copious amount of water & soap with special attention to hair, nail & eyes. Remove contaminated clothes
- Atropine sulfate 2 mg i.v is the mainstay of treatment. It is repeated every 15 min until full atropinization occurs i.e dilation of pupils take place & all the Muscarinic symptoms & signs are reversed

- Atropine is then given as maintenance dose at 12 hourly interval depending upon severity condition
- Pralidoxime (2 PAM) which is a cholinesterase reactivator should be given within 24 – 48 hr (if it is not given promptly aging of enzyme occurs & reactivation does not occur after poisoning
- The dose is 1 – 2 gm dissolved in 250 ml of 5% glucose solution & injected over 15 – 30 min
- It relieves the nicotinic effects (muscle weakness, twitching & respiratory depression & also Muscarinic effects of organophosphorus poisoning
- Pralidoxime is hazardous in poisoning by carbamate insecticides
- Other measures: keep the airway clear, start mechanically assisted pulmonary ventilation, give gastric lavage with activated charcoal
- Lastly observe the patient closely for at least 72 hrs with constant monitoring of cardiac & pulmonary functions

Manifestations of Ageing

- Delayed neurotoxicity in the form of severe polyneuritis, ataxia, reduced tendon reflex, weakness & ultimately flaccid paralysis
- No specific therapy is known
- Pralidoxime has most marked action at skeletal neuromuscular junction & almost insignificant effect in CNS & autonomic effector sites

Basis of Pralidoxime in Organophosphorus poisoning

1.Organophosphoruscompounds phosphorylate the esteratic site of AChE irreversible by forming a covalent bond à during this, the labile group is released leaving the remaining part of the drug molecule attached covalently with the esteratic site of AChE through its phosphorus atom à AChE becomes inactive & complex becomes very stable

2.Pralidoxime reactivates the enzyme AChE by attaching with the anionic site which lies vacant in the phosphorylated enzyme

3.Oxime group in the Pralidoxime is closer to phosphorylated esteratic site, attracts phosphate group (phosphate transfer to –NOH group of 2-PAM) à the oxime-phosphate complex diffuses out, leaving the regenerated AChE enzyme in an active form

- All oximes are ineffective as antidotes if poisoning has occurred due to carbamate group of anti-AChE drugs (e.g., Propoxur)
- Carbamates attach themselves with anionic site is not free for attachment to Pralidoxime which is prerequisite for their mode of action

Antimuscarinic Drugs or Anticholinergics

- Anticholinergic includes both Antimuscarinic and Antinicotinic drugs

Classification of Antimuscarinic Drugs

1. Natural alkaloids

- Atropine (dl-hyoscyamine)
- Scopolamine (l-hyoscine)

2. Semi synthetic derivatives: Homatropine, Atropine methionitrate, Hyoscine methylbromide, Anisotropine, Benatropine, Ipratropium bromide, Tiotropium bromide

3. Synthetic derivatives

a) Tertiary amines: Eucatropine, Cyclopentolate, Tropicamide, Dicyclomine, Flavoxate, Oxybutinin, Pirenzepine, Telenzepine, Trihexyphenidyl, Procyclidine, Biperiden

b) Quaternary amines: Propantheline, Methantheline, Oxyphenonium, Glycopyrrolate, Clidinium, Isopropamide, Pipenzolate methylbromide

4. Miscellaneous group of drugs possessing anti-muscarinic effects

- Antihistamines: Diphenhydramine, Promethazine, Orphenadrine
- Phenothiazine group of antipsychotics: Chlorpromazine, Thioridazine
- Butyrophenone group of anipsychotics: Haloperidol
- Tricyclic antidepressants: Amitriptyline, Imipramine

Pharmacokinetics

- Absorption: these drugs are well absorbed from the gut & across the conjuctival membrane
- Distribution: except quaternary compounds, rest of the drugs gets widely distributed in all body compartments. Scopolamine is rapidly & fully distributed in CNS & has greater effects
- Metabolism: 50% atropine & 80% of scopolamine is metabolized by liver as conjugates
- Excretion: 50% of atropine is excreted unchanged through urine, $t_{1/2}$ is 3 hrs

Pharmacological Actions

- Sensitiveness of different smooth muscles & glands toward atropine action

Sweat, Bronchial & Salivary glands >> Heart & Eye >> Bladder & GIT >> Gastric glands

<u>Central Nervous System</u>

- Scopolamine has the greater permeability through BBB
- Atropine has effect on CNS only in higher doses & toxic doses
- In higher doses à stimulates higher cerebral centres
- In toxic doses à central excitation & leading to restlessness, irritability, disorientation, hallucinations & delirium
- With still large doses, the stimulation followed by depression leading to circulatory collapse, paralysis, coma & respiratory failure leading to death
- Scopolamine in therapeutic doses produces drowsiness, amnesia, fatigue, dreamless sleep (with reduction in REM sleep) & depression of vomiting centre by suppressing vestibular excitation
- In toxic doses, it causes agitation, excitement & hallucinations
- Still higher dose à stimulation is followed by depression leading to coma & respiratory failure

<u>Eye</u>

- They block M_3 receptors in papillary constrictor muscle à produces mydriasis
- The normal papillary responses being blocked, the eyes become unresponsiveness to light (loss of light reflex)

- They also block M_3 receptors at the ciliary muscle of lens à the suspensory ligaments get tightened resulting in flattening of the lens (i.e. becomes less convex) à eye set for distant vision à this effect is termed as paralysis of accommodation or "Cycloplegia"
- Both mydriasis & cycloplegia à precipitates rise in IOP in elderly persons or in individuals with shallow anterior chambers or with narrow angle glaucoma à this effect is due to falling of iris back over the canal of Schlemm which obstructs the drainage of aqueous humor
- They also blocks M_3 receptors at lacrimal glands à decrease in lacrimation à dry or sandy eyes

Cardio Vascular System

- In clinical doses, Atropine causes a transient bradycardia initially à due to M_1 antagonism
- Further dose leads Tachycardia à due to M_2 antagonism on the SA node
- Higher doses of atropine à dilates cutaneous blood vessels especially in face

Respiratory System

- Atropine decreases the secretions of nose, mouth, pharynx & bronchi à dry the mucus membrane of respiratory tract
- Also reduce the laryngospasm during General Anesthesia
- Drying of mucus secretions & suppression of mucociliary clearance à leads to formation of mucus plugs in patients with airway diseases à obstruct the air flow à predispose the patient to infection
- Ipatropium antagonize bronchoconstriction induced by histamine, bradykinin & $PGF_2\alpha$ à they block the indirect effects of inflammatory mediators that are released during the attacks of asthma
- Besides, these drugs have lesser drying effects on sputum (no risk of forming mucus plugs) & don't inhibit mucociliary movements

Gastro Intestinal Tract

- These drugs reduce the basal secretions (fasting phase) than intestinal phase secretions (secretions stimulated due to food, nicotine or alcohol) [M_1 & M_3 antagonism]

- They reduce the tone & motility of the gut from stomach to colon à prolongation of gastric emptying time, closure of sphincters, decrease in tone, amplitude & frequency of peristaltic movements [M_3 antagonism]
- They also posses spasmolytic activity à hey relax the gut in absence as well as in the presence of cholinoceptor stimulants
- These drugs also relax the bile duct & gall bladder

Genitourinary Tract

- They relax the smooth muscles of ureters & urinary bladed wall à voiding is slowed (urinary retention)

Sweat glands

- They cause decrease in sweating à skin becomes dry and hot (rise in body temperature occurs only in higher doses) à Atropine fever

Therapeutic Uses

Motion Sickness

- Scopolamine (0.6mg – 1.0mg s.c.) is effective in motion sickness caused during landing & takeoff by an aero plane or while traveling on a ship or traveling high altitude

Basis: during landing & takeoff by an aero plane or while traveling on a ship or traveling high altitude à due to disparity between sensory inputs received from non-vestibular proprioceptors *(muscle spindle, Golgi tendon organs & deep connective tissue receptors)* & vision as well as sensory outputs from vestibular apparatus to cerebellum. à results in dizziness, loss of balance, nausea and vomiting

- Diphenhydramine, Cyclizine or Meclizine à prevention of Motion sickness & for treatment of vertigo due to labyrinth dysfunction
- Cinnarizine à antivertigo drug à also used for the prevention of Motion sickness à its antihistaminic, anticholinergic, antiserotonin & Ca^{+2} channel blocking à by inhibiting the influx of Ca^{+2} from endolymph into the vestibular apparatus à blocks labyrinthine reflexes

Parkinson's disease

- Tremors & rigidity associated with Parkinson's disease seem o result from the relative dominance of cholinergic activity in the basal ganglia
- The combination of Antimuscarinic drug with a dopaminergic drug provides more effective-
§ Muscarinic receptors antagonists are used to treat the extrapyramidal side effects
- The centrally acting anticholinergic drugs are
- Benzotropine (1-5 mg/day)
- Benzhexol (2-10mg/day)
- Procyclidine (5-15mf/day)

Diagnosis of Alzheimer's Disease

- Tropicamide is used to diagnosis the AD (it is instilled in the eyes of patient with suspected AD has been found to exhibit unexpectedly marked dilatation of the pupil à due to changes in receptor sensitivity associated with the disease)

Lie detector

- Hyoscine with morphine produces twilight sleep with amnesia during labour
- It was famous as lie detector agent during World War – II as it produces sedation with amnesia

As Mydriatic

- During the Ophthalmoscopic examination of the retina

To prevent the adhesions in inflammatory conditions

- They are used along with miotics to prevent adhesions between the iris & the anterior surface of the lens as in iridocyclitis, iritis or uveitis

Bronchial Asthma & COPD

- Chronic Obstructive Pulmonary Disease (COPD) à where cholinergic tone is more important contributory factor
- Ipatropium reduces bronchial secretions, least drying effect n sputum, do not interfere with mucociliary clearance & cause bronchodilatation à so they are preferred in COPD

- Ipatropium can be given with β2 agonist it the treatment of Asthma due to longer bronchodilator activity

Preanesthetic Medication

- To reduce bronchial secretions (which is contributory factor in producing laryngospasm) & to prevent excessive vagal effect on heart
- But now a days no body using these drugs
- Scopolamine has an advantage because of its CNS depressants effects (amnesia & tranquillisation)
- Glycopyrolate causes less tachycardia & reduces bronchial , salivary secretions à so it is preferred in preanesthetic medication

Peptic Ulcer

- Propranthelin & Glycopyrolate were more preferred because they don't cross the BBB & less side effects
- These drugs reduce the basal secretions (fasting phase) [M_1 & M_3 antagonism]
- These drugs are not useful in the management of gastric ulcers as they increase the gastric emptying time à prolong the exposure of the ulcer bed to gastric acid
- Pirenzepine & Telenzepine are selective M_1 antagonists
- They are used along with other drugs in the management of peptic ulcer

Antispasmodics

- Methylatropine, Hyoscine methylbromide, Dicyclomine, Propantheline are used in the conditions of hypermotiliy of the gut as in intestinal colic, traveler's diarrhea, irritable bowel syndrome, mild dysentery
- These drugs are also used for the treatment of Biliary colic

To reduce excessive salivation

- These are used to reduce the excessive salivation associated with heavy metal poisoning or parkinsonism

Therapeutic uses related with Genitourinary tract

- Dicyclomine & Oxybutinin are used in the treatment of renal colic & to relieve urethral smooth muscle spasm
- Oxybutinin improves the bladder capacity
- Flavoxate, a directly acting smooth muscle relaxant à which anticholinergic drug used in in urinary incontinence & for suprapubic pain in cystitis & urethritis

Miscellaneous Uses

- Treatment of Mushroom poisoning
- Treatment of Muscarinic side effects of neostigmine
- Treatment of Organophosphorus poisoning along with AChE reactivating drugs

Adverse Effects & Toxicity

Most common side effects are

o Dryness of mouth

o Blurred vision & photophobia

o Constipation

o Urinary retention

o Decreased sweating

o Precipitation of glaucoma

Toxicity occurs due to overdosing (above 80 mg orally)

Symptoms of poisoning (Atropine Poisoning)

o Dry skin (as dry as bone)

o Hyperpyrexia

o Flushing of face (as red as beet)

o Mydriasis

o Photophobia (as blind as bat)

o Dry mouth

o Slurred speech

o Difficulty in micturation

o Confusion, delirium

o Hallucinations (as mad as hen)

o Tachycardia

Treatment (Atropine Poisoning)

- The right antidote is Physostigmine (1 – 4 mg slowly i.v every 2 hourly) till satisfactory Muscarinic blockade produced by atropine is countered or overcome

- Basis: Physostigmine is a reversible anticholesterase & chemically a tertiary amine à crosses BBB & indirectly increase the concentration of ACh à it can competitively overcome the antagonistic effect of atropine at Muscarinic & nicotinic receptors all over the body including in CNS

- Other measures-§ Control of hyperpyrexia by cold sponging, artificial respiration, oxygen by facemask

- Removal of unabsorbed drug by gastric lavage & putting universal antidote in stomach

- To control excitement & convulsion, give diazepam 2 mg i.m.

Anti-manic drugs or mood-stabilisers drugs

Antimanic agents help to calm episodes of mania in people with **bipolar disorder**, and they may be used in other conditions where people periodically display periods of great excitement or euphoria, delusions, or over-activity. The term mood stabilizer may also be used to describe an antimanic agent, although technically, antimanic agents are those mood stabilizers that only treat episodes of mania, not **depression**. Three mood stabilizers that are effective at treating both mania and depression are lamotrigine, lithium, and quetiapine.

Lithium, some anticonvulsants (such as carbamazepine, lamotrigine, valproate), and some atypical antipsychotics (for example, aripiprazole, olanzapine, quetiapine) are the most common drugs used for their mood stabilizing effects and in the control of mania.

Although experts do not fully understand how antimanic agents work to stabilize episodes of mania, it is believed that they either influence levels of chemical neurotransmitters in the brain, such as dopamine, GABA, norepinephrine, or serotonin; or, for anticonvulsants, reduce the excitability of nerve impulses in the brain. An effective antimanic agent should:

- Reduce acute episodes of mania to a more manageable level
- Relieve symptoms such as **agitation**, inappropriate behavior, and sleep problems
- Prevent symptom relapses and hospitalization.

Side effects vary depending on the type of antimanic agent used.

Lithium

Lithium acts upon various neurotransmitter systems in the brain. Through its effects on glycogen synthase kinase-3 b and the reduction of protein kinase C, lithium may cause neuroplastic changes within the brain associated with mood stabilization. Different salts of lithium are available and preparations vary in bioavailability, so it should always be prescribed by brand. Lithium has a low therapeutic index and most toxic effects are dose related. Ongoing essential monitoring includes measurement of serum lithium concentration every 3 months and thyroid function tests, serum urea and electrolytes and serum calcium/ parathyroid hormone every 6 months.

Valproate

Valproate has multiple actions: it has effects on glycogen synthase kinase-3 b to aid mood stabilization,9 increases g-aminobutyric acid (GABA) concentrations and reduces protein kinase C. It may also deplete inositol. Valproate is available as sodium valproate, valproic acid and semi-sodium valproate (a 1:1 molar combination of sodium valproate and valproic acid). The majority of clinical studies have used semi-sodium valproate, though the therapeutic differences between sodium valproate and semi-sodium valproate have not been established.7 Ongoing essential monitoring includes liver function tests, full blood count and weight every 6 months.

Carbamazepine

Carbamazepine blocks voltage-dependent sodium channels, thereby inhibiting repetitive neuronal firing. It also decreases

glutamate release and decreases the turnover of noradrenaline and dopamine. NICE considers carbamazepine to be a third-line prophylactic agent.1 Although there is evidence for its use as a mood stabilizer, it is not particularly well tolerated.5 Carbamazepine is a potent inducer of hepatic cytochrome enzymes and is metabolized by CYP3A4, so one should always be alert to the potential for interaction with other medications. Ongoing essential monitoring includes liver function tests, full blood count, serum concentration and weight every 6 months.

Lamotrigine

The mood stabilization effect of lamotrigine is related to the inhibition of sodium and calcium channels in pre-synaptic neurones and subsequent stabilization of the neuronal membrane. Lamotrigine has been shown to be effective as a mood stabilizer, particularly where depression predominates.1,5 Dose recommendations must be adhered to closely to reduce the risk of rash, but the necessity for slow titration may limit clinical use. Patients taking lamotrigine should be advised to see a doctor urgently if a rash develops, as there is a risk of serious skin reactions including StevenseJohnson syndrome. No other specific monitoring is required with lamotrigine.

ATYPICAL ANTIPSYCHOTICS

• Olanzapine, risperidone, aripiprazole, quetiapine, with or without a BZD, are now the first line drugs for control of acute mania

• for urgent parenteral therapy, but older neuroleptics are still the most effective.

• **Aripiprazole** has emerged as the favoured drug for treatment of mania in bipolar disorder • used both as monotherapy as well as adjuvant to lithium or valproate • prevents mania, but not depressive episodes • Lack of metabolic effects, favours its long-term use

• **Olanzapine** is also approved for maintenance therapy of bipolar disorder. • both manic and depressive phases are suppressed

• not considered suitable for long-term therapy due to higher risk of weight gain, hyperglycaemia, etc.

• **Quetiapine** is effective in bipolar depression.

• Combination of an atypical antipsychotic with valproate or lithium has demonstrated high efficacy in acute phases as well as for maintenance therapy of bipolar disorder.

Novel targets for treatment of Bipolar disorder

GLYCOGEN SYNTHASE KINASE 3 (GSK-3) INHIBITION

• GSK-3 is a kinase involved in the regulation of cell apoptosis and synaptic plasticity.

• Its inhibition influences gene transcription, with consequent anti-apoptotic effect

• GSK-3 inhibition increases hippocampal levels of β-catenin, a function implicated in mood stabilization

• Both Li+ and valproate treatment inhibit the activity of glycogen synthase kinase-3β (GSK-3β)

PKC INHIBITION

• Excessive intracellular calcium influx results in increased apoptosis, destruction of the cytoskeleton and intensification of the oxidative stress.

• These disturbances in calcium mobilization are related in part to hyperactivity of PKC, which has been demonstrated among subjects with BD

• Therefore, drugs whose putative effects implicate PKC inhibition may play a role in the treatment of BD

• Lithium and valproic acid inhibit PKC

• Tamoxifen, an estrogen antagonist (used in the treatment of breast cancer) can cross BBB & has strong inhibitory effects on PKC.

• Omega-3 fatty acids might represent a protective factor against the development of BD

• Omega-3 Fatty acids act as antagonists of the PI-PKC signal transduction pathway, ultimately inhibiting PKC activity

BRAIN-DERIVED NEUROTROPHIC FACTOR (BDNF) MODULATION

• BDNF and other neurotrophic factors increase cell survival by direct neurotrophic effect and apoptosis inhibition.

• There is evidence suggesting that chronic administration of lithium and valproate may result in increased transcription of those factors

ENHANCED BCL2 EXPRESSION

• Bcl2 is a protein with marked anti-apoptotic activity

• involved in neuronal protection and regeneration

• In rats, chronic administration of lithium and valproate is associated with increased levels of Bcl2 in the prefrontal areas

• atypical antipsychotic olanzapine is associated with increased expression of Bcl2 in the prefrontal cortex and hippocampus of rodents

• Pramipexole is a dopamine agonist currently approved for treatment of Parkinson's disease and is associated with increased expression of Bcl2 in the frontal cortex

EFFECTS ON OXIDATIVE STRESS

• increased oxidative stress contributes to cellular death in BD patients.

• Lithium and olanzapine have demonstrated antioxidant properties, which may be partially responsible for their neuroprotective effects

MODULATION OF GLUTAMATERGIC TRANSMISSION

• the effects of lithium on the glutamatergic system are possibly related to its neuroprotective properties.

• Glutamate is the main excitatory neurotransmitter in the CNS

• involved in the regulation of several processes, including neuronal and synaptic plasticity, memory consolidation and information processing

• increases in the glutamatergic transmission in the CNS bring about prolonged synaptic excitatory transmission, with excitotoxicity and, ultimately, neuronal death.

• Lithium is believed to inhibit the calcium influx that results from the stimulation of the NMDA glutamate receptors and lamotrigine, a well-established mood stabilizer, blocks the neuronal sodium channels, thus inhibiting the release of glutamate

• drugs with demonstrated effect on the glutamatergic system may be of particular interest in the management of the depressive phase of BD.

• Memantine: low-affinity antagonist of the NMDA glutamate receptor, currently FDA-approved for treatment of Alzheimer's disease.

• Amantadine: non- competitive antagonist of the NMDA receptor currently approved for treatment of Parkinson's disease.

• Ketamine: an anesthetic, ketamine is a high-affinity NMDA antagonist seems effective in the treatment of resistant unipolar depression

• Riluzole: a potent glumatergic modulator, currently FDA- approved for treatment of amiotrophic lateral sclerosis

RAMELTEON

• Ramelteon acts as a selective agonist of melatonin receptors (MT1 & MT2) within the suprachiasmatic nucleus (SCN).

• Although approved to treat insomnia, Ramelteon is under investigation as a treatment for bipolar disorder.

• It's efficacy for bipolar maintenance and mania attenuation may be because of its ability to regulate circadian rhythms.

• Regulation of circadian rhythms minimizes likelihood of mood stability and prevents cycling to a manic and/or depressive state.

Antidepressants drugs

Antidepressants are used to treat several conditions. They include, but are not limited to: depression, generalized anxiety disorder, agitation, obsessive compulsive disorders (OCD), manic-depressive disorders, childhood enuresis (bedwetting), major depressive disorder, diabetic peripheral neuropathic pain, neuropathic pain, social anxiety disorder, posttraumatic stress disorder (PTSD) etc.

the major classes of antidepressant drugs include the **tricyclic and related antidepressants**, **selective serotonin re-uptake inhibitors (SSRIs)**, the **selective serotonin and norepinephrine re-uptake inhibitors (SNRIs)** and the **monoamine oxidase inhibitors (MAOIs**). A small number of drugs don't easily fall into this classification and are listed under **Atypical antidepressants** below.

There is little to choose between the different classes of antidepressant drugs in terms of efficacy, so choice should be based on the individual patient's requirements, including the presence of other existing disease and therapy, suicide risk, and previous response to antidepressant therapy.

SSRIs are better tolerated and are safer in overdose than other classes of antidepressants and should be considered first-line for treating depression. Notably, **sertraline** has been shown to be safe in patients who have had a recent myocardial infarction or who have unstable angina. TCAs have similar efficacy to SSRIs, but their more troublesome side-effects leads to patients being more likely to discontinue treatment. TCAs are also more toxic in overdose than SSRIs. MAOIs have dangerous interactions with some foods and drugs, and should be reserved for use by specialists.

Anxiolytics or antipsychotic drugs should be used with caution in depression which often presents as anxiety, as they can mask the true diagnosis, but are useful adjuncts in agitated patients.

Selective serotonin re-uptake inhibitors (SSRIs)

SSRIs are the most commonly prescribed class of antidepressants. They are highly effective and generally well tolerated compared to other types of antidepressants**.** Side effects of SSRIs may include nausea, vomiting, diarrhoea, sexual dysfunction, headache, weight gain, anxiety, dizziness, dry mouth, and insomnia. Caution should be used when prescribing SSRIs alongside other drugs that increase the risk of bleeding. SSRIs should not be used in patients with poorly controlled epilepsy or in patients entering manic phase. Common shared side-effects (often dose-related) include abdominal pain, constipation, diarrhoea, dyspepsia, nausea and vomiting. An uncommon, but potentially serious side-effect is serotonin syndrome.

Citalopram- used to manage depressive illness and panic disorder.

Escitalopram (the active enantiomer of citalopram)- used to manage depressive illness, generalised anxiety disorder, obsessive-compulsive disorder, panic disorder and social anxiety disorder.

Paroxetine- used to manage major depression, social anxiety disorder, post-traumatic stress disorder (PTSD), generalised anxiety disorder, obsessive-compulsive disorder and panic disorder

Fluoxetine (Prozac)- used to treat major depression, bulimia nervosa and obsessive-compulsive disorder. Prescribers should consider the long half-life of when adjusting dosage, especially in regards to overdosage.

Fluvoxamine- used to manage depressive illness and obsessive-compulsive disorder.

Sertraline- used to manage depressive illness, obsessive-compulsive disorder, panic disorder, social anxiety disorder and PTSD.

Failure to respond to initial treatment with an SSRI may require an increase in the dose, or switching to a different SSRI or **mirtazapine**. Other second-line choices include **lofepramine**, **moclobemide**, and **reboxetine**.

Selective serotonin and norepinephrine re-uptake inhibitors (SNRIs)

None of these drugs should be prescribed within 14 days of an MAOI and at least 7 days should be allowed between stopping their use and administering a MAOI.

Desvenlafaxine (not UK)- indicated for major depressive disorder.

Duloxetine- used to manage major depressive disorder, generalised anxiety disorder, diabetic neuropathy and moderate to severe stress urinary incontinence. Use caution when prescribing alongside drugs that increase risk of bleeding.

Venlafaxine- indicated for major depression, generalised anxiety disorder and social anxiety disorder. Contra-indicated in patients with conditions associated with high risk of cardiac arrhythmia or uncontrolled hypertension.

Milnacipran (not UK)- used to treat the chronic pain caused by fibromyalgia, not used to treat depression.

Levomilnacipran (not UK)- used to treat major depressive disorder.

Most common side-effects of SNRIs are nausea, dizziness, and sweating. Other side-effects include tiredness, constipation, insomnia, anxiety, headache, and loss of appetite**.**

Duloxetine and milnacipran should not be used in patients with uncontrolled narrow angle or angle-closure glaucoma.

Tricyclic antidepressants (TCAs) and related antidepressants

TCAs share a similar chemical structure and biological effects**.** TCAs block the re-uptake of both serotonin and noradrenaline, although to different extents. For example, **clomipramine** is more selective for serotonin re-uptake, and **reboxetine** and **lofepramine** are somewhat more selective for noradrenaline re-uptake. Other TCAs such as **nortriptyline**, show no such selectivity. Evidence indicates that the secondary amine tricyclic antidepressants, including **desipramine** HCl, may have greater activity in blocking the re-uptake of norepinephrine. Tertiary amine tricyclic antidepressants, such as **amitriptyline**, may have greater effect on serotonin re-uptake. Additionally, TCAs block muscarinic M_1, histamine H_1, and alpha-adrenoceptors. Tricyclic and related antidepressant drugs can be roughly divided into those with additional sedative properties (**amitriptyline**, **clomipramine**, **dosulepin**, **doxepin**, **mianserin**, **trazodone**, and **trimipramine**) and those that are less sedating (**imipramine**, **lofepramine**, and **nortriptyline**). Agitated and anxious patients tend to respond best to the sedative

compounds, whereas withdrawn and apathetic patients will often obtain most benefit from the less sedating ones.

TCAs are approved for treating several types of depression, obsessive compulsive disorder, and bedwetting (nocturnal enuresis). Also used for several off-label conditions such as panic disorder, bulimia, chronic pain (for example, migraine, tension headaches, diabetic neuropathy, and post herpetic neuralgia), phantom limb pain, chronic itching, and premenstrual symptoms

Although effective, TCAs have largely been replaced by newer antidepressants that generally cause fewer side-effects.

Amitriptyline - not recommended for depressive illness because of its toxicity in overdosage- used for migraine prophylaxis, neuropathic pain, abdominal pain or discomfort (in patients who have not responded to laxatives, loperamide, or antispasmodics)

Doxepin- used for depressive illness (especially where sedation is required) and pruritus of eczema (topical application). This TCA acts as a selective noradrenaline reuptake inhibitor. Dizziness and drowsiness are very common side-effects, as are agitation, anxiety, confusion, irritability, paraesthesia and sleep disturbance.

Lofepramine- used to treat depressive illness. Common side-effects include dizziness, agitation, anxiety, confusion, irritability, paraesthesia, postural hypotension and sleep disturbance

Dosulepin hydrochloride- used for depressive illness (especially where sedation is required). Common side-effects include dizziness, agitation, anxiety, confusion, irritability, paraesthesia, postural hypotension and sleep disturbance

Desipramine hydrochloride (not UK), is approved in the US to treat symptoms of depression. Use of desipramine in patients being treated with MAOI antidepressants (e.g. linezolid) is contraindicated because of an increased risk of serotonin syndrome. Desipramine may cause exacerbation of psychosis in schizophrenic patients. Concomitant use of tricyclic antidepressants with drugs that can inhibit cytochrome P450 2D6 may require lower doses than usually prescribed for either the tricyclic antidepressant or the other drug.

Imipramine hydrochloride – used for depressive illness and nocturnal enuresis. Common side-effects include fatigue, flushing, headache, palpitations and restlessness.

Nortriptyline – prescribed for depressive illness and neuropathic pain. Treatment should be stopped if the patient enters a manic phase. Common side-effects include fatigue, hypertension, mydriasis and restlessness

Amoxapine (not UK)- used to treat symptoms of depression, anxiety, or agitation. Do not use this medicine within 14 days of taking an MAOI antidepressant.

Clomipramine hydrochloride- prescribed for depressive illness, phobic and obsessional states and as an adjunctive treatment of cataplexy associated with narcolepsy. Common side-effects include abdominal pain, aggression, diarrhoea, fatigue, flushing, hypertension, impaired memory, muscle hypertonia, muscle weakness, mydriasis, myoclonus, restlessness and yawning.

Maprotiline (not UK)- used to treat major depressive disorder, depressive neurosis, and manic-depression illness. Avoid alcohol as it can increase some of the side-effects of

maprotiline. Maprotiline can impair thinking or reactions, so patients are recommended to avoid activities that require alertness (e.g. driving)

Trimipramine- used to treat depressive illness (particularly where sedation is required). Side-effects can include agitation, anorexia, anxiety, arrhythmia, blurred vision, confusion, constipation, dizziness and dry mouth. Trimipramine is also a serotonin 5-HT_2 receptor antagonist.

Protriptyline (not UK)- used to treat symptoms of depression. Do not use this medicine within 14 days of taking an MAOI antidepressant. Common side-effects can include nausea, vomiting, loss of appetite, anxiety, insomnia, dry mouth, little or no urinating and constipation.

Monoamine oxidase inhibitor antidepressants (MAOIs)

MAOIs block the activity of monoamine oxidase, an enzyme that breaks down norepinephrine, serotonin, and dopamine in the brain and other parts of the body. MAOIs are used much less frequently than tricyclic and related antidepressants, or SSRIs and related antidepressants because of the dangers of dietary and drug interactions. MAOIs exhibit some benefit for phobic patients and depressed patients with atypical, hypochondriacal, or hysterical features, but should only be prescribed by specialists. In general, MAOIs have been replaced by newer antidepressants that are safer and cause fewer side-effects. Common side-effects include postural hypotension, weight gain, and sexual side effects.

Isocarboxazid, phenelzine and **tranylcypromine** are non-selective, irreversible MAOIs, used to manage depressive illness.

Rasagiline and **selegiline** are irreversible MAOB inhibitors used not to treat depression, but to treat Parkinson's disease as a monotherapy or as an adjunct to co-beneldopa or co-careldopa to manage 'end-of-dose' fluctuations.

Atypical antidepressants

Each drug in this category has a unique molecular mechanism of action, or a chemical structure that excludes them from the classification above. However, like other antidepressants, atypical antidepressants affect the levels or effects of dopamine, serotonin, and norepinephrine in the brain.

Bupropion- used to aid smoking cessation in combination with motivational support in nicotine-dependent patients. This drug should not be used in patients with seizure disorders, eating disorders, and within 2 weeks of using MAOI. It generally does not cause weight gain or sexual problems.

Mirtazapine- a presynaptic α_2-adrenoceptor and serotonin 5-HT_2 receptor antagonist which increases central noradrenergic and serotonergic neurotransmission. Used to manage major depression.

Nefazodone (not UK)- a serotonin 5-HT_2 receptor antagonist also inhibiting serotonin and norepinephrine re-uptake. Used to manage depression, including major depressive disorder. Nefazodone should not be prescribed to patients with active liver disease.

Trazodone- principally a serotonin 5-HT_2 receptor antagonist, used to manage depressive illness, particularly where sedation is required.

Vilazodone (not UK)- a potent serotonin 5-HT_{1A} receptor partial agonist, with combined inhibitory action against serotonin re-uptake. Used to manage major depressive disorder. Vilazodone is not associated with significant weight gain or sexual dysfunction.

Vortioxetine (not UK)- a partial agonist of 5-HT_{1A} and 5-HT_{1B} receptors and antagonist of the 5-HT_7 receptor used to manage major depressive disorder. May also inhibit re-uptake of serotonin.

Side-effect profiles are as unique as their mechanisms of action. Some common side effects include dry mouth, constipation, dizziness, and light headedness. Mirtazapine and trazodone cause drowsiness and are usually taken at bedtime

Antipsychotics drugs

Antipsychotics, also known as **neuroleptics**, are a class of medication primarily used to manage psychosis (including delusions, hallucinations, paranoia or disordered thought), principally in schizophrenia and bipolar disorder. Antipsychotics are usually effective in relieving symptoms of psychosis in the short term.

The long-term use of antipsychotics is associated with adverse effects such as involuntary movement disorders, gynecomastia, impotence, weight gain and metabolic syndrome.

First-generation antipsychotics, known as typical antipsychotics, were discovered in the 1940s. Most second-generation drugs, known as atypical antipsychotics, have been developed more recently, although the first atypical antipsychotic, clozapine, was discovered in the 1960s and introduced clinically in the 1970s.[2] Both generations of medication block receptors in the brain for dopamine, but atypicals tend to act on serotonin receptors as well.

CLOZAPINE

Reports of clozapine being effective for psychosis first appeared in the mid 1960s . The use of this drug was controversial because clozapine did not possess high D2 affinity and produce extrapyramidal effects which were thought to be required of an effective antipsychotic at that time. Soon after clozapine began to be widely used in the early 1970s, eight patients in Finland died from agranulocytosis while taking the drug. The use of clozapine declined until the late 1980s when it reemerged as a treatment for a selected group of treatment-refractory patients. Therapeutic use now includes a monitoring system for agranulocytosis. In 1990 clozapine was marketed in the United States. Clozapine is the only drug approved and effective for the treatment of therapy-refractory schizophrenia. A great deal of interest has been generated in understanding what pharmacological properties of clozapine contribute to its superior efficacy. Clozapine has an increased ratio of D1 to D2 antagonism, greater D3 and D4 blockade, 5-HT2A and 5-HT2C antagonistic properties, anticholinergic and antiadrenergic properties and increased mesolimbic specificity with relative sparing of nigrostriatal dopaminergic neurons. An intriguing finding about predicting which new drugs may be effective in treatment-resistant schizophrenia has been the fact that people with treatment-resistant schizophrenia appear to have lower catecholamine levels in the CSF. Greater clozapine response has been associated with low ratios of CSF homovanillic acid to 5-hydroxy-indoleacetic acid. Clinical trials have consistently found clozapine to be superior to traditional antipsychotics for treatment refractory patients . Approximately 30-50% of patients with treatment resistant schizophrenia are reported

to respond to clozapine treatment. Kane and others performed the landmark study regarding clozapine efficacy. His group compared clozapine to chlorpromazine in a very stringent study design. Thirty percent of patients responded to clozapine while only 4% responded of those receiving chlorpromazine. Clozapine is often rapidly effective in people who have responded poorly to other medication for years, once an effective does is reached, and appears to be effective even in the face of nonresponse to other second-generation antipsychotics or in partially responsive people . This suggests that there remains a neuropharmacologic effect associated with clozapine that is, so far, unique to this drug. It may also have a differential effect regarding symptoms associated with suicidality in chronically psychotic people . While clozapine currently remains the standard for treatment-resistant schizophrenia, its widespread use is hindered by its propensity to cause agranulocytosis, seizures, sedation, enuresis, anticholinergic effects, weight gain, and hypersalivation. Current recognition that most people who will respond to clozapine do so at doses lower than those commonly used when the drug was first introduced have lead to safer and more tolerable dosing strategies for this drug. The optimal plasma level of clozapine is at minimum 200 to 350 ng/mL. This usually corresponds to a daily dose of 200 to 400 mg although dosage must be individualized . Clozapine remains clinically underutilized despite the fact that it is more effective than typical antipsychotic drugs in reducing symptoms of schizophrenia, producing clinically meaningful improvements and postponing relapse and that patients were more satisfied with clozapine treatment than with typical neuroleptic treatment.

RISPERIDONE

Risperidone, a benzisoxazole derivative, was the first SGA to be marketed following the release of clozapine. This antipsychotic has high binding affinity to both 5-HT2A and D2 receptors and binds to alpha1 and alpha2 receptors, with very little blockade of cholinergic receptors . Multi center clinical trials that led to the FDA approval of risperidone found that it had efficacy that was at least equal if not superior to that of haloperidol and produced significantly fewer extrapyramidal symptoms. The U.S. results of the U.S. Canadian collaborative investigation were reported by Marder and Meibach in 1994. They reported that 6 mg/day of risperidone was superior to 20 mg daily of haloperidol. Fiftyseven percent of patients on 6 mg/day of risperidone were found to have a 20% decrease in symptoms as measured by the PANSS scale. In comparison, only 30% receiving haloperidol and 22% receiving placebo also had this symptom reduction. Extrapyramidal symptoms required that 47% of haloperidol treated patients be treated with antiparkinsonian medications while 20% of

those on risperidone required treatment at 6 mg/daily. A follow-up factor analysis also reported risperidone to demonstrate superior efficacy for both positive and negative symptoms as compared to haloperidol. Since its introduction, studies have demonstrated that doses lower than 6 mg daily of risperidone may be most effective for all symptom domains . Risperidone, although, not possessing a clozapine-like effect in treatment resistance may provide relief for up to 25% of patients with refractory symptoms . At clinically effective doses (<6 mg/day), extrapyramidal side effects are indistinguishable from placebo, although higher doses are clearly associated with EPS. All clinical doses of risperidone are usually associated with prolactin elevation, and effect similar to conventional antipsychotics. This effect can, but does not always lead to clinical symptoms. Recently it has been seen that patients chronically treated with other antipsychotics show marked clinical improvement and declines in cholesterol and triglyceride levels when changed to risperidone therapy. Stable patients changed to risperidone therapy have very low rates of rehospitalization compared to those changed to haloperidol.

OLANZAPINE

Olanzapine has a pharmacological profile of activity similar to that of clozapine. In preclinical studies, olanzapine demonstrated a range of receptor affinities distinct from conventional antipsychotics and generally comparable to those of clozapine. However, in clinical trials olanzapine has not been found to be as efficacious for treatment-resistant schizophrenia as is clozapine . Olanzapine has greater affinity for 5-HT2A than for D2 receptors. In addition, the compound has affinity at the binding sites of D4, D3, 5-HT3 5-HT6, H1, alpha1 adrenergic, muscarinic M1-5 receptors, and histamine H1 receptors . Both United States and international multi center clinical trials reported effectiveness of olanzapine that was at least equal to that of haloperidol for the treatment of positive symptoms. Olanzapine's efficacy on negative symptoms have been found to be equivalent or superior to haloperidol. The clinical trials which brought olanzapine to market compared a low (mean 6.6 mg/day), moderate (11.6 mg/day), and high dose (16.3 mg/day) of olanzapine. There were no significant differences in efficacy among dosage groups. However, the highest dose range appeared to offer the greatest benefits for both positive and negative symptoms compared to haloperidol. Olanzapine has also recently been shown to be effective as for patients suffering from acute bipolar disorder. Overall, olanzapine demonstrated superior efficacy compared with placebo in the short-term treatment of patients with bipolar I disorder with manic or mixed episodes, with or without psychotic features. Olanzapine has a low rate of extrapyramidal symptoms and prolactin elevation. However, clinically significant weight gain has been noted with olanzapine in all of the large clinical trials testing it. The degree of weight gain is similar to clozapine and probably greater

than that observed with risperidone. It is also associated with hypertriglyceridemia and new onset type II diabetes.

QUETIAPINE

Structurally, quetiapine is related to clozapine and olanzapine. Quetiapine has high affinity for 5-HT2A receptors and lower affinity for D2 and D1 receptors. This drug has some affinity for alpha1, alpha2, and H1 receptors, and very little for muscarinic receptors. The efficacy of quetiapine for psychosis was established in two controlled trials. One trial evaluated five fixed doses (75, 150, 300, 600 and 750mg/day) versus placebo. The maximum efficacy was found to occur at 300 mg day. Quetiapine was also tested in a flexible dose study (<250 mg/day vs. 250-750 mg/day). The mean dose in the high-dose group was 360 mg/day and 209 in the low-dose group. The greatest efficacy for positive symptoms occurred at doses > 250 mg/day. In contrast to other SGAs, quetiapine has not been shown to be superior to haloperidol in any symptom dimension, such as positive or negative symptoms. Because of its low D2 occupancy, extrapyramidal symptoms and prolactin elevations are usually not seen with quetiapine. However, there remains a significant question of dose with this drug: it is possible that the most clinically effective doses are those outside of the generally recommended range.

ZIPRASIDONE

Ziprasidone was developed within a structure-activity investigation intended to find a compound that potently blocks D2 receptors but that binds with even greater affinity to central 5-HT2A receptors. As a result, ziprasidone has a binding affinity ratio of 11:1 for 5-HT2A/D2. Ziprasidone also binds with relatively high affinity for 5-HT2C, 5-HT1D, alpha1 adrenergic and D1 receptors . Several short-term clinical trials compared with placebo have been completed prior to marketing of this antipsychotic which led to the recommended dose range of 40-160 mg daily with food . The major problem currently with ziprasidone is the relative lack of published efficacy data. From its product label, it appears that over its recommended dose range, only 160 mg per day was always better than placebo in the treatment of people with schizophrenia. Eighty mg per day was more effective in three of four studies and 40 mg per day more effective in only two of four. If this is the case, it would suggest a very narrow effective dose range for this drug. More data is needed before a full judgment of its efficacy can be made. Liability for extrapyramidal side effects and weight gain were very low in the clinical trials of this drug. Ziprasidone is associated with some prolongation of the QTc interval in adults. However, drug overdose data and studies for pharmacokinetic interactions thus far show little evidence that significant QTc prolongation or Torsades de Pointes may occur.

ARIPIPRAZOLE

Aripiprazole was discovered in the early 1980's as an attempt to find an antipsychotic that would function as a potential entity with both antagonist and agonist activity to the D2 receptor. *In vitro* data suggested that the dopamine autoreceptor agonists were effective in treating negative symptoms of schizophrenia. Potent dopamine post-synaptic receptor antagonism was believed to be necessary for positive symptoms of schizophrenia. Hence, aripiprazole is the first potent D2 partial agonist for the treatment of schizophrenia. In a hyperdopaminergic state, aripiprazole functions as an antagonist while under conditions of hypodopaminergic activity, it functions more like an agonist. This novel mechanism has been labeled a dopamine system stabilizer. Aripiprazole also has high affinity for D3 receptors. It is also a partial agonist at 5-HT1A receptors and an antagonist at 5HT2A receptors. Aripiprazole has a moderate affinity for alpha1 and H1 receptors with no appreciable affinity for the M1 receptor. The efficacy of aripiprazole was demonstrated in four short-term (4-6 weeks) placebo-controlled trials in patients with schizophrenia or schizoaffective disorder. Three phase III pivotal trials were performed with one each including haloperidol and risperidone. The first trial found both the 15 and 30 mg/day dose to be superior to placebo and similar to haloperidol. A second trial found 20 and 30 mg to be superior to placebo and similar to risperidone. The third trial also found 10, 15 and 20 mg to be superior to placebo. Significant improvements were seen for all symptom domains such as PANSS total, positive and negative symptoms. Longerterm studies have shown lower relapse rates than placebo and similar to haloperidol. The recommended starting dose is 10 to15 mg QD given without regard to meals. No titration is required as the starting dose is an effective dose. Ten to 30 mg daily are recommended as the dosing range and doses greater than 30 mg have no been systematically evaluated. Doses less than 10 mg/day have not been consistently found to be effective. Side effects are low with sedation and nausea/ vomiting occurring the most frequently.

CENTRALLY ACTING MUSCLE RELAXANTS

Strains, sprains and other muscle injuries can result in pain, stiffness and muscle spasms. Muscle relaxants do relax muscles ease discomfort and stop muscle spasms. Muscle pain is the characteristic feature of several conditions. For example, in certain viral fevers such as Chicken gunya, the patient experience severe muscle pains. Similarly in case of Arthritis, the patient will be thrown into discomfort initially and may become disable in severe condition. People belonging to risky jobs in various fields such as workers in mine, software engineers suffer from joint pains and severe chronic back pain. During injuries in particular athletes during sports, post operative conditions, as side effects of several antimicrobial drugs induction, during accidents, also at the time of various infections, during over exercise, centrally acting muscle relaxants play an important role in releasing the pain. In view of the increasing importance to these conditions, muscle relaxant drugs have been selected and studied. The discovery of central acting muscle relaxants dates back to 1910. Berger and Bradely in 1946, observed the muscle relaxant activity present in large number of glycerol mono ether and analogues.

Skeletal muscle relaxants consist of both anti spasticity and spasmodic agents. Approximately 2 million people per year report using a skeletal muscle relaxant, primarily for back pain, with an estimated 3,00,000 of the patient being elderly. Sparmolytic agents generally work by either enhancing the level of inhibition, or reducing the level of excitation. The benzodiazepines, such as diazepam, interact with the GABA receptor in the central nervous system and Baclofen is considered to be an effective as diazepam in reducing spasticity and cause much less sedation. Dantrolene is a spasmolytic agent with a unique mechanism of action out side the CNS.

Other common spasmolytic agents include Methocarbomol, Carisoprodol, Chlorzoxazone, Metaxalone and Orphenadrine. Meprobomate, a potent adenosine reuptake inhibitor and related drugs include Carisoprodol and Tybamate.

MEPROBAMATE:

Introduction: Meprobamate was first synthesized by Bernard John Ludwig and Frank Milan Berger at caster products in 1950. It became the first block buster psychotropic drug in American history (Andrea, 2009). It is classified under substituted alkanediols and analogues.

Chemistry: A good member of 1,3 – alkanediols and their structural analogues have been reported to be potent muscle relaxant drugs.

Mechanism of Action: Meprabomate binds to GABA receptors which interrupt neuronal communication in the reticular formation and spinal cord, causing sedation and altered perception of pain. It has the ability to activate currents even in the absence of GABA also and a potent adenosine reuptake inhibitor (ADORI). Related drugs include Carisoprodol and Tybamate.

Indications: Meprobamate gives short term relief of anxiety, and tension. It has anticonvulsant and muscle relaxant properties.

Toxicity: Drowsiness, sluggishness, unresponsiveness, or coma, loss of muscle control, severe impairment or cessation of breathing, or shock.

CARISOPRODOL:

Introduction: A centrally acting skeletal muscle relaxant whose mechanism of action is not completely understood but may be related to its relative actions. It is used as an adjunct in the symptomatic treatment of musculoskeletal conditions associated with painful muscle spasms.
Mechanism of Action: Carisoprodol is a central nervous system depressant that act as a relative and skeletal muscle relaxant. Carisoprodol interrupts neuronal communication within the reticular formation and spinal cord, resulting in radiation and alteration in pain perception. Its exact mechanism of action is not yet known.

Indications: For the relief of discomfort associated with acute, painful, musculo skeletal conditions.

Toxicity: Symptoms of over dose include drowsiness, giddiness, nausea, indigestion, or rash. Other adverse effects attributed to therapeutic use of Carisoprodol include dizzinees, irritability, insomnia, diplopia, temporary loss of vision, ataxia, weakness, headache and dysarthria.

DANTROLENE: Chemically, Dantrolene is a hydantoin derivative, but does not exhibit antiepileptic activity like ether hydantoin derivative such as Phenytoin.

Mechanism of Action: Dantrium has been shown to produce relaxation by affecting the contractive response of the muscle at a site beyond the myoneural junction. In skeletal muscle, Dantrium dissociates excitation – contraction coupling probably by interfering with the release of Ca+2 from the sarcoplasmic reticulam by binding to the ryanodine receptor1. Ryanodine receptor mediates the release of calcium from the sarcoplasmic reticulum, an essential step in muscle contraction.

Indications: It is currently used for the management of the fulminant hyper metabolism of skeletal muscle, characteristic of malignant hyperthermia crises in patient of all ages.

Toxicity: Symptoms of overdose include muscular weakness and alternations in the state of consciousness (eg, lethargy, coma), vomiting diarrhea.

BACLOFEN:

Chemistry: Baclofen is a gamma- amino – butyric acid (GABA) derivative used as a skeletal muscle relaxant. It is especially useful in treating muscle splasticity associated with spinal cord injury.

Mechanism of Action: It is a capable of inhibiting both monosynaptic and polysynaptic reflexes at the spinal level, possibly by hyper polarization of afferent terminals, although action at supra spinal site may also occur and contribute to its clinical effect.

Indications: For the elevation of signs and symptoms of spasticity resulting from multiple sclerosis, particularly for the relief of flex or spasms and concomitant pain, claws and muscular rigidity.

METAXALONE:

Metaxalone is a muscle relaxant used to relax muscle and relieve pain caused by strains, spains and other musuloskeletal conditions. It is considered to be moderately strong muscle relaxant, with relatively low incidence of side effects.

Mechanism of Action: The mode of action of this drug has not been clearly identified, but may be related to sedative properties. Metaxalone does not directly relax tense skeletal muscles in

man. The mechanism of action in humans may be due to general central nervous system depression.

Indications: For the treatment of painful peripheral musculoskeletal conditions and spasticity from upper motor neuron syndromes.

CNS Stimulant

The central nervous system directs the functions of all tissues of the body. The peripheral nervous system receives thousands of sensory inputs and transmits them to the brain via the spinal cord. The brain processes this incoming information and discards 99% as unimportant. After sensory information has been evaluated, selected areas of the central nervous system initiate nerve impulses to organs or tissue to make an appropriate response.

Chemical influences are capable of producing a myriad of effects on the activity and function of the central nervous system. Since our knowledge of different regions of brain function and the neurotransmitters in the brain is limited, the explanations for the mechanisms of drug action may be vague. The known neurotransmitters are: acetylcholine which is involved with memory and learning; *norepinephrine* which is involved with mania-depression and emotions; and *serotonin* which is involved with biological rhythms, sleep, emotion, and pain.

Central Nervous System Stimulants

Stimulants are drugs that exert their action through excitation of the central nervous system. Psychic stimulants include caffeine, cocaine, and various amphetamines. These drugs are used to enhance mental alertness and reduce drowsiness and fatigue. However, increasing the dosage of caffeine above 200 mg (about 2 cups of coffee) does not increase mental performance but may increase nervousness, irritability, tremors, and headache. Heavy coffee drinkers become psychically dependent upon caffeine. If caffeine is withheld, a person may experience mild withdrawal symptoms characterized by irritability, nervousness, and headache.

Caffeine and the chemically related xanthines, theophylline and theobromine, decrease in the order given in their stimulatory action. They may be included in some over-the-counter drugs. The action of caffeine is to block adenosine receptors as an antagonist. As caffeine has a similar structure to the adenosine group. This means that caffeine will fit adenosine receptors as well as adenosine itself. It inhibits the release of neurotransmitters from presynaptic sites but works in concert with norepinephrine or angiotensin to augment their actions. Antagonism of adenosine receptors by caffeine would appear to promote neurotransmitter release, thus explaining the stimulatory effects of caffeine.

Amphetamines

The stimulation caused by amphetamines is caused by excessive release of norepinephrine from storage sites in the peripheral nervous system. It is not known whether the same action occurs in the central nervous system. Two other theories for their action are that they are degraded slower than norepinephrine or that they could act on serotonin receptor sites. Therapeutic doses of amphetamine elevate mood, reduce feelings of fatigue and hunger, facilitate powers of concentration, and increase the desire and capacity to carry out work. They induce exhilarating feelings of power, strength, energy, self-assertion, focus and enhanced motivation. The need to sleep or eat is diminished.

Levoamphetamine (Benzedrine), dextroamphetamine (Dexedrine), and methamphetamine (Methedrine) are collectively referred to as amphetamines. Benzedrine is a mixture of both the dextro and levoamphetamine isomers. The dextro isomer is several times more potent than the levo isomer.

The misuse and abuse of amphetamines is a significant problem which may include the house wife taking diet pills, athletes desiring an improved performance, the truck driver driving non-stop coast to-coast, or a student cramming all night for an exam.

Ephedrine

Ephedrine is a sympathomimetic amine similar in molecular structure to the well-known drugs phenylpropanolamine and methamphetamine, as well as to the important neurotransmitter epinephrine(adrenaline). Ephedrine is commonly used as a stimulant, appetite suppressant, concentration aid, and decongestant, and to treat hypotension associated with anaesthesia.

In chemical terms, it is an alkaloid with a phenethylamine skeleton found in various plants in the genus *Ephedra* (family Ephedraceae). It works mainly by increasing the activity of norepinephrine(noradrenaline) on adrenergic receptors. It is most usually marketed as the *hydrochloride* or *sulfate* salt.

The herb (*Ephedra sinica*), used in traditional Chinese medicine (TCM), contains ephedrine and pseudoephedrine as its principal active constituents. The same may be true of other herbal products containing extracts from other *Ephedra* species.

Methylenedioxypyrovalerone (MDPV) is a psychoactive drug with stimulant properties that acts as a norepinephrine-dopamine reuptake inhibitor (NDRI). It was first developed in the

1960s by a team at Boehringer Ingelheim.[88] MDPV remained an obscure stimulant until around 2004, when it was reported to be sold as a designer drug. Products labeled as bath salts containing MDPV were previously sold as recreational drugs in gas stations and convenience stores in the United States, similar to the marketing for Spice and K2 as incense.

Incidents of psychological and physical harm have been attributed to MDPV use.

Mephedrone is a synthetic stimulant drug of the amphetamine and cathinone classes. Slang names include drone[93] and MCAT.[94] It is reported to be manufactured in China and is chemically similar to the cathinone compounds found in the khat plant of eastern Africa. It comes in the form of tablets or a powder, which users can swallow, snort, or inject, producing similar effects to MDMA, amphetamines, and cocaine.

Mephedrone was first synthesized in 1929, but did not become widely known until it was rediscovered in 2003. By 2007, mephedrone was reported to be available for sale on the Internet; by 2008 law enforcement agencies had become aware of the compound; and, by 2010, it had been reported in most of Europe, becoming particularly prevalent in the United Kingdom. Mephedrone was first made illegal in Israel in 2008, followed by Sweden later that year. In 2010, it was made illegal in many European countries, and, in December 2010, the EU ruled it illegal. In Australia, New Zealand, and the US, it is considered an analog of other illegal drugs and can be controlled by laws similar to the Federal Analog Act. In September 2011, the USA temporarily classified mephedrone as illegal, in effect from October 2011.

Methylphenidate is a stimulant drug that is often used in the treatment of ADHD and narcolepsy and occasionally to treat obesity in combination with diet restraints and exercise. Its effects at therapeutic doses include increased focus, increased alertness, decreased appetite, decreased need for sleep and decreased impulsivity. Methylphenidate is not usually used recreationally, but when it is used, its effects are very similar to those of amphetamines.

Methylphenidate acts a norepinephrine-dopamine reuptake inhibitor, by blocking the norepinephrine transporter (NET) and the dopamine transporter (DAT). Methylphenidate has a higher affinity for the dopamine transporter than for the norepinephrine transporter, and so its effects are mainly due to elevated dopamine levels caused by the inhibited reuptake of dopamine, however increased norepinephrine levels also contribute to various of the effects caused by the drug.

Methylphenidate is sold under a number of brand names including Ritalin. Other versions include the long lasting tablet Concerta and the long lasting transdermal patch Daytrana.

A 2018 Cochrane review found tentative evidence that methylphenidate may result in serious side effects such as heart problems, psychosis, and death.

Cocaine is an SNDRI. Cocaine is made from the leaves of the coca shrub, which grows in the mountain regions of South American countries such as Bolivia, Colombia, and Peru. In Europe, North America, and some parts of Asia, the most common form of cocaine is a white crystalline powder. Cocaine is a stimulant but is not normally prescribed therapeutically for its stimulant properties, although it sees clinical use as a local anesthetic, in particular in ophthalmology. Most cocaine use is recreational and its abuse potential is high (higher than amphetamine), and so its sale and possession are strictly controlled in most jurisdictions. Other tropane derivative drugs related to cocaine are also known such as troparil and lometopane but have not been widely sold or used recreationally

Nicotine is the active chemical constituent in tobacco, which is available in many forms, including cigarettes, cigars, chewing tobacco, and smoking cessation aids such as nicotine patches, nicotine gum, and electronic cigarettes. Nicotine is used widely throughout the world for its stimulating and relaxing effects. Nicotine exerts its effects through the agonism of nicotinic acetylcholine receptor, resulting in multiple downstream effects such as increase in activity of dopaminergic neurons in the midbrain reward system, and acetaldehyde one of the tobacco constituent decreased the expression of monoamine oxidase in the brain. Nicotine is addictive and dependence forming. Tobacco, the most common source of nicotine, has an overall harm to user and self score 3 percent below cocaine, and 13 percent above amphetamines, ranking 6th most harmful of the 20 drugs assessed, as determined by a multi-criteria decision analysis.

Phenylpropanolamine (PPA; Accutrim; β-hydroxyamphetamine), also known as the stereoisomers norephedrine and norpseudoephedrine, is a psychoactive drug of the phenethylamine and amphetaminechemical classes that is used as a stimulant, decongestant, and anorectic agent.[112] It is commonly used in prescription and over-the-counter cough and cold preparations. In veterinary medicine, it is used to control urinary incontinence in dogs under trade names Propalin and Proin.

In the United States, PPA is no longer sold without a prescription due to a proposed increased risk of stroke in younger women. In a few countries in Europe, however, it is still available either by prescription or sometimes over-the-counter. In Canada, it was withdrawn from the

market on 31 May 2001. In India, human use of PPA and its formulations were banned on 10 February 2011.

DRUG FOR ALZHEIMER'S DISEASE

Alzheimer's disease is a progressive form of dementia. Dementia is a broader term for conditions caused by brain injuries or diseases that negatively affect memory, thinking, and behavior. These changes interfere with daily living.

According to the Alzheimer's Association, Alzheimer's disease accounts for 60 to 80 percent of dementia cases. Most people with the disease get a diagnosis after age 65. If it's diagnosed before then, it's generally referred to as early onset Alzheimer's disease.

There's no cure for Alzheimer's, but there are treatments that can slow the progression of the disease.

Alzheimer's facts

Although many people have heard of Alzheimer's disease, some aren't sure exactly what it is. Here are some facts about this condition:

- Alzheimer's disease is a chronic ongoing condition.
- Its symptoms come on gradually and the effects on the brain are degenerative, meaning they cause slow decline.
- There's no cure for Alzheimer's but treatment can help slow the progression of the disease and may improve quality of life.
- Anyone can get Alzheimer's disease but certain people are at higher risk for it. This includes people over age 65 and those with a family history of the condition.
- Alzheimer's and dementia aren't the same thing. Alzheimer's disease is a type of dementia.
- There's no single expected outcome for people with Alzheimer's. Some people live a long time with mild cognitive damage, while others experience a more rapid onset of symptoms and quicker disease progression.

Symptoms of Alzheimer's disease

Everyone has episodes of forgetfulness from time to time. But people with Alzheimer's disease display certain ongoing behaviors and symptoms that worsen over time. These can include:

- memory loss affecting daily activities, such as an ability to keep appointments
- trouble with familiar tasks, such as using a microwave
- difficulties with problem-solving
- trouble with speech or writing
- becoming disoriented about times or places
- decreased judgment
- decreased personal hygiene
- mood and personality changes
- withdrawal from friends, family, and community

Symptoms change according to the stage of the disease.

Alzheimer's stages

Alzheimer's is a progressive disease, which means the symptoms will gradually worsen over time. Alzheimer's is broken down into seven stages:

- **Stage 1.** There are no symptoms at this stage but there might be an early diagnosis based on family history.
- **Stage 2.** The earliest symptoms appear, such as forgetfulness.
- **Stage 3.** Mild physical and mental impairments appear, such as reduced memory and concentration. These may only be noticeable by someone very close to the person.
- **Stage 4.** Alzheimer's is often diagnosed at this stage, but it's still considered mild. Memory loss and the inability to perform everyday tasks is evident.
- **Stage 5.** Moderate to severe symptoms require help from loved ones or caregivers.

- **Stage 6.** At this stage, a person with Alzheimer’s may need help with basic tasks, such as eating and putting on clothes.
- **Stage 7.** This is the most severe and final stage of Alzheimer’s. There may be a loss of speech and facial expressions.

Drugs

Cholinesterase inhibitors

The main compounds used are the cholinesterase inhibitors (also known as anti-cholinesterase drugs). Four have been licensed for use in many countries. These drugs work by reducing the breakdown of acetylcholine in the brain. Acetylcholine is a chemical substance that occurs naturally in the brain and enables nerve cells in the brain to pass messages to each other. Research has shown that many people with Alzheimer's disease have a reduced amount of acetylcholine, and it is thought that the loss of this chemical interferes with memory function.

The cholinesterase inhibitors include donepezil , galantamine , and rivastigmine. An earlier drug of this type was tacrine , which has mostly been superseded by the newer compounds because of its significant side effects. Side effects of these drugs may include diarrhoea, nausea, insomnia or vivid dreams, fatigue and loss of appetite.

It is important to realise that these drugs are not a cure, and can only stabilise some of the symptoms of early to mid stage Alzheimer's disease for a limited period of time.

NMDA receptor antagonist

More recently, a different type of drug has become available, which works to modify the function of the NMDA receptor. This is involved with the chemical transmitter glutamate, and research has suggested that too much glutamate is damaging or toxic to the nerve cell. Memantine has been licensed in several countries for treatment of moderate to severe Alzheimer's disease. It is the first drug for people in the later stages of the disease. Although memantine can help with the symptoms, there is no evidence that it modifies the underlying pathology of the disease.

VITAMIN E

Vitamin E, an antioxidant, is thought to mitigate the inflammatory effects of plaque formation in the brain. In vitro, vitamin E protects nerve cells from the effects of _-amyloid, but it does

not protect against other central nervous system diseases such as Parkinson's disease, in which oxidation is thought to play a part in neuronal destruction. The argument for the use of vitamin E comes from the Alzheimer's Disease Cooperative Study,25 which evaluated the effects of 10 mg of selegiline once daily and/or 1,000 IU
of vitamin E twice daily as treatments for Alzheimer's disease. The researchers concluded that these agents delayed disability and nursing home placement but not deterioration of cognitive function. The study population appeared to be highly selected: the subjects were younger but had more severe dementia than control patients and were not taking psychoactive medication. Consequently, there have
been questions about whether the results of the study are applicable to a clinical setting.
A recent Cochrane review concluded that after adjusting for differences between patient groups in the
Alzheimer's Disease Cooperative Study, there was insufficient evidence to recommend vitamin E. The Cochrane review also found weak evidence of side effects associated with the use of vitamin E. The risks may be higher in the general population, in which many patients with Alzheimer's disease also have serious coexisting illnesses

SELEGILINE

A number of studies have examined evidence for the use of selegiline (Eldepryl), a selective monoamine oxidase inhibitor, in the treatment of Alzheimer's disease. Most of these studies have shown some improvement in cognition, behavior, and mood, but little evidence of a global benefit in cognition, functional ability, and behavior. In 2000, the authors of a meta-analysis of 15 clinical trials concluded that there was not enough evidence to recommend selegiline as a treatment for Alzheimer's disease.
Because of the risk of stupor, rigidity, severe agitation, and elevated temperature, selegiline therapy is contraindicated in patients who are taking meperidine, and this precaution often is extended to other opioids. Concurrent use of selegiline with tricyclic antidepressants and selective serotonin reuptake inhibitors also should be avoided. These restrictions may limit the use of selegiline in patients with Alzheimer's disease.

ESTROGEN

Several descriptive studies have shown that postmenopausal women who take estrogen have a lower incidence of Alzheimer's disease. In addition, a recent review of estrogen and neuroimaging studies demonstrated improved cerebral metabolism in women taking estrogen. Although estrogen may have a neuroprotective effect, it does not appear to improve cognition

or function in patients with Alzheimer's disease,33 and the combination of estrogen and progestin actually may increase the risk for
dementia and stroke.

ANTI-INFLAMMATORY DRUGS

Inflammation surrounding _-amyloid plaques with resultant destruction of neurons is thought to be a key factor in the pathogenesis of Alzheimer's disease. Observational studies have found that persons who regularly use nonsteroidal anti-inflammatory drugs (NSAIDs) have a decreased incidence of Alzheimer's disease Thus,NSAIDs likely have some neuroprotective effect. However,several studies of anti-inflammatory drugs do not show a benefit for treatment.

Epilepsy and Seizures

The term *epilepsy* is a collective designation for a group of chronic central nervous system (CNS) disorders characterized by recurrent abnormal discharges of CNS neurons. The abnormal discharge may be limited to a focal area or encompass diffuse areas of the brain. Although the abnormal discharge itself may have no clinical manifestations, such a discharge often leads to a seizure. The epileptic seizure takes many forms, ranging from brief cessations of responsiveness without loss of consciousness to convulsions with accompanying loss of consciousness. **Table 11.1** describes the different seizure types.

Table 11.1 **Types of Seizures**

	Seizure Type	**Features**
Partial seizures (focal, local)	Simple	Motor, somatosensory, autonomic, or psychic symptoms, with loss of consciousness
	Complex	Impaired consciousness at the outset Simple partial seizure followed by impaired consciousness
Generalized seizures (convulsive or nonconvulsive)	Absence Typical Atypical	Sudden brief lapses of consciousness with loss of posture Typical form + brief motor activity or loss of muscle tone
	Myoclonic	Isolated jerking movements
	Clonic	Repetitive jerking movements without muscle rigidity
	Tonic	Muscle rigidity without jerking movements
	Tonic-clonic	Muscle rigidity followed by rhythmic jerking movements
	Atonic	Loss of muscle tone
* Partial seizures can evolve to generalized tonic-clonic.		

Misdiagnosis or improper drug selection generally makes epilepsy worse, so it is critical that the correct seizure disorder is identified and that it is treated with the most efficacious drug. If the drug of choice fails to control the seizures, then a follow-up agent is used.

Status epilepticus

Status epilepticus is the term used to describe prolonged seizures (usually lasting 30 minutes or more) or multiple seizures that occur without recovery of consciousness. Status epilepticus constitutes a medical emergency, as the risk of death or brain damage increases the longer the seizures continue. Treatment involves maintaining the patient's airway and giving oxygen, a bolus of glucose (as the brain is a huge consumer of glucose), and intravenous (IV) or rectal diazepam to terminate the seizure. IV diazepam is given in the form of an emulsion to prevent thrombophlebitis (inflammation of a vein due to a blood clot).

Antiepileptic Agents

Phenytoin

Mechanism of action. Phenytoin limits the repetitive firing of action potentials in brain neurons by slowing the rate of recovery of voltage-activated Na^+ channels from inactivation (**Fig. 11.1**).

Pharmacokinetics

– Slow, unpredictable absorption

– Ninety percent bound to plasma proteins

– Metabolized in liver to inactive metabolites

Uses

– Effective in all types of epilepsy except absence and atonic seizures

– Trigeminal neuralgia

Side effects. Phenytoin is relatively safe, but the following may occur:

– Gingival hyperplasia is the most common side effect in children (20% of patients). Infections are minimized by good oral hygiene.

– CNS: nystagmus, ataxia, vertigo, and diplopia

– Hyperglycemia, osteomalacia, lymphadenopathy, rashes (Stevens-Johnson syndrome [erythema multiforme bullosum]), and hematological reactions (leukopenia, megaloblastic anemia, thrombocytopenia, agranulocytosis, and aplastic anemia). These are allergic reactions that require cessation of therapy.

– Hirsutism

– Fetal abnormalities

– Cardiovascular collapse can occur after IV phenytoin.

Carbamazepine

Mechanism of action. Carbamazepine limits the repetitive firing of action potentials by slowing the rate of recovery of voltage-activated Na^+ channels from inactivation (fig.1)

Neuronal sites of action of antiepileptics.

Antiepileptic drugs act at many neuronal sites to inhibit excitation of the neuron. Gamma-aminobutyric acid (GABA) mimetics enhance the inhibitory effects of GABA at the $GABA_A$ receptor/Cl^- channel. Other antiepileptics block voltage-dependent Na^+ channels, which can inhibit the release of the excitatory neurotransmitter glutamate, or they can act on the neurons themselves to inhibit action potentials. Other drugs block the *N*-methyl-d-aspartate (NMDA) glutamate receptor or T-type Ca^{2+} channels.

Pharmacokinetics

– Absorption slow and erratic

– Metabolized in liver; may induce hepatic enzymes

Uses

– Generalized tonic-clonic seizures

– Complex partial seizures

– Trigeminal neuralgia

Note: Carbamazepine is ineffective for absence seizures.

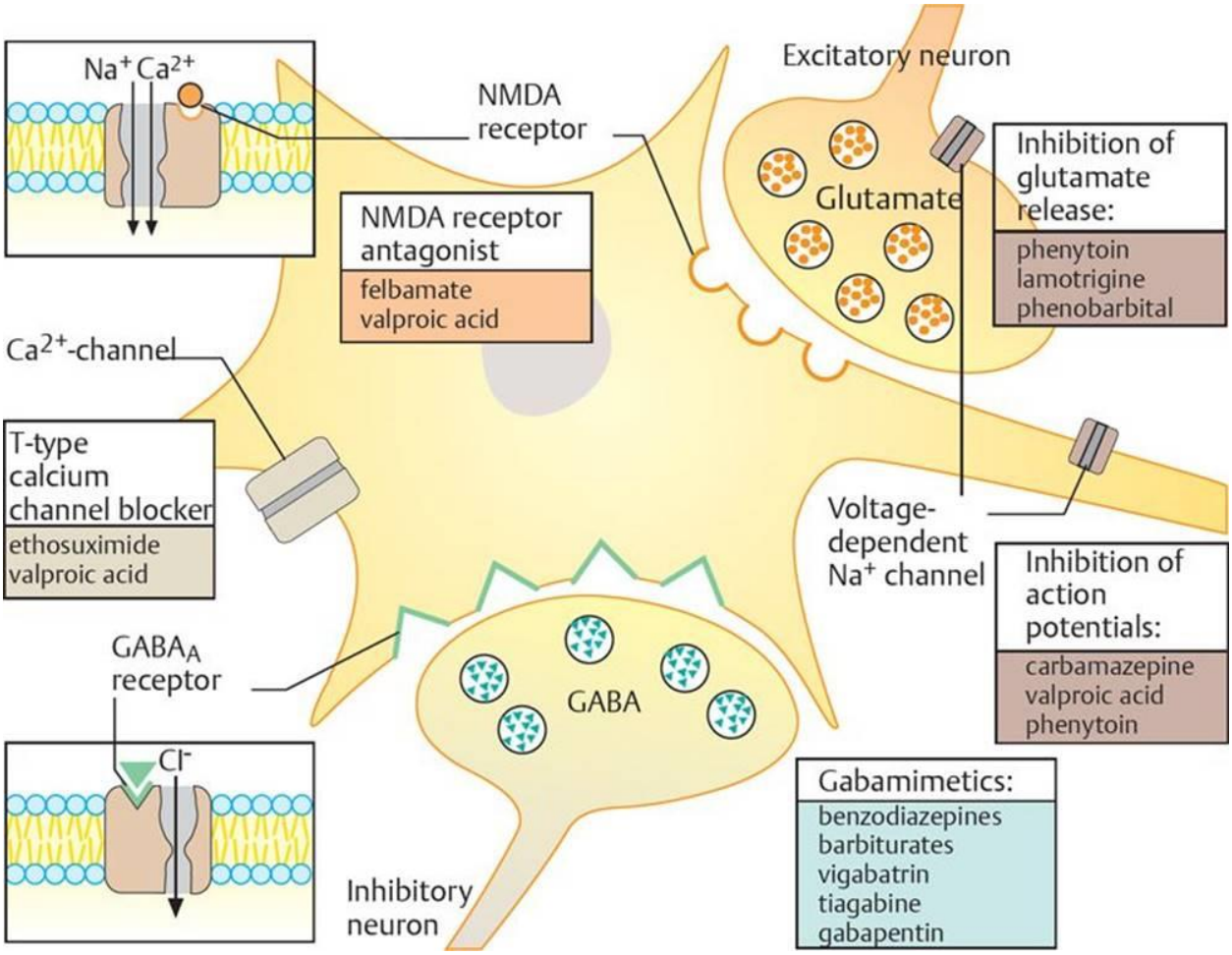
Side effects

– Gastrointestinal (GI) upset

– Vertigo, diplopia, and blurred vision

– Hematological disorders: aplastic anemia, thrombocytopenia (low platelet count), agranulocytosis (failure of bone marrow to produce white blood cells), and leucopenia (low white blood cell count)

– Hypersensitivity



Phenobarbital

Mechanism of action. Phenobarbital is a long-acting barbiturate that potentiates and mimics gamma-aminobutyric acid (GABA). It increases the threshold for action potential firing and inhibits the spread of activity from focus **(Fig. 1)**

Pharmacokinetics

– Effective orally

– Induces hepatic enzymes

Uses

– Generalized tonic-clonic epilepsy

– Partial seizures

– Prophylaxis or treatment of febrile convulsions

Side effects

– Sedation (tolerance develops)

– Rashes are seen in 1 to 2% of patients. These may be scarlatiniform or morbilliform and are symptomatic of allergic reaction.

– Nystagmus (a rapid, involuntary, oscillatory motion of the eyeball) and ataxia (the inability to coordinate voluntary muscular movement) at excessive doses

Febrile convulsions

Febrile seizures (seizures associated with elevated body temperature) are the most common type in children, affecting 2 to 5% between the ages of 6 months and 5 years, with the peak incidence at 18 months. These seizures are not associated with trauma, infection, metabolic disturbances, or a history of seizures, and most last less than 10 minutes. More serious i llnesses must be ruled out, but treatment of simple febrile seizures with anticonvulsants is generally not recommended, as the potential drug toxicities associated with these medications outweigh the relatively minor risks associated with the convulsion. There is also no need to specifically cool the child in a cooling bath or to administer an antipyretic drug, e.g., acetaminophen, to reduce the fever. Most febrile convulsions will stop on their own after a few minutes.

Primidone

Mechanism of action. Mechanism is similar to that of phenobarbital.

Pharmacokinetics. Primidone is metabolized in the liver to phenobarbital and phenylethylmalonamide (PEMA).

Uses

– Complex partial seizures (primidone is more effective than phenobarbital)

– Generalized tonic-clonic seizures and simple partial seizures

– Frequently combined with phenytoin in refractory cases

Side effects

– Rashes, leukopenia, thrombocytopenia, and systemic lupus erythematosus

– CNS depression

Valproic Acid

Mechanism of action. Valproic acid increases Na^+ channel inactivation, increases GABA-mediated synaptic inhibition, and inhibits T-type Ca^{2+} channel activation (**Fig. 11.1**). Its anti-convulsant action continues after the drug has been withdrawn.

Pharmacokinetics

– Ninety percent bound to plasma proteins

– Metabolized by the cytochrome P-450 enzymes, but it does not induce these enzymes.

Uses

– Absence seizures, especially of the myoclonic types that are difficult to treat with other drugs. It appears to have an equivalent effect as ethosuximide for absence seizures.

– Combination therapy in the treatment of generalized tonic-clonic seizures and for complex partial seizures

Side effects

– Alopecia (reversible) in 5% of patients

– Transient GI effects in 16% of patients

– CNS: mild behavioral effects, ataxia, and tremor; not a CNS depressant

– Hepatic failure has been reported but is rare.

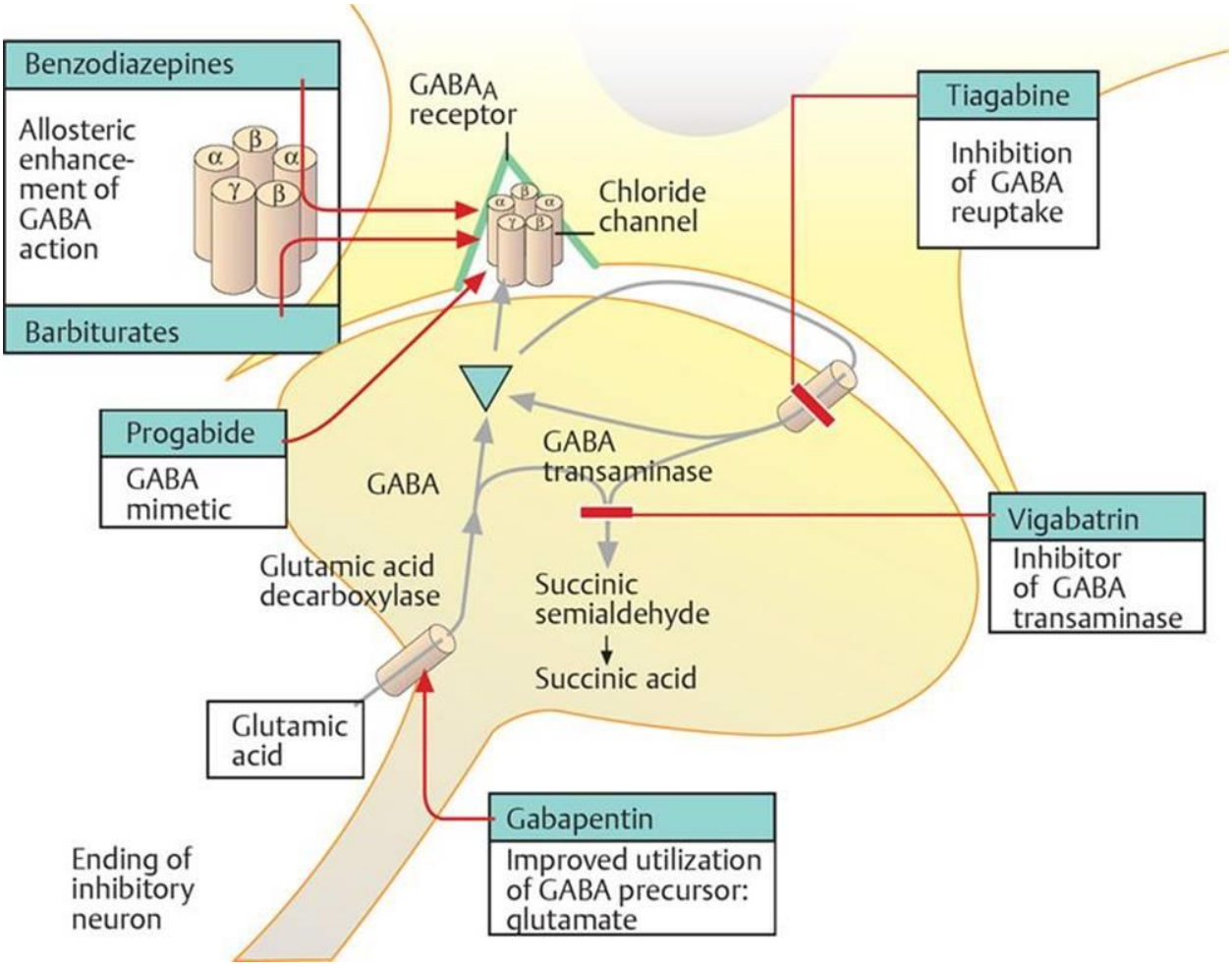
Note: Valproic acid should not be used in pregnancy, as it has been shown to be teratogenic in animals.

Benzodiazepines

Mechanism of action. Benzodiazepines augment the action of GABA at $GABA_A$ receptors, which are ligand-gated chloride ion channels (**Figs. 2**).

Fig. 2 **Sites of action of antiepileptics in GABAergic synapse.**

Many antiepileptic drugs act on GABA in a number of ways. Some drugs act presynaptically to increase the production of GABA or to reduce its degradation. Others act to inhibit the reuptake of GABA from the synaptic cleft. Progabide mimics the inhibitory effects of GABA at the $GABA_A$receptor, whereas benzodiazepines act on the $GABA_A$ receptor to enhance the effects of GABA.



Uses

– Chronic treatment of epilepsy (clonazepam and clorazepate)

– Status epilepticus (lorazepam or diazepam IV)

– Atonic and akinetic seizures, especially as adjuncts

– Absence seizures, but not preferred because of CNS depression

Note: Benzodiazepines do not prevent generalized tonic-clonic seizures

Side effects

– Sedation is the most common side effect.

– Ataxia

– Behavioral problems, such as aggression, anxiety, and restlessness

– Amnesia

Ethosuximide

Mechanism of action. The mechanism of action for ethosuximide is unknown, but it does enhance CNS inhibition.

Uses. Ethosuximide is effective only in absence seizures. It is the drug of choice for this condition.

Side effects

– GI irritation: nausea, vomiting, and anorexia (a lack or loss of appetite for food)

– CNS depression: drowsiness, lethargy, euphoria, dizziness, headache, and hiccups

– Rashes: urticaria (hives) and Stevens-Johnson syndrome (rare)

– Blood dyscrasias (an abnormal condition of the blood) (rare)

Gabapentin

Mechanism of action. The mechanism of action for gabapentin is unknown. Gabapentin is chemically related to GABA but is not an agonist at GABA receptors. It may enhance GABA release (**Fig. 2**).

Uses

– Treatment of partial seizures as an adjunctive to other drugs

Side effects

– Sedation, dizziness, ataxia, nystagmus, and tremor

Note: Gabapentin should be used with caution in children because it may produce adverse psychiatric symptoms, including thought disorders and hostility.

Drug interactions. This agent does not alter serum concentration of other a nticonvulsants.

Felbamate

Uses

– Partial seizures

– Lennox-Gastaut syndrome in children

Side effects

– CNS: insomnia and headache

– GI: anorexia, vomiting, and nausea

– Allergic reactions: hematological and dermatological reactions

– Acute liver failure

Drug interactions. Felbamate may alter concentrations of other anticonvulsants.

Lennox-Gastaut syndrome

Lennox-Gastaut syndrome is a disorder of childhood characterized by multiple difficult-to-treat seizure types. It is usually accompanied by some form of cognitive impairment. Antiepileptic drugs may control seizures for a time, but tolerance frequently develops.

Lamotrigine

Mechanism of action. Lamotrigine inhibits voltage-dependent Na^+ channels of presynaptic membrane, which decreases the release of excitatory amino acid neurotransmitters.

Uses

– Monotherapy and adjunctive therapy for partial and secondarily generalized tonic-clonic seizures in adults

– Lennox-Gastaut syndrome in both children and adults

Side effects. Approximately 1 in 1000 people experience severe and potentially life-threatening skin rashes. These are rarely fatal, but children are at higher risk. This can be reduced by slowly increasing the dose.

Topiramate

Mechanisms of action

– Inhibits voltage-dependent Na^+ channels of presynaptic membrane

– Potentiates the action of GABA by a unique mechanism, different from that of the benzodiazepines or barbiturates

– Blocks excitatory amino acid receptors

Uses

– Monotherapy in patients 10 years of age and older with partial onset or primary generalized tonic-clonic seizures

– Adjunctive therapy in partial seizures

Side effects

– Mainly involve CNS depression: fatigue, dizziness, ataxia, and decreased cognition

– Hypersensitivity

Tiagabine

Mechanism of action. Tiagabine is a GABA reuptake inhibitor (**Fig. 11.2**).

Uses

– Adjunctive therapy in partial seizures

Side effects

– Mainly involve CNS depression: fatigue, dizziness, ataxia, and decreased cognition

Levetiracetam

Mechanism of action. The mechanism of action for levetiracetam is unknown.

Uses

– Adjunctive therapy in partial seizures

Side effects

– Mainly involve CNS depression: fatigue, dizziness, ataxia, and decreased cognition

Zonisamide

Mechanism of action. Zonisamide prolongs Na^+ channel inactivation and inhibits T-type Ca^{2+} current.

Uses

– Adjunctive therapy in partial seizures

Side effects

– Mainly involve CNS depression: fatigue, dizziness, ataxia, and decreased cognition

General anesthetics

General anaesthetics (GAs) cause a controlled and reversible loss of consciousness, analgesia and amnesia, but despite having been in use for over 150 years, the precise mechanism of action of commonplace GAs is still not fully understood. A variety of compounds with widely different chemical structures can act as GAs. Central nervous system (CNS) areas affected by GAs include the cerebral cortex, thalamus, reticular activating system and spinal cord, and potential molecular targets include GABA, NMDA, serotonin (5-HT) and glycine receptors, as well as voltage-gated ion channels. GAs are delivered intravenously (IV) or are inhaled, by specially trained anaesthesiologists who must closely monitor the patient's vital signs during the procedure. Muscle relaxants (neuromuscular blockers) such as **pancuronium**, **rocuronium**, **vecuronium**, **atracurium**, **mivacurium**, and **succinylcholine** are used alongside the GA agents. The effect of these neuromuscular blockers can be reversed at the end of surgery by administration of anticholinesterase drugs (e.g. **neostigmine**).

Following a premedication step, general anaesthesia is described as a four stage process: Stages 1-3 represent the safe clinical window during which surgery can proceed, stage 4 must be avoided.

Several different types of drug are given together during general anaesthesia.

Stage 1: induction - is the time between administration of the drug and loss of consciousness. Administered IV or by inhilation.

Stage 2: excitement - this stage is characterised by erratic breathing and heart rate, and is associated with a vomiting risk. Modern, fast-acting drugs have been designed to limit the time spent in stage 2.

Stage 3: surgical anesthesia - during this stage muscles relax, motor reflexes are blunted, vomiting stops, breathing is depressed and eye movements cease. Anaesthesia is then maintained for the duration of the procedure using IV or inhalational anaesthetics.

Stage 4- overdose- administration of medication overdose causes brain stem or medullary suppression and leads to respiratory and cardiovascular collapse.

Malignant hyperthermia is a rare but potentially lethal complication of anaesthesia, most commonly associated with use of the volatile anaesthetics. This condition is characterised by a rapid rise in temperature, increased muscle rigidity, tachycardia, and acidosis. **Dantrolene** sodium is used in the treatment of malignant hyperthermia.

A number of different neurotransmitters and receptors are also known to be involved in general anesthesia:

- ***N*-Methyl-D-aspartic acid (NMDA) receptors:** some general anesthetics bind to NMDA receptors, including ketamine and nitrous oxide (N_2O). They are known to be important in controlling synaptic plasticity and memory functions
- **5-hydroxytryptamine (5-HT) receptors:** normally activated by the neurotransmitter serotonin, they play a part in controlling the release of a number of other neurotransmitters and hormones
- **Glycine receptor:** glycine can act as a neurotransmitter and has a number of roles. It has been shown to improve sleep quality.

Classification • Inhalation Gas: Nitrous Oxide

• Volatile Liquid: Halothane, Enflurane, Isoflurane, Desflurane, Sevoflurane

• Intravenous – Inducing Agent: thiopentone Sod., methohexitone, Sod Propfol, Etomidate

– Slower acting drugs: Benzodiazepam, Diazepam, Lorazepam, Midazolam facebook.com/notesdental

Nitrous oxide

Mechanism

The pharmacological mechanism of action of N_2O in medicine is not fully known. However, it has been shown to directly modulate a broad range of ligand-gated ion channels, and this likely plays a major role in many of its effects. It moderately blocks NMDAR and β_2-subunit-containing nACh channels, weakly inhibits AMPA, kainate, $GABA_C$ and $5\text{-}HT_3$ receptors, and slightly potentiates $GABA_A$ and glycine receptors.[54][55] It also has been shown to activate two-pore-domain K^+
channels. While N_2O affects quite a few ion channels, its anaesthetic, hallucinogenic and euphoriant effects are likely caused predominantly, or fully, via inhibition of NMDA receptor-mediated currents.[54][57] In addition to its effects on ion

channels, N_2O may act to imitate nitric oxide (NO) in the central nervous system, and this may be related to its analgesic and anxiolytic properties. Nitrous oxide is 30 to 40 times more soluble than nitrogen.

The effects of inhaling sub-anaesthetic doses of nitrous oxide have been known to vary, based on several factors, including settings and individual differences however, from his discussion, Jay suggests that it has been reliably known to induce the following states and sensations:

- Intoxication
- Euphoria/dysphoria
- Spatial disorientation
- Temporal disorientation
- Reduced pain sensitivity

A minority of users also will present with uncontrolled vocalisations and muscular spasms. These effects generally disappear minutes after removal of the nitrous oxide source

Halothane

Fluothane (halothane) is an inhalation anesthetic. Induction and recovery are rapid, and depth of anesthesiacan be rapidly altered. Fluothane (halothane) progressively depresses respiration. There may be tachypneawith reduced tidal volume and alveolar ventilation. Fluothane (halothane) is not an irritant to the respiratorytract, and no increase in salivary or bronchial secretions ordinarily occurs. Pharyngeal and laryngeal reflexes are rapidly obtunded. It causes bronchodilation. Hypoxia, acidosis, or apnea may develop during deep anesthesia.

Fluothane (halothane) reduces the blood pressure and frequently decreases the pulse rate. The greater the concentration of the drug, the more evident these changes become. Atropine may reverse the bradycardia. Fluothane (halothane) does not cause the release of catecholamines from adrenergic stores. Fluothane (halothane) also causes dilation of the vessels of the skin and skeletal muscles.

Cardiac arrhythmias may occur during Fluothane (halothane) anesthesia. These include nodal rhythm, AV dissociation, ventricular extrasystoles, and asystole. Fluothane (halothane) sensitizes the myocardial conduction system to the action of epinephrine and norepinephrine, and the combination may cause serious cardiac arrhythmias. Fluothane (halothane) increases cerebrospinal-fluid pressure. Fluothane (halothane) produces moderate muscular relaxation. Muscle relaxants are used as adjuncts in order to maintain lighter levels of anesthesia. Fluothane (halothane) augments the action of nondepolarizing relaxants and ganglionic-blocking agents. Fluothane (halothane) is a potent uterine relaxant.

The mechanism(s) whereby Fluothane (halothane) and other substances induce general anesthesia is unknown. Fluothane (halothane) is a very potent anesthetic in humans, with a minimum alveolar concentration (MAC) determined to be 0.64%. The MAC has been found to decrease with age.

Glaucoma

Glaucoma is 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. If left untreated, glaucoma will cause progressive loss of outer field of vision (peripheral vision), then developed tunnel vision, and resulted in permanent total blindness.

Glaucoma is usually caused by abnormally high pressure inside the eye (intraocular pressure), but can be happened with normal intraocular pressure. Glaucoma is described as open-angle or angle-closure, depending on the mechanism of the obstruction of drainage.

Treatment

Glaucoma cannot be cured and damage produced cannot be reversed. But if detected early and treated appropriately, further damage to vision may be prevented or delayed. Treatment aims to control the condition and minimize future damage. Currently, the most effective way of treating glaucoma is to decrease the intraocular pressure by using glaucoma drugs, laser treatment, eye surgery or a combination of these based on the patient's type of glaucoma, severity, medical history and health conditions. The mechanisms involved are mainly through improving drainage of fluid in the eye or lowering the amount of fluid produced in the eye.

Acute angle-closure glaucoma develops rapidly, so the condition needs to be treated quickly. Besides topical eye preparations and systemic medicines to quickly reduce the pressure in your eye, laser iridotomy which uses high-energy beams of light to create holes in your iris and enable fluid to flow, or other surgery may be used. If you also have a cataract, removing it may open the angle in the eye and increase the outflow of the fluid so as to reduce the intraocular eye pressure.

Types of Medications

Alpha Adrenergic Agonists

This medication both reduces aqueous humor production and increases its outflow.

Allergic reactions frequently occur with this class of medication.

Examples include:

- Apraclonidine
- Brimonidine
- Epinepherine
- Dipivefrin

Beta Blockers

This type of medication works to lower eye (intraocular) pressure by reducing aqueous humor production and decreasing the rate at which the fluid flows into the eye.

Examples include:

- Timolol
- Levobunolol
- Carteolol
- Metipranolol
- Betatoxol
- **Carbonic Anhydrase Inhibitors**

  These are eye drops or pills that reduce fluid production in the eye. Examples include:

- Dorzolamide
- Brinzolamide
- Acetazolamide: an oral medication
- Methazolamide): an oral medication

Miotics

This type of medication is a cholinergic agent, which causes the pupil to become much smaller in diameter and helps increase fluid drainage from the eye. Examples include:

- Pilocarpine
- Echothiophate

Prostaglandin Analogs

This medication reduces eye pressure by increasing the outward flow of fluid from the eye. Examples include:

- Tafluprost ophthalmic solution
- Latanoprost
- Bimatoprost
- Travoprost
- Unoprostone isopropyl ophthalmic solution
- Latanoprostene bunod ophthalmic solution
- **Rho Kinase Inhibitors**
- Netarsudil ophthalmic solution

Combinations

Combinations of eye drops may also be used to achieve better results. Examples include:

- Dorzolamide and timolol
- Latanoprost and timolol
- Brimonidine and timolol
- Brinzolamide and brimonidine
- Netarsudil and latanoprost

Hallucinogens

Hallucinogens are a type of drug that changes a person's perception of reality. Also known as 'psychedelic drugs', hallucinogens make a person see, feel and hear things that aren't real, or distort their interpretation of what's going on around them. Some are quick acting, others take longer to take effect. Being under the influence of a hallucinogen is commonly called 'tripping'.Some hallucinogens are manufactured, like LSD (lysergic acid diethylamide), PCP (phencyclidine, or 'angel dust') and ketamine. Others are naturally occurring compounds found in particular plants. For instance, the peyote cactus produces the hallucinogen mescaline, while psilocybin is found in certain mushrooms, known as 'magic mushrooms'.

Types of hallucinogens

Hallucinogens come in a number of different forms. For example:

- **LSD** is a powerful drug – typically, small squares of blotting paper or gelatine are soaked in LSD, which are then swallowed, although it may also come in tablets or capsules.
- **PCP** usually comes in the form of tablets, capsules or powders of various colours. It is usually swallowed, sniffed or injected, but is sometimes smoked.
- **Ketamine** is used by medical practitioners and veterinarians as an aesthetic. It is often used illegally as a hallucinogenic drug. It can be made into tablets or pills, or dissolved in liquid. It is usually swallowed, snorted or injected.
- **Magic** mushrooms can be cooked, boiled into a drink or eaten raw.
- **Mescaline** from the peyote cactus can be found as a white powder, while dried, ground peyote buttons can be found as capsules. It is usually swallowed, but can be chewed or smoked.
- **Ayahuasca** is a plant based hallucinogenic tea. Traditionally used in parts of South America, Ayahuasca has become popular amongst western travellers.

Some depressant and stimulant drugs also have a hallucinogenic effect in high doses, including cannabis and ecstasy. Since a person's sense of distance, time and objective reality are warped when under the influence of hallucinogens, serious injury and accidental death are real risks.

Synthetic hallucinogens

In recent years, a wide range of synthetic products, claiming to have similar effects to hallucinogens, have also been available in Australia. The active ingredient in these products can potentially be a number of chemicals. These synthetic hallucinogens include NBOMes and PMA, and are often sold as other drugs, yet contain very different ingredients, leading to potentially harmful and unexpected effects

How hallucinogens work

Hallucinogens target specific centres of the brain to alter its understanding of sensory input. For instance, a person may be looking at a blank wall, but their hallucinating brain may interpret the blank wall as moving and swirling, or perhaps covered in insects.

Effects of hallucinogens

The effects of hallucinogens depend on the type of drug, the strength of the dose, the functioning of the person taking them and their state of mind.

Generally, some of the common effects of hallucinogens include:

- hallucinations of sight, sound, taste and touch
- a blurring of the senses, such as sounds being ‘felt’ or colours being ‘heard’
- feeling detached from the body
- distortions of time, direction and distance
- relaxation
- accelerated heart rate
- dilated pupils
- nausea and loss of appetite

What Hallucinogens Do in the Brain

While there are multiple different kinds of hallucinogens, they basically all affect one of two pathways in the brain. The first is the serotonin pathway, and the second is the glutamate system.

Serotonin is a chemical that regulates many of the body's basic functions, from mental cognition and thought processes to digestion and sleep patterns. According hallucinogens like LSD that interact with this system stop the activity of serotonin – an event that also occurs when a person is asleep and dreaming. While the dreamlike visions created by use of these hallucinogens is similar to the way dreaming occurs during sleep, there is little understanding of how these hallucinogens actually work. In fact, there could be a number of other systems involved. However, because serotonin affects so many other functions of the body, hallucinogen use can disrupt many of those functions by interfering with the pathway, including causing problems with:

- Sleep patterns
- Heart rate
- Digestion (nausea or vomiting)
- Cognitive capabilities
- Perception of sensory input or time

TREATMENT OR REMEDY FOR HALLUCINOGENIC ADDICTS

Treatment for hallucinogen can be categorized into two which includes:

♣ Medical Base Therapy

♣ Psychotherapy/ Counselling

MEDICAL BASE THERAPY Adjust or Reduce Parkinson Disease Medication.

These medications relieve motor symptoms such as muscle stiffener and tremor by increasing dopamine in the brain which when in excess triggers hallucination and delusion. The following medication is however recommended ♣ Anticholinergic(ARTANE,COGENTIN) ♣ Amantadine ♣ Dopamine Agonist(MIRAPEX,REQUIP,PARLODEL) ♣ COMT inhibitor(COMTAN) ♣ Selegiline

Initiation of Antipsychotic Treatment.

These are agents which balance abnormal chemical levels in the brain by reducing excess dopamine release example ♣ Pimavanserin ♣ Closapine ♣ Risperidone ♣ Olanzipine ♣ Systematic Desensitization. These involves gradual production of the amount of hallucinogen

being by the individual to wean them of the addiction while treating any associated withdrawal symptoms such as paranoia.

Hallucinogenic abuse rehabilitation is offered for a range of Hallucinogenic drugs. Commonly abused Hallucinogens include: Ketamine, LSD, Magic Mushrooms, DMT, MDMA, Mescaline, PCP, Peyote and many more. Inpatient and outpatient treatment is recommended to help treat the underlining cause for the dependence and or addiction. Treatment programs available in Hallucinogen rehabs are designed specifically to assist an individual with the learning process of addiction. Rehab also helps you with learning more about yourself in order to put a stop to the vicious cycle of Hallucinogenic addiction. Get the support you need to get into recovery from Hallucinogen abuse and addiction today.

Inpatient Hallucinogenic Rehab ♣ Inpatient treatment is a setting where an individual will stay at the treatment center for a specific period of time, typically for 30, 60 or 90 days. Consisting of counseling, group counseling and to change an individual's surroundings that were present at the time of addiction development. This is usually best done by getting treatment out of one's home town. Inpatient rehab also works to treat the underlining cause of the addiction psychological, history or environmental. This form of treatment has the best track record as it usually leads to lasting recovery.

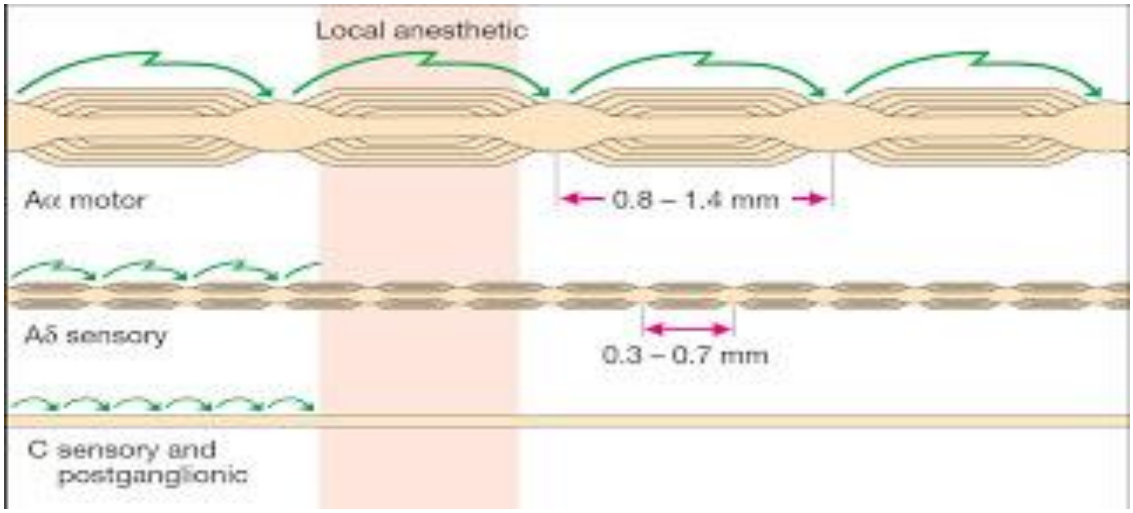
PSYCHOTHERAPY AND COUNSELLING ♣ Individual Therapy- This involves the interaction and counselling between the hallucinogen addict and a psychologist. ♣ Group Therapy. This involves at least six individual with similar conditions being counselled on the use of hallucinogens

Local Anesthetics

- Local Anesthetics(LA) reversibly block the impulse conduction in any part of nervous system & in all nerves including sensory & motor types

-They provide a transient loss of sensation in a restricted region of the body à preferred for performing minor surgeries à neither loss of consciousness nor maintenance of vital functions during the surgery

The steps of local anesthesia



· Smaller C-fibers which are un-myelinated & B-fibers which are lightly myelinated are blocked first à Pain, temperature, touch sensation are blocked first

· Small type A delta fibers which are myelinated blocked next followed by heavily myelinated A alpha, beta, gamma fibers are blocked last à loss of skeletal muscle tone

Classification

Amide Type

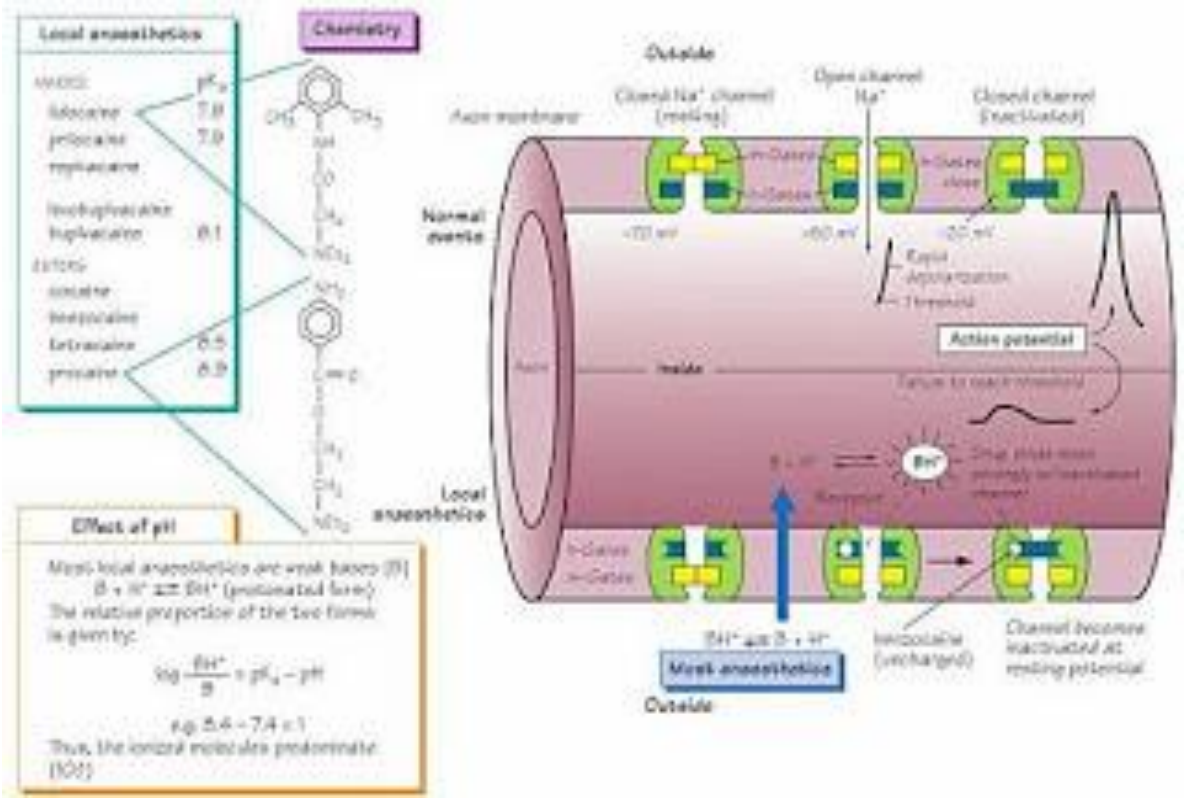
- **Longer Acting:** Bupivacaine, levo-Bupivacaine, Etidocaine, Ropivacaine, Dibucaine
- **Intermediate acting:** Lidocaine (Xylocaine), Mepivacaine, Prilocaine

Ester Type

- **Longer Acting:** Tetracaine (Amethocaine)
- **Intermediate Acting:** Cocaine
- **Short Acting:** Procaine, Chloroprocaine, Benzocaine, Betambenm Proparacaine

Miscellaneous: Pramoxine (Pramocaine), Dyclonine, Oxetacaine

Mechanism of Action



- Local Anesthetic molecules consist of an aromatic part & a basic amine side à both are linked with an ester or amide bond
- These are weak bases à partly ionized with acids à unionized parts is lipophilic in nature and which helps the LA to penetrate into nerve membrane à after going inside the ionized part which is active at the receptor side
- LAs à block the voltage gated Na+ channels during depolarisation à Na^+ permeability decreases à consequently nerve conduction is blocked
- Blocking action of LA is favouored by depolarization & resting membrane is less sensitive to LA
- Na+ channel has an Activation Gate (AG) on its extracellular site & Inactivation Gate (IG) on its intracellular site
- Voltage – Gated Na+ channels exist in 3 functional states

o Resting or Closed state à at the normal resting potential à AG is closed

o Activated or Open state à favoured by brief depolarization à open AG to allow Na+ ions to follow in along concentration gradient

o Inactivated or Blocked state à occlusion of channel by a floppy part of the intracellular region of the channel protein

- Na+ ions flow ceases as soon as inactivation gate closes
- LA receptor is located in the transmembrane pore of NA+ channel in its intracellular half
- LA diffuses through the membrane in unionized lipophilic form à it then reionises & binds to the LA receptor à binding of LA to its receptor stabilizes the channel in the inactivated state à Inactivation gate closes & Na+ ion flow ceases à LAs prevent the initiation & propagation of the nerve impulse by reducing the passage of Na+ ions through voltage-gated Na+ channels
- Effect of pH on LA action
- LAs are basic in nature so à they are action is strong at alkaline pH & less at acidic pH à unionized form is needed for its diffusion through axon membrane
- LAs are less effective in infected tissue, because in infected area the extracellular pH is acidic à LAs are poorly diffuses in infected tissue due to more ionization

Prolongation of Action

- Anything that delays the absorption of LA into the circulation will prolong its action & reduce its systemic toxicity
- Adrenaline is most commonly uses and it doubles the duration of LA action à Adrenaline due to its alpha action causes vasoconstriction and delays the diffusion of LA
- A vasoconstrictor should not be used for nerve block of an extremity or end organ (like on fingers, toes, nose, and penis) àintense vasoconstriction leads to total ischaemia & necrosis
- To avoid cardiac complications with use of Adrenaline, a synthetic vasoconstrictor Felypressin (a synthetic vasopressin) can be usedà it doesn't affect the heart rate, BP & also preferred in patients with cardiovascular diseases

Give the rational for not prescribing Adrenaline along with Local Anesthetic during circumcision?

- Circumcision of Penis à Adrenaline leads to ischaemia à necrosis

Pharmacokinetics

- The presence of ester or amide bond à governs the biotransformation & hypersensitivity reactions
- Ester type of LAs à hydrolysed by plasma esterases & liver esterases à rapidly hydrolysed à so shorter duration of action ßaction may be prolonged in genetic enzyme deficiency

The spinal fluid contains negligible esterases à intrathecal injection of ester type LAs usually have a longer duration of action

Amide type LAs à degraded by hepatic microsomes through N-dealkylation & subsequent hydrolysis à they have longer duration of action

Hypersenstivity reactions is more common with ester type of LAs à as they are metabolized to PABA or PABA derivatives

Allergic reactions with amide type of LAs are very rare

Ester group of LAs are degraded to PABA, they antagonize the action of sulfonamides

Type of Local Anaesthesia

According to the technique or anatomical site

Topical Anaesthesia

The sensory nerve endings are chief nerve structures affected

It is restricted to mucous membranes, damaged skin surface, wounds or burns à it doesn't work in well n intact skin

The corneal surface, mucosa of mouth, nose, pharynx, trachea and urethra are easily anesthetized

It is also used to facilitate endoscopic procedures & to reduce the pain of haemorrhoids or anal fissure

LAs are à Tetracaine (2%), Lidocaine (2-5%), Eutectic mixture of Lidocaine & Prilocaine (5%), Benzocaine (5%), Dicyclonine (0.5-1%), Pramoxine (1%)

Infiltration Anaesthesia

The dilute solution of LA is injected under the skin to reach sensory nerve terminals

This is used for minor surgeries like incisions or excisions

Adrenaline or Felypressin may be added to retard absorption

LAs are à Lidocaine (1%), Bupivacaine (0.25%), Etidocaine (0.5-1%), Ropivacaine (0.5-1%), mepivacaine (1-3%), Prilocaine (1-4%)

Conduction Block Anaesthesia

LA is injected around the nerve trunk so that the area is distal to the site of injection is anaesthetized

It is of 2 types à 1) Field Block 2) Nerve Block

1) Field Block

o LAs are injected subcutaneously in the surrounding area of the nerve à all the nerves coming to that field are blocked

o Field blocks are applied to the scalp & anterior abdominal walls ß as nerves travel superficially in this area

o Drugs used are Lidocaine (1%), Bupivacaine (0.25%), Etidocaine (0.5-1%), Ropivacaine (0.5-1%), mepivacaine (1-3%), Prilocaine (1-4%)

2) Nerve Block

LA is injected around anatomically localizes nerve trunks i.e., close to the mixed nerve (it is usually described with the name of the nerve e.g., radial nerve block, ulnar nerve block)

Nerve block lasts longer than field block

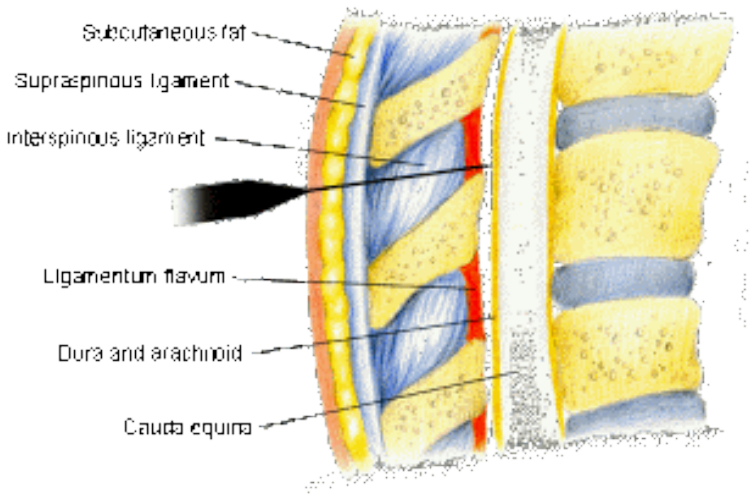
LA is never intentionally injected into the nerve à because this is painful & also lead to nerve damage à LA is deposited as close to the nerve as possible à LA then diffuses from the site of injection into the nerve where it acts

Choice of drug depends on the type of the nerve to be blocked, duration of anesthesia required, the size & health of the patient

<u>Central Nerve Block Anaesthesia</u>

This includes Epidural & Spinal anaesthesia

Epidural Block Anaesthesia



- It is widely used to provide analgesia or anaesthesia in surgical & obstetric practice
- It involves injecting a LA such as lidocaine, bupivacaine or ropivacaine alone or with a small dose of opioid analgesic into the epidural space in the lumbar, thoracic or cervical regions
- Cudal block is also an epidural block but in the caudal (sacral) region
- Introduction of a canula into the epidural space enables prolonged anaesthesia à use of additional dose or continuous infusion of LA can be done

- A vasoconstrictor may also be added to reduce systemic exposure to the LA

Spinal Block Anaesthesia

- It is also referred to as subarachnoid or intrathecal block anaesthesia or as spinal analgesia
- LAs à Lidocaine (3 – 5%), Tetracaine (0.3-0.5%), Bupivacaine (0.5-0.7%) in the spinal subarachnoid space between L_2 & L_3 or L_3 & L_4
- The primary site of action is the nerve root in cauda equine rather than the spinal cord à it is used to anaesthetize lower abdomen & hind limbs
- Vasconstrictors are added to prolong the duration of the block à there is always a danger of restricting the blood supply to the spinal cord
- With proper expertise à the complications of spinal anaesthesia are minimal except for headache, nausea & vomiting [respiratory paralysis, hypotension & cauda equine syndrome (loss of control over bladder & bowel sphincters) à rare complications]

Intravenous Regional Anaesthesia

- It is also named as Bier's block
- It it mainly used for the upper limb & for orthopaedic procedures

Adverse Effects

CNS

-At low doses: tongue numbness, sleepiness, mild headache, visual & auditory disturbances

-At higher conc: Nystagmus, muscular twitching

CVS

-LAs block cardiac Na+ channels & depress abnormal cardiac pacemaker activity, excitability, conduction

- Most LAs produce hypotension (except cocaine)

Blood

- Larger doses of Prilocaine à lead to accumulation of the metabolite Orthotoluidine à which oxidizes haemoglobin to methaemoglobin à higher levels leads to cyanosis ß reducing agents like methylene blue or ascorbic acid may be given intravenously to convert methaemoglobin to haemoglobin

Allergic Reactions

- Ester type LAs are metabolized to PABA derivatives which in turn are responsible for allergic reactions à contact dermatitis, rashes, asthma (rare)
- Amide group of LA don't metabolise to PABA à allergic reactions are very rare

Neuromuscular Junction

- LAs block neuromuscular transmission & enhance the effects of d-tubcurarine à this stabilizing effect is the result of blockade of the nicotinic receptor ion channel

Lidocaine (Lignocaine or Xylocaine)

- It is mostly used multipurpose LA
- It is **used topically on the mucous membranes** in the form of aqueous solutions, jelly, ointment, or as viscous solutions
- It is **used in Infiltration, Nerve block & Epidural anesthesia**
- For **Spinal analgesia** à higher concentration (5%) made hyperbaric with 7.5% dextrose is used
- It is also **combined with Adrenaline** à Adrenaline blocks α_1 receptors located on the blood vessels à which causes vasoconstriction and there will be the less blood supply at the site of injection of Lignocaine à absorption of Lignocaine is delayed à slow absorption of Lignocaine à action is prolonged & toxicity will be reduced [***Q) Basis " for the use of Adrenaline along with Local Anesthetic"***]
- Lignocaine also combined with an Opioid in Intrathecal or Epidural anesthesia à it gives synergistic effect à Mechanism is unknown à its most commonly **used combination in management of pain**
- It has rapid onset of action & which lasts for 1-2 hours
- It is also used Intravenously in the management of Ventricular Arrhythmias occurring during Myocardial Infarction [it shouldn't be given along with propranolol à Propranolol impairs the clearance of Lignocaine à toxicity wil be enhanced]

A/Es

- Dizziness, paraesthesia, euphoria with normal therapeutic doses
- Higher doses – confusion, vertigo, tinnitus & nausea
- Severe toxicity may precipitates Seizures [Diazepam is used]
- Overdose toxicity – Cardiac arrhythmias, lowering BP, coma, respiratory arrest

Myasthenia gravis (MG)

Myasthenia gravis (MG) is an autoimmune disorder of the postsynaptic neuromuscular junction characterized by fluctuating weakness involving variable combinations of ocular, bulbar, limb, and respiratory muscles.

Once uniformly disabling and sometimes fatal, MG can be managed effectively with therapies that include anticholinesterase agents, rapid immunomodulatory therapies, chronic immunosuppressive agents, and thymectomy. Treatment is individualized and depends upon the age of the patient; the severity of the disease, particularly dictated by respiratory or bulbar involvement; and the pace of progression

Myasthenia gravis is an autoimmune disease which results from antibodies that block or destroy nicotinic acetylcholine receptors at the junction between the nerve and muscle.[1] This prevents nerve impulses from triggering muscle contractions. Rarely, an inherited genetic defect in the neuromuscular junction results in a similar condition known as congenital myasthenia.[5][6] Babies of mothers with myasthenia may have symptoms during their first few months of life, known as neonatal myasthenia.[1] Diagnosis can be supported by blood tests for specific antibodies, the edrophonium test, or a nerve conduction study.

CAUSES

- Myasthenia gravis may be inherited, genetic disease, acquired by babies born to mothers with MG

- Nerves communicate with the muscles by releasing chemicals, called neurotransmitters, which fit precisely into receptor sites on the muscle cells.

- In myasthenia gravis, immune system produces antibodies that block or destroy many of the muscles' receptor sites for a neurotransmitter called acetylcholine.

- With fewer receptor sites available, muscles receive fewer nerve signals, resulting in weakness.

SYMPTOMS

Face and throat muscles In about 15 percent of people with myasthenia gravis, the first symptoms involve face and throat muscles, which can cause difficulties with:

♣ Speaking. The speech may be very soft or sound nasal, depending upon which muscles have been affected.

♣ Swallowing. May choke very easily, which makes it difficult to eat, drink or take pills. In some cases, liquids may come out of the nose.

♣ Chewing. The muscles used for chewing may wear out halfway through a meal, particularly if eating something hard to chew, such as sugarcane.

♣ Facial expressions. Family members may note "lost smile" if the muscles that control facial expressions are affected.

Arm and leg muscles

♣ Myasthenia gravis can cause weakness in arms and legs, but this usually happens in conjunction with muscle weakness in other parts of the body – such as eyes, face or throat.

♣ The disorder usually affects arms more often than legs.

♣ If it affects legs, may waddle when walking. Normal dumbbell Weakness dumbbell

Treatment of MG

If diagnosed promptly, some patients may be cured of MG byremoval of the thymus gland (thymectomy) or aggressive immunosuppressant therapy. The effectiveness of treating MG depends on many factors, such as the severity of the disease, the duration of the disease, the patient's age and the patient's overall health. For the most part, however, MG can be well-controlled with the following treatment approaches:

- **Cholinesterase inhibitors:** These are commonly used drugs to treat MG, but they are most useful in mild forms of the condition. These drugs work by preventing the breakdown of acetylcholine, thus increasing the muscle's ability to contract. The most commonly prescribed form of this drug is pyridostigmine (Mestinon).

- **Immunosuppressants:** Corticosteroids and other drugs such as cyclosporine and azathioprine help patients with MG by suppressing the activity of the immune system. These treatments are generally for more severely ill patients. Although they are often very effective, these drugs can have serious associated side effects. The patient should consult with his or her doctor regarding the potential value of these drugs in treating MG.
- **Thymectomy:** A thymectomy is a surgical removal of the thymus gland. There is evidence that thymectomy can lead to remission or reduced drug dependency, but it is more likely to work if undertaken within 6-12 months of the first onset of symptoms. A controlled clinical study of the efficacy of thymectomy in MG is currently underway.
- **Plasmapheresis:** Plasmapheresis is a blood plasma exchange process. It "filters" the blood of acetylcholine receptor antibodies by replacing the patient's plasma with donor plasma. Plasmapheresis can be a life-saving tool in the treatment of MG; however, it is expensive, time-consuming, and can be associated with side effects such as low blood pressure, infection, and blood clots.
- **IVIg:** Intravenous infusion of immunoglobulin can modulate the immune system and reduce the effects of causative autoantibodies in MG. It is used to treat MG with acute worsening, especially with breathing involvement.

For patients with MG, a healthy lifestyle and education about one's disease can maximize management. Some of the best ways to accomplish this include:

- Eating foods that are high in potassium such as bananas, tomatoes, apricots, and broccoli
- Avoiding overexertion
- Advising physicians of the diagnosis prior to taking prescribed drugs that may aggravate MG
- Avoiding excessive heat.

Neurotransmitters Gamma-aminobutyric acid (GABA)- A molecule of relaxation

Feeling stressed and anxious? All you need is GABA!

During those stressful weeks in school or at work, your brain becomes very excited and as a response, your body normally produces GABA to bring your nervous system back to a state of calm. Without GABA, you will increasingly become restless and anxious, and might experience seizures.

What exactly is 'GABA'?

GABA is an amino acid which acts as a neurotransmitter in the central nervous system. GABA's natural function is to reduce the activity of the neurons to which it binds. It inhibits nerve transmission in the brain, calming nervous activity. This can make a person feel more tranquil and give him or her sense of wellbeing.

How does GABA work?

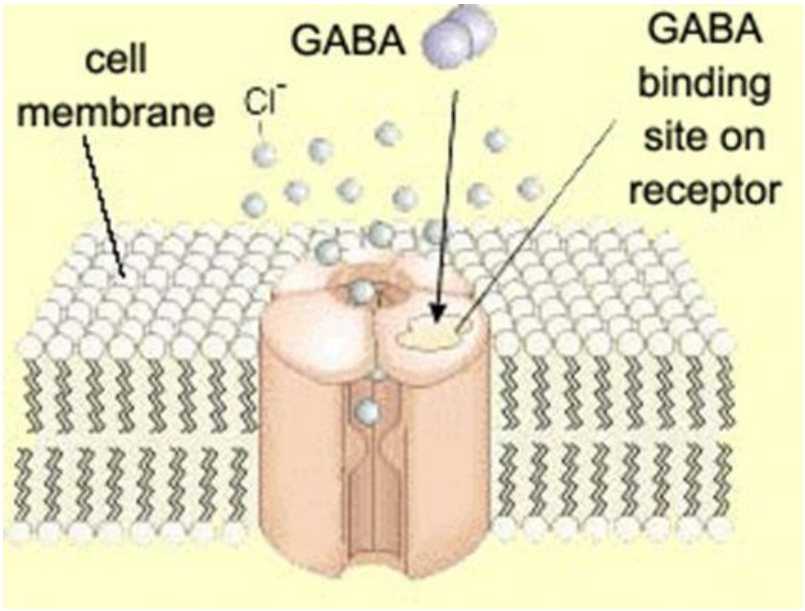
The nervous system is made up of individual nerve cells called neurons. They serve as the body's wiring. Nerve signals are transmitted through the length of a neuron as an electrical impulse. When a nerve impulse reaches the end of the neuron it can jump over to the next cell using chemical messengers called neurotransmitters.

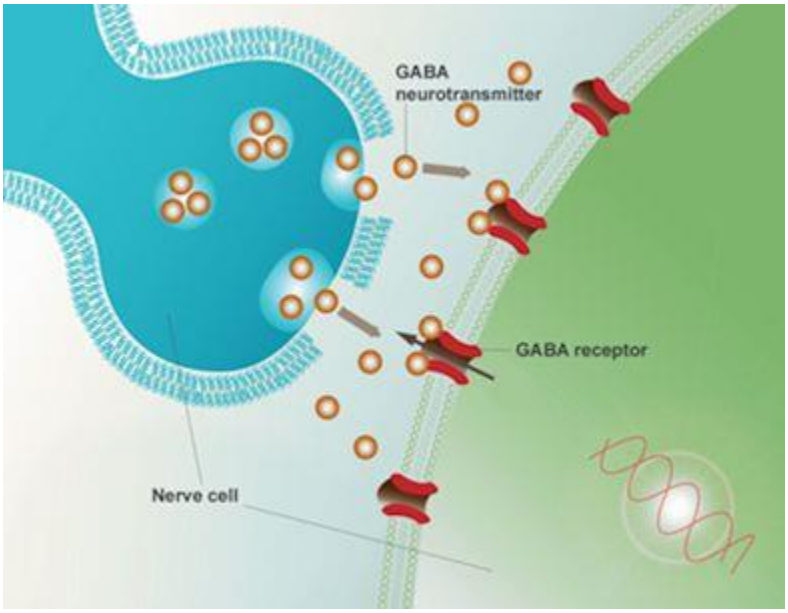
In the central nervous system, which consists of the brain and the spinal cord, neurotransmitters pass from neuron to neuron.

Neurotransmitters are stored at the end of each neuron. When neurotransmitters reach neighbouring neuron, the neurotransmitters click into specialized receptor sites much as a key fits into a lock. When enough neurotransmitters attach to the receptors, the neuron "fires," sending an electrical impulse down its length.

GABA is made in brain cells from glutamate, and functions as an inhibitory neurotransmitter – meaning that it blocks nerve impulses. Glutamate acts as an excitatory neurotransmitter and

when bound to adjacent cells encourages them to “fire” and send a nerve impulse. GABA does the opposite and tells the adjoining cells not to “fire”, not to send an impulse.





What would happen if GABA did not exist?

Without GABA, nerve cells fire too often and too easily. Anxiety disorders such as panic attacks, seizure disorders, and numerous other conditions including addiction, headaches, Parkinson's syndrome, and cognitive impairment are all related to low GABA activity. GABA hinders the

transmission of nerve impulses from one neuron to another. It has a calming or quieting influence. A good example to help understand this effect is caffeine. Caffeine inhibits GABA release. The less GABA, the more nerve transmissions occur. Think what too much coffee feels like: that is the sensation of glutamate without enough GABA.

The reason caffeine does this is that other molecules can bind to the neuron near the GABA binding site and influence GABA's effect.

What's the history of GABA

1883: Gamma-aminobutyric acid was first synthesized, was first known only as a plant and microbe metabolic product.

1950: GABA was discovered to be an integral part of the mammalian central nervous system.

What are the uses of GABA

Many people take GABA as a supplement to improve mood and relieve anxiety. However, there has not been enough research to uncover the side effects and risks of GABA supplements.

There is little evidence that it does anything. Recent medical belief is that GABA will not pass the blood brain barrier. The blood brain barrier is a biologic firewall between the body's general blood circulation and the blood circulation that supplies the brain. It prevents many of the chemicals and drugs which circulate in the blood from reaching the brain. This would mean GABA cannot cross from the body into the brain; consequently it leaves people dubious if then GABA would work.

Nevertheless, people may still take GABA because it could act as a placebo. Also, it may have some affect that hasn't been reported yet, therefore more research needs to be done.

General mechanism of action Neuromuscular blocking agents

Block transmission through the neuromuscular junction (NMJ) at nicotinic receptors, thus decreasing skeletal muscle tone.

NMJ blockers

- **Non-depolarising**

Bind to receptors and prevent acetylcholine (ACh) from stimulating receptors
Model = Curare

Effect: compete with ACh for nicotinic receptor binding sites. The blockade is competitive, hence muscle paralysis occurs gradually.

Examples include tubocurarine, gallamine, atracurium, vecuronium, mivacurium, rocuronium and cisatracurium. These drugs are highly ionised at body pH and contain two quaternary ammonium groups. They are poorly lipid soluble and poorly protein bound.

- **Depolarising**

Produce what appears to be a "persistent" depolarisation of the NMJ. Cause depolarisation by mimicking the effect of Ach but without being rapidly hydrolysed by acetylcholinesterase. Propagation of an action potential is prevented by the area of inexcitability that occurs around the ACh receptors.

Examples include suxamethonium (1951) and decamethonium (1948)
Model = succinylcholine

Action occurs in two phases:

- **Phase I** - initial brief depolarisation of post-junctional membrane skeletal muscle, thus

causing contraction; fasciculations are seen and repolarisation is inhibited

- **Phase II**-"desensitisation blockade"

After the drug has been present for a period of time, the motor end plate loses its sensitivity and depolarisation cannot occur; desensitisation continues for several minutes, even after drug is no longer present. Depolarising NMJ blockers produce persistent depolarisation = desensitisation

Fasciculations can be prevented by pretreatment with a competitive agent.

Histamine release

This is a feature of tubocurare and succinylcholine (others to lesser extent)

Effects of histamine release:

- bronchospasm
- dilatation of peripheral blood vessels (decreased blood pressure)
- excessive secretions
- anticoagulant effect

Interactions of NMJ blockers

Blockade is potentiated with general inhalational anaesthetics; antibiotics, e.g. gentamycin (decrease Ach release) and tetracyclines (chelate calcium and decrease Ach release).
Blockade is reduced with anticholinesterase agents. Results in increased Ach levels at the NMJ, thus antagonising the effects of competitive agents.

parkinson’s disease

What is parkinson’s disease?

Parkinson’s disease (PD) is a progressive neurological disorder, which is associated with a loss of cells that generate dopamine in the brain which results in numerous complex symptoms, and results in progressive loss of motor control (Figure 1).

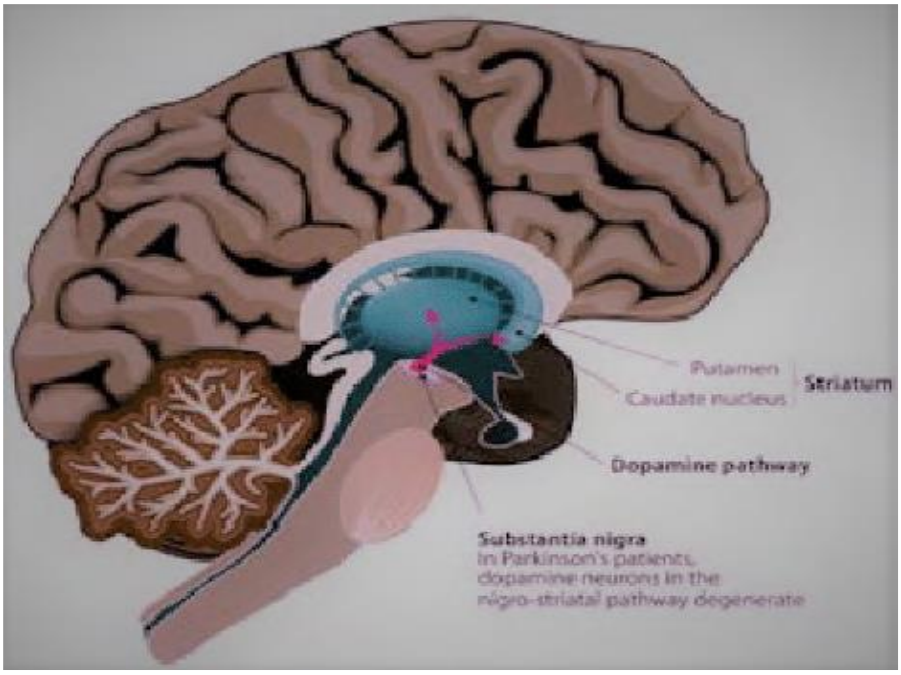


Figure 1: *Parkinson's disease.*

Parkinson’s disease belongs to motor system disorders. The main symptoms are:

• There may be tremor or trembling in body parts such as hands, arms, legs, jaw, and face;

• There occurs rigidity or stiffness of the limbs and trunk;

• Patient may suffer from bradykinesia or slowness of movement;

• Patient may experience postural instability or impaired balance and coordination.

Patients experience difficulty in walking, talking, or completing other simple tasks as the mentioned symptoms become more pronounced.

The disease is chronic and progressive, it persists over a long period of time and its symptoms grow worse over time. PD is not contagious nor is it usually inherited that is, it does not pass directly from one family member or generation to the next. The most common form of Parkinsonism is PD. The result of the loss of dopamine-producing brain cells is primary symptoms mentioned above. PD is called as primary Parkinsonism or idiopathic Parkinson’s disease. A term mentioning a disorder for which there is no cause has been found is described

condition idiopathic. The cause of PD is known or suspected in other form of PD. PD is a neurodegenerative brain disorder which progresses very slowly in many people in worldwide. A production of neurotransmitter called dopamine is stop by person's brain. Therefore insufficient amount of dopamine present in brain. Due to the less amount of dopamine present in brain, person loss ability to regulate the body movements, body and emotions. There are serious complications from the disease. The complications from PD are rated as the 14th top cause of death in the United States by Centers for Disease Control and Prevention (CDC).The condition when dopamine production decreases in brain is PD (Figure 2)

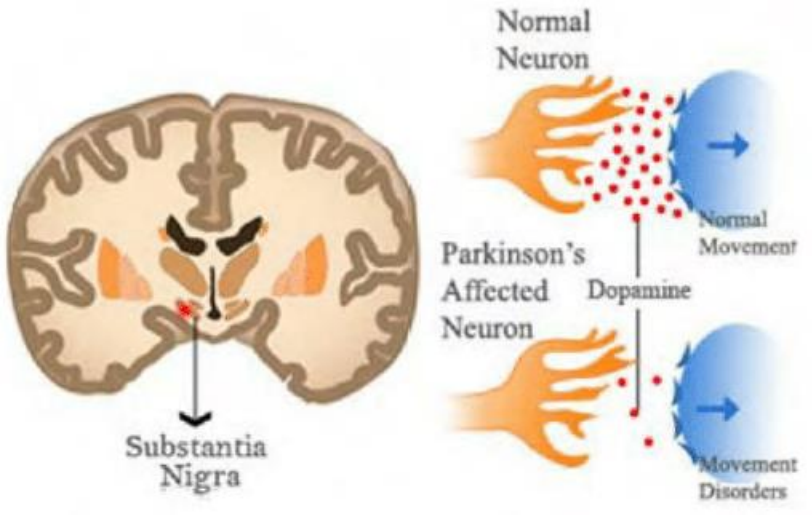


Figure 2: *Dopamine level in parkinson's disease.*

No total cure is there for PD. Dopamine is normally produced by brain cells known as neurons in the human brain. Substantia nigra is particular area of the brain where these neurons are concentrating. Dopamine is a chemical that relays messages between the substantia nigra and other parts of the brain to control movements of the human body (Figure 3). The smooth, coordinated muscle movements in human body are due to dopamine. The motor symptoms of Parkinson's disease appear when approximately 60 to 80% of the dopamine-producing cells are damaged, and do not produce enough dopamine,. This process of impairment of brain cells is called neuro degeneration.

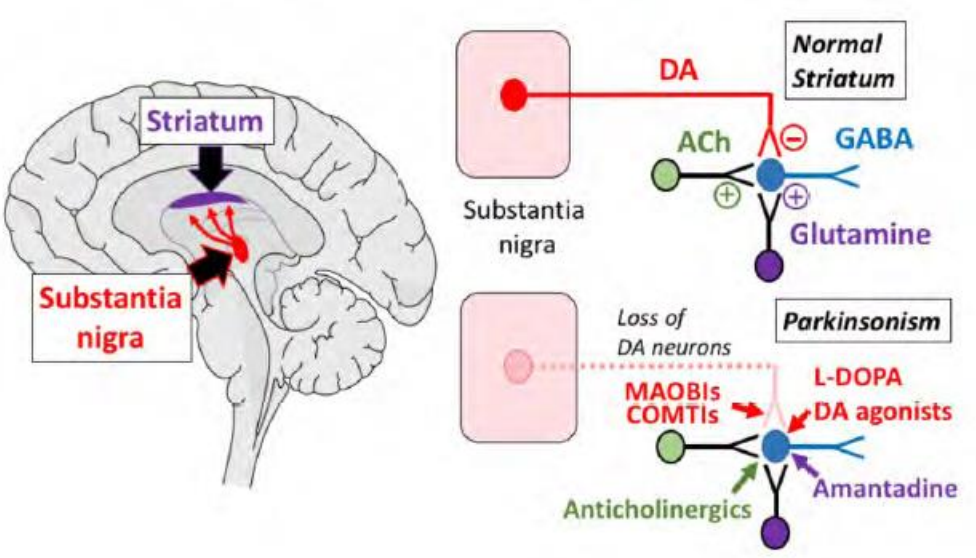


Figure 3: *Dopamine production in substantia nigra.*

The enteric nervous system, the medulla and in particular, the olfactory bulb, which controls your sense of smell involves earliest signs of Parkinson's, which is current theory called as Braak's hypothesis. The theory explains that over the years PD only to the substantia nigra and cortex. For classify the degree of pathology in Parkinson's disease and Alzheimer's disease Braak staging refers to two methods. By performing an autopsy of the brain clinical diagnosis of these diseases obtained. For detection of PD as early as possible researchers are mainly worked on these "non-motor" symptoms.

Person might hear his doctor refer to his Hoehn and Yahr stage. This scale, first introduced in 1967, is a simple rating tool used by clinicians as a means to generally describe how motor symptoms progress in Parkinson's. It takes into account factors other than motor symptoms, including mental functioning, mood and social interaction.

While symptoms are unique to each person, and the progression of symptoms varies from person to person, knowing the typical stages of Parkinson's can help you cope with changes as they occur. In some people, it could take 20 years to go through these stages. In others, the disease progresses more quickly.

Stages of Parkinson's Diseases

Stage one

The person has mild symptoms that commonly do not interfere with daily activities are observed in stage one. On the one side of body only, tremor and other movement symptoms may occur. The other person may observe changes in walking, posture and facial expression of patient.

Stage two

The symptoms are getting worst in stage two. On the both side of body, tremor, rigidity and other movement symptoms may occur. In this stage there is difficulty for patient in completing day to day tasks. Walking problems and poor posture may become apparent.

Stage three

Mild stage in progression of PD is stage three. Main symptoms of this stage are loss of balance and slowness of movements. Patient is still fully independent in third stage. Symptoms significantly impair activities of daily living such as dressing and eating.

Stage four

Symptoms are severe and limited in this stage. Patient can stand without assistance but walker is required foe standing. For completing daily living activities, person needs help.

Stage five

Most advanced stage of PD is stage five. IT is impossible to stand and walk because of Stiffness in the legs. Wheelchair, around-the-clock nursing care is required for patients care. Hallucination and delusion may observe in patient .

Causes of parkinson's disease

Genetic factor and environmental factor are considered as cause of PD. The risk of causing PD is more in persons whose family member is suffer from OD or person who gets more contact with pesticide, toxins. The head injuries also lead to causing PD.

Parkinson's disease is caused by a loss of nerve cells in a specific part of the brain called the substantia nigra. Dopamine which is important chemical for brain is produced by these neurons. Cells in the substantia nigra communicate with other movement control centers in the brain by secreting dopamine and other neurotransmitters. Secretion of dopamine gets stop when substantia cell are die and movement of other control centers become unregulated. This disturbance in the movement control centers of the brain cause the main symptoms of Parkinson's disease.

Environmental toxins that may cause Parkinsonism include

- Manganese
- Carbon monoxide
- Organic solvents
- Certain pesticides.

The cause of this disease is due to combination of four mechanisms which are as follows:

- Oxidative damage,
- Environmental toxins,
- Genetic predisposition,

• Accelerated aging .

Sign and symptoms of parkinson's disease

• Tremors or shaking in hands, arms, legs, jaw, and face

• Rigidity or stiffness of limbs and trunk

• Slowness of movement

• Difficulties with balance, speech, and coordination

There are also non-motor symptoms which may develop years before the onset of motor problems. These may include:

• Poor sense of smell Constipation

• Depression

• Cognitive impairment

• Fatigue, cramped handwriting or other writing changes

• Tremor, especially in finger, hand or foot

• Uncontrollable movements during sleep

• Limb stiffness or slow movement (bradykinesia), voice changes

• Rigid facial expression or masking

• Stooped posture

• Muscular: Difficulty standing, difficulty with bodily movements, involuntary movements, muscle rigidity, problems with coordination,

rhythmic muscle contractions, slow bodily movement, stiff muscles, or slow shuffling gait

• Tremor: Can occur at rest, in the hands, limbs, or can be postural

• Whole body: Dizziness, fatigue, poor balance, or restlessness

• Cognitive: Amnesia, confusion in the evening hours, dementia, or difficulty thinking and understanding

• Sleep: Early awakening, nightmares, or restless sleep

• Speech: Impaired voice, soft speech, or voice box spasms

Mood: Anxiety or apathy

• Nasal: Distorted sense of smell or loss of smell

• Urinary: Dribbling of urine or leaking of urine

• Facial: jaw stiffness or reduced facial expression

• Also common: blank stare, constipation, daytime sleepiness, depression, difficulty swallowing, drooling, falling, fear of falling, limping, loss in contrast sensitivity, neck tightness, small handwriting, trembling, unintentional writhing, or weight loss.

Early symptoms

Early symptoms of PD involve tiredness in patient or notice a general malaise, patient have little shaky or have difficulty getting out of a chair, speak too softly or that their handwriting looks cramped and spidery, lose track of a word or thought, or they may feel irritable or depressed for no apparent reason, person's face lacks expression and animation or that the person remains in a certain position for a long time or does not move an arm or leg normally, person seems stiff, unsteady, and unusually slow, may begin to interfere with daily activities, shaking makes reading a newspaper difficult.

Major symptoms

The major symptoms observed in PD patient are generally tremor, rigidity, bradykinesia, postural instability which is observed in higher stages of PD patient.

Tremor

PD have tremor with characteristic appearance. Pill rolling is term when tremor takes form of rhythmic back and forth motion of the thumb and forefinger at three beats per second. Tremor is normally begun in hand; foot or jaw. In many patients during the early stage of the PD tremors may affect only one side of the body. It is disappear during sleep, rarely disabling and improve with intentional movement.

Rigidity

A major principle of body movement is that all muscles have an opposite muscle. Rigidity is comes out in PD patient he delicate balance of opposing muscle is disrupted in response to signal from the brain. When other person tries to do movement of arm or leg of PD patient then rigidity becomes obvious.

Bradykinesia

Bradykinesia is a condition when there a difficulty in next movement for patient after doing one movement which also noted as allowing down in spontaneous movement and loss of automatic movement. The patient cannot rapidly perform routine movements.

Postural instability

Impaired balance and coordination or postural instability causes patient to fall easily. It is occurs at higher stage of Parkinsonism disease. There is more problem for patient for performing different activities.

Treatment and drugs

For the treatment of PD there are many medicine are available which provide some relief from symptoms of PD but not complete cure of PD. In some later cases, surgery may be advised.

Medication

Carbidopa-Levodopa

Levodopa is a natural chemical that passes into human brain and then converted into dopamine which is very effective medication for PD. Carbidopa when combined with levodopa, which protect levodopa form conversion into dopamine outside brain and minimize side effects such as nausea or light-headedness. As disease progresses after years the benefit form levodopa may become less stable. After taking higher dose of Levodopa, person may experience dyskinesia (involuntary movements)

Dopamine agonists

Dopamine antagonist cannot convert into dopamine but they mimic dopamine effects in brain and they are not more effective but can control symptoms of disease. They can be used with Levodopa to smooth the off-and-on effects of Levodopa. Dopamine agonists include pramipexole, ropinirole and rotigotine. Some of the side effects of dopamine include hallucinations, sleepiness and compulsive behaviors such as hyper sexuality, gambling and eating.

MAO-B Inhibitors

Selegilie and Rasagiline are MAO_B inhibitors which prevent the breakdown of dopamine in brain by inhibiting the monoamine oxidase B which is brain enzyme which metabolized brain dopamine. Nausea and insomnia are side effects of these drugs. The risk of hallucination may increase when it given with carbidopa-levodopa.

Catechol-O-methyltransferase (COMT) inhibitors

Primary medication of this class is Entacapone. The effect of levodopa therapy mildly prolongs due to use of this medication by blocking an enzyme which breakdown dopamine. Increased risk of involuntary movements, diarrhea are side effects. Another drug of this class which is rarely prescribed due to the risk of serious liver damage and liver failure is Tolcapone.

Anticholinergic

To control the tremor associated with PD this drugs are used from many years. Benztropine or trihexyphenidyl are available medication. Impaired memory, confusion, hallucination, constipation, dry mouth and impaired urination are side effects .

Amantadine

To provide short term relief from symptoms of PD this drug is used. It may give along with Carbidopa-Levodopa therapy at later stages of PD which results in control involuntary movements induced by Carbidopa-Levodopa. A purple mottling of skin, ankle swelling and hallucination are side effects of drug .

There are different drugs are used for the treatment of PD. The mechanism of action of all drugs which are used to treat PD is as shown in figure 4

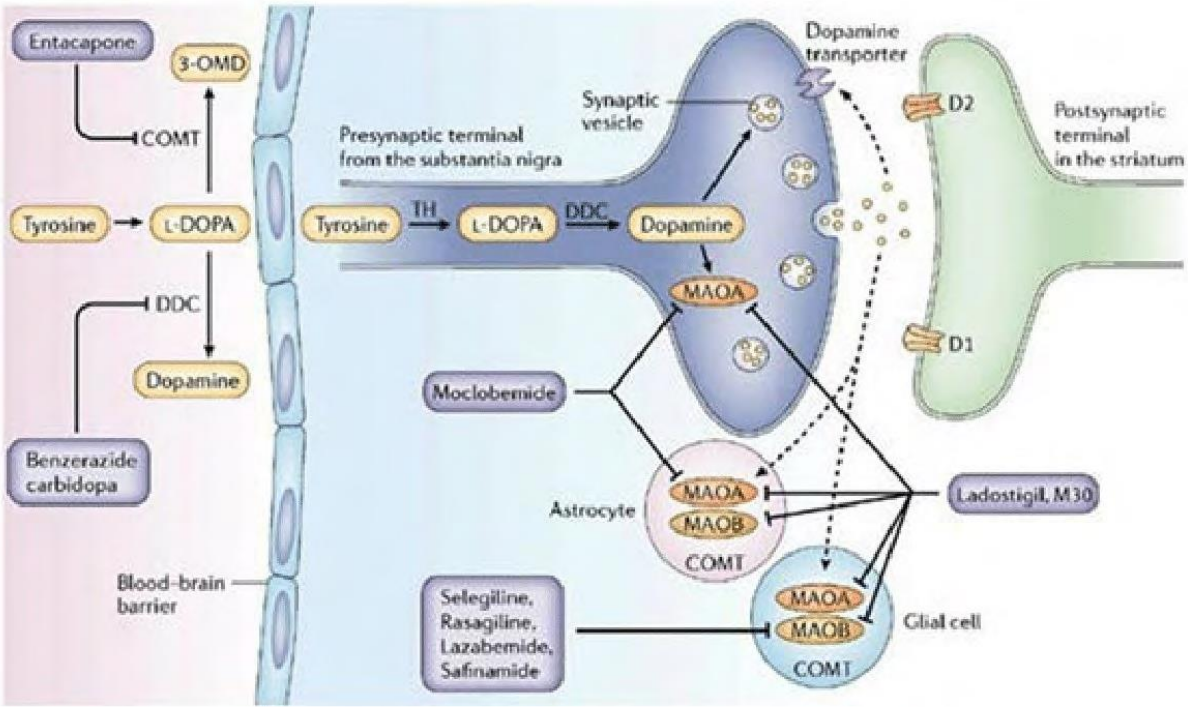


Figure 4: *Summary of the treatment of parkinson's disease.*

PRE-ANESTHETICS MEDICATION

Preanaesthetic medication refers to the use of drugs before anaesthesia to make it more pleasant and safe. The major objectives of preanaesthetic medication are to decrease the stress response with preservation of hemodynamic parameters, facilitate anaesthesia induction and produce amnesia. Preanaesthetic medication is also defined as a group of drugs that are used before anaesthesia to prepare the patient, administered from half an hour before the surgery to the night before.

PURPOSES OF PREMEDICATION The two general purposes of preanaesthetic medication proposed by Beecher in 1955 are as follows: (1) to present a tranquil and well rested patient to the surgeon and (2) to decrease the hazards incurred by anesthesia and surgery. Atropine was once used before anesthesia to prevent "vagal inhibition" and to decrease secretion induced by chloroform or ether. Morphine had also been used to reduce reflex irritability of patients and decrease the amount of ether requirement. As the new halogenated inhalational anesthetics and intravenous anesthetics have dramatically shortened the induction time of anesthesia, the main purpose of premedication today is no longer to prevent radical movement or reduce secretion of patients, but to allay patient fears and lessen patient anxiety. Other purposes of anesthetic premedication, as found in the literatures, are to: (1) prevent postoperative pain, (2) provide effective prophylaxis against PONV, (3) decrease perioperative shivering, (4) decrease postoperative pruritus, (5) decrease gastric secretions, (6) prevent allergic reactions, (7) suppress reflex responses to surgical stimuli, and (8) decrease anesthetic requirement for the surgical procedure. [9]

TO DECREASE ANXIETY Preoperative anxiety can occur in as high as 80% of surgical patients. Two vulnerable groups of patients are females and children. Both psychological and pharmacological approaches are effective in decreasing preoperative anxiety. Midazolam has been proved to be effective in reducing the preoperative anxiety level in many studies. Except for midazolam, α2-agonists, antidepressants, and anticonvulsants are all effective in reducing the preoperative anxiety level.

TO REDUCE POSTOPERATIVE PAIN The concept of preemptive analgesia to deliver an analgesic regimen prior to the surgical stimulus to reduce the severity and duration of

postoperative pain originated with the goals of (1) inhibiting the development of chronic postsurgical pain (CPSP), (2) decreasing acute postoperative pain after peripheral nerve damage and tissue injury, (3) preventing central neuron sensitization. The concepts of preventive analgesia that adopt a multimodal approach combining several interventions, which will produce a sufficiently dense, extensive and long duration of blockade, will pave the way for future direction of postoperative analgesia.

TO PREVENT CPSP CPSP is a pain persisting for >3 months after surgery. Nerve damages and central sensitization play important roles in the development of CPSP. Pharmacological strategies to prevent CPSP include: (a) regional anaesthesia (b) NMDA receptor antagonists (c) gabapentinoids

TO PROVIDE FOR PROPHYLAXIS AGAINST PONV

i. **Postoperative Nausea And Vomiting**

About one-third of surgical patients who receive a general anaesthesia consisting of inhalational anaesthetics and opioids experience PONV. The incidence of PONV will dramatically escalate to 70-80% in a high-risk group of patients without PONV prophylaxis. Based on these findings, modern PONV prophylaxis adopts the principle of multimodal approach to treat high-risk patients with at least two or three different kinds of receptor antagonists, rather than just increasing the dosage of one single receptor antagonist, to prevent the occurrence of PONV.

ii. **Postdischarge Nausea And Vomiting**

Postdischarge nausea and vomiting (PDNV) receive more attention when more surgical procedures are conducted on an outpatient basis. The overall incidence of PDNV was 37% in the first 48 hours after discharge from hospital. The five independent risk factors for PDNV are (1) female sex, (2) age 50 years, (3) a history of PONV, (4) opioid use in the postanaesthesia care unit, and (5) nausea in the postanaesthesia care unit. Depending on the number of risk factors, the risk of PDNV can be predicted as 10%, 20%, 30%, 50%, 60%, and 80%, respectively.

TO DECREASE PERIOPERATIVE SHIVERING Both general and regional anaesthesia can impair thermoregulation during cold exposure, and postanaesthetic shivering has been reported

in 40-64% of patients (average 55%) with no prophylaxis. A variety of pharmacological and nonpharmacological interventions were tested to prevent patients from developing hypothermia, which showed equal effectiveness. Here, we describe the effects of pharmacological prophylaxis only. Antishivering medications found in the literatures can be categorized into several classes: (1) opioid receptor agonists or antagonists, (2) other centrally acting analgesics such as tramadol and nefopam, (3) α2- receptor agonists such as clonidine and dexmedetomidine, (4) cholinesterase inhibitors such as physostigmine and anticholinergic: atropine, (5) central nervous stimulants such as methylphenidate, (6) N-methyl-D-aspartate receptor antagonists such as ketamine and magnesium sulfate, (7) antiserotonergic agents such as ondansetron, granisetron, dolasetron, and urapidil, (8) g-aminobutyric acid receptor agonists such as midazolam and propofol, (9) sodium channel blockers such as lidocaine, (10) benzodiazepine receptor antagonists such as flumazenil, and (11) anti-inflammatory agents such as dexamethasone

TO DECREASE POSTOPERATIVE PRURITUS Pruritus is the most common side effect of neuraxial opioids, with an incidence varying from 30% to 100%. Parturients seem to be more susceptible to pruritus, with an increased incidence between 60% and 100%, and it appears to be estrogen related and dose dependent. Pharmacological strategies to prevent or treat such an event include the following: 5-HT3 receptor antagonists, opioid antagonists, antihistamines, NSAIDs and droperidol.

TO DECREASE GASTRIC SECRETIONS Prevention of aspiration pneumonitis caused by regurgitated gastric juice from the full stomach of inadequately fasting patients or from the stomach of a parturient is always a challenge for anaesthesiologists. Except for fasting, appropriate measures to prevent aspiration include gastric decompression, acceleration of emptying, and application of the technique of rapid sequence intubation along with Sellick's maneuver. Premedication that can inhibit gastric juice secretion and reduce gastric juice volume and acidity, such as H2- receptor antagonists (H2RAs) or proton pump inhibitors (PPIs) are also given.

PSYCHOLOGICAL APPROACH Psychological education before an operation is a major part of premedication in terms of reducing the level of anxiety. Women and children are two vulnerable groups; most of the patients (as high as 70-80%) of these groups usually suffer from anxiety prior to operation. Psychological effects of a preoperative visit include not only building

a friendly rapport among patients and anaesthesiologists, but also reducing anxiety through reassurance about anaesthesia from an anaesthesiologist. Compared to adults, psychological preparation can be more difficult in pediatric patients, as reassurance will not be effective in such young patients and separation anxiety can exist in parents and children. Some behavioral programs had been developed, such as parental presence during induction of anaesthesia and clown intervention and distraction techniques, with varying results.

PHARMACOLOGICAL APPROACH

SEDATIVE-ANTIANXIETY DRUGS The most popular premedicants belong to the sedative-hypnotic group of drugs, which includes both the benzodiazepines and the barbiturates. All sedative hypnotics produce a similar dose-dependent spectrum of central nervous system (CNS) activity. Although the slopes of their individual dose-response curves may differ, all drugs in this group produce a similar pattern of CNS depression. Comparative studies have indicated that benzodiazepines are more effective in producing anxiolysis and amnesia and are associated with higher patient acceptance than the barbiturates. More recent data indicate that the benzodiazepines (e.g., flurazepam, triazolam, lorazepam) may also be superior to the barbiturates as hypnotics on the evening prior to surgery

Benzodiazepines Benzodiazepines belong to a broad category of drugs that are referred to as gamma-amino butyric acid (GABA) agonists. GABA is the principal inhibitory neurotransmitter in the central nervous system (CNS). They bind to GABA receptors which causes an influx of chloride ions. This influx causes the post-synaptic nerve to be hyperpolarized, which increases the level of stimulation required to depolarize the nerve. GABA-A receptor subtypes have been identified, which are alpha-1 and alpha-2. It is thought that alpha-1 receptors mediate sedation and alpha-2 receptors are responsible for anxiolysis. Currently available formulations of benzodiazepines are not selective for GABA receptor subtypes.

Benzodiazepines bind to specific binding sites in the GABAA receptor–chloride channel complex in the brain, and facilitate the opening of the channel in the presence of GABA; this increases hyperpolarization-induced neuronal inhibition . Benzodiazepines are the most commonly used drug for anxiolysis of children prior to induction of GA. Their properties consisting of: anxiolysis, sedation, muscle relaxation, anti-convulsant effect, and anterograde

amnesia confer their popularity. The large therapeutic window in combination with minimal respiratory and cardiac depression makes them an excellent choice in the preoperative phase where monitoring is minimal. Benzodiazepines should be administered under direct supervision with the patient placed in a closely monitored bed space in the preoperative holding area

Midazolam Is a water-soluble benzodiazepine with a short elimination half-life (2-4 hr). Midazolam is approximately twice as potent as diazepam with respect to its sedative and anxiolytic properties. Because of its rapid onset of sedative-anxiolytic effect and low incidence of postoperative side effects, midazolam appears to be an excellent intramuscular premedicant for pediatric patients. Commercially prepared midazolam formulation is rapidly absorbed with patients demonstrating a satisfactory degree of sedation and anxiolysis within 10 minutes of consumption with a higher percentage at 20 minutes

Diazepam Is the prototypic benzodiazepine which produces dose-dependent anxiolysis, sedation, and amnesia with a plasma half-life of 1.5–2.5 hours. [2.7] Diazepam has a greater fat solubility than midazolam and a faster CNS effect after intravenous administration (1.6 min); however it is metabolized to desmethyldiazepam with a pharmacologic activity equal to the parent compound. When administered rectally, diazepam appears to be less effective than rectal midazolam. The intramuscular route is not recommended because it is painful and absorption is erratic.

Phenothiazine Promethazine is a widely used phenothiazine which improves the relief of anxiety and the level of sedation as well as patient acceptance when added to morphine premedication. In addition to being a sedative, promethazine has the advantage to possess several beneficial effects such as being an antihistaminic (H1blocker), an antiemetic, anti-motion sickness, and an anticholinergic.

OPIOIDS Opioids have been prescribed for premedication in an effort to facilitate the induction of anaesthesia and to decrease the inhaled anaesthetic requirement. Opioids are substances that act on opioid receptors to produce morphine-like effects that are blocked by antagonists such as naloxone. Cohen and Beecher stated many years ago that "unless there is pain, there is no need for a narcotic in preanaesthetic medication." Opioids bind to specific opioid receptors in the nervous system and other tissues

Morphine Is the principal alkaloid in opium and still widely used. It relieves both the perception of pain and the emotional response to it. Morphine sulfate may be administered intramuscularly (0.1 to 0.2 mg/kg) or intravenously (0.05 to 0.1 mg/kg) or orally. Absorption may not be adequate when given rectally.

Pethidine The actions of pethidine are similar to those of morphine. It causes similar respiratory depression, vomiting and gastrointestinal smooth muscle contraction to morphine, but does not constrict the pupil, release histamine or suppress cough. It produces little euphoria, but does cause dependence. Pethidine is sometimes used in obstetrics because it does not reduce the activity of the pregnant uterus, but morphine is often preferred.

Fentanyl is a synthetic opioid and is the most commonly employed analgesic supplement during anaesthesia which may be administered by parenteral, transdermal, nasal, and oral routes. Fentanyl is strongly lipophilic, and is readily absorbed from the buccal mucosa with an overall bioavailability of approximately 30-50%. Fentanyl is rapidly and extensively metabolized, the t1/2 being two to four hours, the short duration of action (the peak effect lasts only 20–30 minutes) being explained by redistribution from brain to tissues.The optimal dose as a preanesthetic medication with minimal desaturation and preoperative nausea appears to be 10 to 15 μg/kg.

ANTICHOLINERGICS The use of anticholinergic compounds as part of routine preanesthetic medication stems mainly from their antisialagogue and vagolytic actions. Anticholinergic drugs are those which block actions of ACh on autonomic effectors and in the CNS exerted through muscarinic receptors. Although the tertiary amine and quaternary ammonium groups of anticholinergic drugs bind to the same anionic site on the receptor those agonists occupy, these drugs do not fit into the narrow cleft and consequently cannot activate the receptor. Atropine or scopolamine was routinely administered before the induction of general anesthesia to block excessive salivary and respiratory secretions induced by certain inhalation anesthetics.

Atropine (0.02 mg/kg) and scopolamine (0.01 mg/kg) both have CNS effects, although the sedating effect of scopolamine is 5 to 15 times greater than atropine. Atropine is more commonly used and is a better vagolytic agent than scopolamine, whereas scopolamine is a better sedative, antisialagogue, and amnestic. Glycopyrrolate is the only agent that does not cross the blood-brain

barrier, so it does not cause confusion. When compared to atropine, it is less effective in attenuating bradycardia during induction. The central sedative effects of both atropine and scopolamine may be antagonized with physostigmine. Preoperative administration of oral atropine or oral glycopyrrolate does not alter the incidence or degree of hypotension during induction of anesthesia. Anticholinergic agents are very useful as an adjuvant to ketamine anesthesia because of their antisialagogue and central sedative effects. The recommended doses of anticholinergics are scopolamine, 0.005 to 0.010 mg/kg, atropine, 0.01 to 0.02 mg/kg and glycopyrrolate 0.01 mg/kg IV, IM

NEUROLEPTICS Neuroleptics or antipsychotic drugs such as haloperidol and chlorpromazine tend to block dopamine D2 receptors in the dopaminergic pathways of the brain. This means that dopamine released in these pathways has less effect. In addition to the antagonistic effects of dopamine, antipsychotics (in particular atypical neuroleptics) also antagonize 5HT2A receptors. Typical antipsychotics are not particularly selective and also block dopamine receptors in the mesocortical pathway, tuberoinfundibular pathway, and the nigrostriatal pathway. Atypical antipsychotic drugs have a similar blocking effect on D2 receptors, however, most also act on serotonin receptors, especially 5-HT2A and 5-HT2C receptors.

HISTAMINE H2 BLOCKERS The H2-blocking drugs have been administered preoperatively to patients considered to be at increased risk to aspiration pneumonitis. The histamine H2 receptor antagonists competitively inhibit histamine actions at all H2 receptors, but their main clinical use is as inhibitors of gastric acid secretion. They can inhibit histamine-, gastrin- and acetylcholine-stimulated acid secretion; pepsin secretion also falls with the reduction in volume of gastric juice. The use of H2-receptor antagonists can increase gastric fluid pH during the preoperative period by producing dose related decreases in basal and nocturnal gastric acid production. In general, multiple dose regimens (e.g., a nighttime dose on the evening prior to surgery and a morning dose on the day of surgery) are more effective than single dose regimens in decreasing gastric acidity and volume. Parenteral administration is more effective than oral when a rapid onset of effect is desired. Both of the commonly used H2-receptor antagonists, cimetidine, 150-300 mg, and ranitidine, 50-100 mg, significantly increase gastric fluid pH within 1 hr after parenteral administration.

Ranitidine Is a nonimidazole (has a furan ring) H2 blocker which as has several desirable features compared to cimetidine (about 5 times more potent than cimetidine). Though its pharmacokinetic profile and t1/2 of 2-3 hr is similar to cimetidine, a longer duration of action with greater 24 hr acid suppression is obtained clinically because of higher potency.

PROTON PUMP INHIBITORS Proton pump inhibitors are benzimidazoles which inhibit the final common step in gastric acid secretion. They react covalently with SH groups of the H+K +ATPase enzyme and inactivate it irreversibly. After diffusing into the parietal cell from blood, proton pump inhibitors gets concentrated in the acidic pH of the canaliculi because the charged forms generated there are unable to diffuse back. Moreover, it gets tightly bound to the H +K +ATPase enzyme. It also inhibits gastric mucosal carbonic anhydrase.

Pantoprazole Is a newer H+K +ATPase inhibitor, similar in potency and clinical efficacy to the prototype, omeprazole, but is more acid stable and has higher oral bioavailability. It is also available for i.v. administration.

ANTIEMETICS These are the drugs used to prevent or suppress vomiting. Prokinetic drugs promote gastrointestinal transit and speed gastric emptying by enhancing coordinated propulsive motility. They acts through both dopaminergic and serotonergic receptors and causes D2 antagonism, 5-HT4 agonism and 5-HT3 antagonism. Neuroleptics are potent antiemetics which act by blocking D2 receptors in the CTZ, antagonize apomorphine induced vomiting and have additional antimuscarinic as well as H1 antihistaminic property. 5-HT3 antagonists block the depolarizing action of 5-HT through 5-HT3 receptors on vagal afferents in the GIT as well as in nucleus tractus solitarius (NTS) and chemoreceptor trigger zones (CTZ).

Ondansetron Is the prototype of 5-HT3 antagonists of antiemetic drugs found to be highly effective in PONV. It blocks the depolarizing action of 5-HT through 5-HT. receptors on vagal afferents in the g.i.t. as well as in NTS and CTZ. Oral bioavailability of ondansetron is 60-70% due to first pass metabolism. It is eliminated in urine and faeces, mostly as metabolites; t1/2 being 3- 5 hrs, and duration of action 4-12 hr.

α2-ADRENERGIC RECEPTOR AGONISTS

Clonidine: is an α2-agonist, causes dose-related sedation by its effect in the locus ceruleus through its inhibition of adenylate cyclase. The plasma concentration peaks at 60 to 90 minutes after oral administration and at 50 minutes after rectal administration. The need to administer clonidine 60 minutes before induction of anaesthesia makes its use impractical in most clinical settings. An oral dose of 3 μg/kg given 45 to 120 minutes before the surgery produces comparable sedation to that of diazepam or midazolam. Clonidine acts both centrally and peripherally to reduce blood pressure and therefore it attenuates the hemodynamic response to intubation. It is usually administered in combination with atropine.

Dexmedetomidine Compared to clonidine, dexmedetomidine is a more selective α2-adrenergic receptor agonist with a faster onset of action, quicker time to reach the peak plasma concentration, and a shorter elimination half-life. Dexmedetomidine premedication can decrease the severity of acute postoperative pain and reduce analgesic requirement.

Sedatives and hypnotics

Definitions

Sedation: state of **decreased responsiveness** to any level of stimulation; associated with some decrease in motor activity and ideation.

Sedatives: these are the drugs which subdue excitement (anxiolytic) and **calm the subject** without inducing sleep, though drowsiness may be produced.

Hypnotic: These are the drugs which induce and/or **maintain sleep**, similar to normal arousable sleep.

"Hypnotic" and "Hypnosis" are totally different terms (hypnosis refers to trans like state).

- A hypnotic drug is more depressant on CNS than a sedative drug.
- Some sedative drugs can act as hypnotic if given in higher doses.

Classification of Sedative and Hypnotic Drugs

Benzodiazepines	**Barbiturates**	**Atypical**
Short-acting: • Triazolam • Lorazepam (Ativan^{R}) • Diazepam (Valium^{R})	Ultrashort acting: • Thiopental	• Zopiclone • Eszopiclone • Zaleplon • Zolpidem
Intermediate-acting: • Alprazolam	Short-acting: • Secobarbital	• Chloral Hydrate • Buspirone
Long-acting:	Long-acting:	• Ramelteon, tasimlteon

• Flurazepam	• Phenobarbital	• Suvorexant

Overview/Introduction of Sedative and Hypnotic Drugs

Sedative and hypnotic drugs are used in the treatment of insomnia and anxiety.

It is important to understand the sleep cycle first to understand the pharmacology of sedative and hypnotic drugs.

There are two main phases of sleep:

1. Non-REM (rapid eye movement) Sleep (70-80%):

Stages	**Status**	**On EEG**
0	Awake, 1-2%	α activity with eyes closed and β activity with eyes open
1	Dozing, 3-6%	α +θ waves
2	Unequivocal sleep, 40-50%	θ waves
3	Deep sleep transition, 5-8%	θ, δ and spindle activity, K complexes can be evoked with strong stimuli
4	Cerebral sleep, 10-20%	**δ activity** predominated, K complexes cannot be evoked

2. REM Sleep (20-30%):

- Marked by irregular, **darting eye movements**.
- **Dreams and nightmares** occur in this stage only, which can be remembered after arousal.
- There is marked fluctuation in **heart rate and blood pressure**.
- Muscles are relaxed.

Important Points:

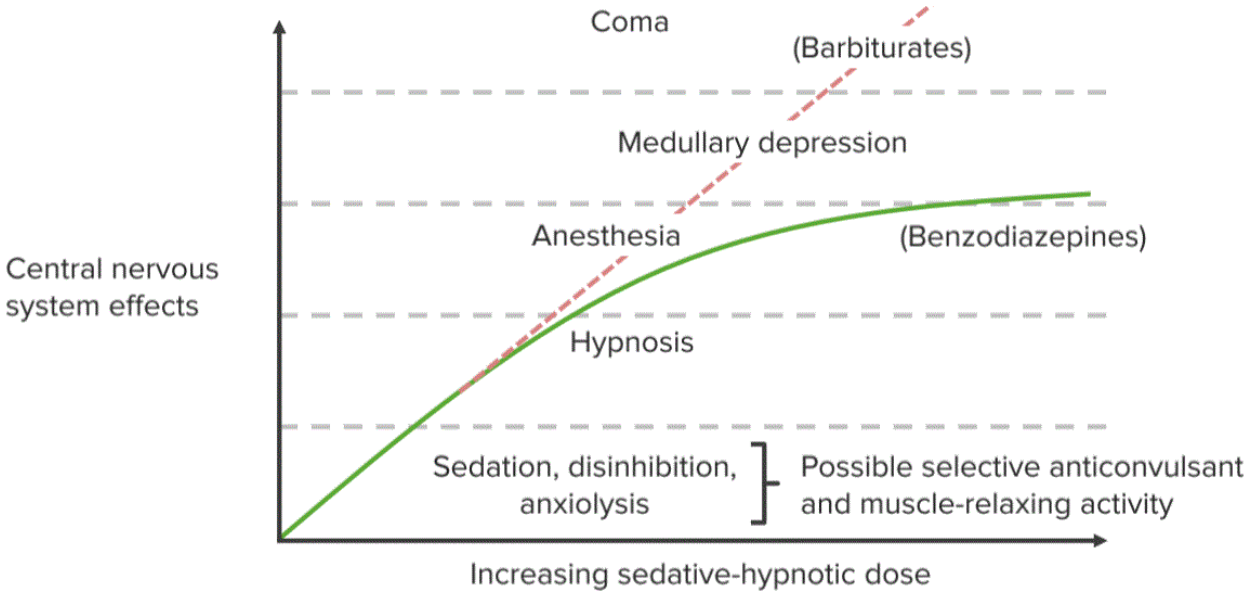
- One sleep cycle is about 80-100 minutes long.

  It repeats with the sequence of 1-4 REM.

Barbiturates

Act at $GABA_A$: BZD receptor-Cl^- Channels →Keeps the GABA induced opening of the channel for **longer duration**→ Increase the ionic flow across the membrane → produces an inhibitory effect

The binding site is α and β subunits. If the concentration of barbiturate is increased, it produces **GABA mimetic action**. It depresses the glutamate-induced neural depolarization through **AMPA receptors.** At high concentrations, it also inhibits **sodium and potassium channels**. Benzodiazepines are frequently prescribed as sedatives and anxiolytics that are positive modulators of $GABA_A$ receptors and CNS depressants. Their depressant effects are potentiated by marijuana, opioids, and antipsychotics. Barbituates are largely replaced by benzodiazepines in medical practice, although are still used as **anticonvulsants**.



Pharmacodynamics

- The effect of the drug becomes less marked with continuous use **(tolerance).**
- **Physical dependence** can be seen following long term use.
- **Withdrawal syndrome** is also observed following discontinuation.
- **Rebound** increase (**rebound phenomenon**) in REM sleep and increased nightmares seen after discontinuation.
- Respiration is depressed at high doses.
- **BP and heart rate** are decreased.
- Reduces **skeletal muscle contraction**.
- **Tone and motility of intestine** are decreased.
- **Urine output** is decreased.

Pharmacokinetics

- Most of the drugs in this category are mainly metabolized by the liver.

- **Redistribution** is observed before final disposal.
- **Secobarbital and Pentobarbital** can have a **cumulative effect** upon multiple doses. Excretion of Phenobarbital can be increased by **alkalization of urine**.

Adverse effects

- Hangover
- Tolerance
- Dependence
- Mental confusion
- Precipitates porphyria
- Hypersensitivity

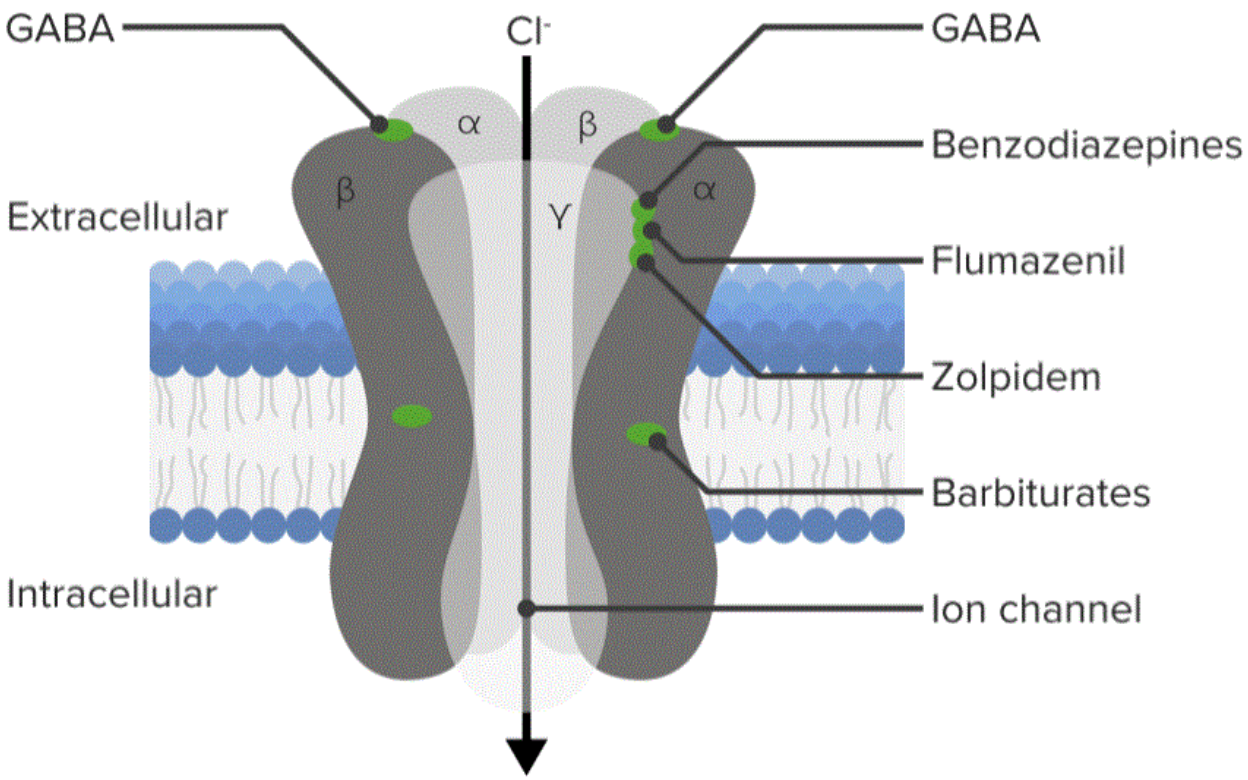
Benzodiazepines (BZD)

They bind to **α/γ interface** of $GABA_A$ receptor – Cl^- Channel Complex**.** They increase the **frequency of opening** of $GABA_A$: BZD receptor-Cl^- Channels. They also enhance the binding of GABA with $GABA_A$ receptor. They **don't have the GABA mimetic action.** They have a higher therapeutic index. Even after 20 times higher hypnotic doses, respiration will not be depressed and death won't occur.

They decrease BP. Diazepam and Lorazepan decrease cardiac output, while Midazolam decreases peripheral resistance. **Rebound phenomenon** is less marked.

Benzodiazepines is present in many regions of the brain:

- Cerebral cortex (confusion, amnesia)
- Thalamus (disinhibition, sedation, motor inhibition)
- Limbic structures (anxiolysis, sedation)



Pharmacodynamics

- Selective anxiolytic, sedative, muscle relaxant and **anticonvulsant action.**
- All BZD reduce the duration of REM except
- Clonazepam and diazepam have higher **muscle relaxant**
- **Anterograde amnesia** is observed.

Pharmacokinetics

- Redistribution is seen following administration.
- **Hepatic metabolism** is the main pathway of disposal.
- Metabolized into more active metabolites.

Adverse Effects

- Dizziness
- Vertigo
- Ataxia
- Disorientation
- Amnesia
- Impaired psychomotor skills

Drug abuse and Toxicity

- **Flunitrazepam** has been used in **"date rape"; chloral hydrate** is also used with alcohol for the **same purpose**.
- **Symptoms of benzodiazepine poisoning** are **similar to ethanol poisoning**, with tachycardia and dilated pupils.
- **Flumazenil** is the **antidote for acute benzodiazepine poisoning**. It binds at the same BZP site.

Pharmacology of Individual Drugs

Barbiturates

Phenobarbital

Mechanism of Action: Act at $GABA_A$: BZD receptor-Cl^- Channels. Furthermore, it has anti-glutamate and calcium ion entry reducing activity.

Clinical use: It has specific anticonvulsant action (used for **generalized tonic-clonic seizures**, simple partial and complex partial seizures and **status epilepticus**, **febrile seizures**), treatment of **congenital non-hemolytic anemia** and **kernicterus**.

Note: It has a half-life of 50-140 hr.

Adverse Effects: Behavioral abnormalities, learning and memory impairments, decreased intelligence, hyperactivity among children, mental confusion among geriatric persons, **rashes**, **megaloblastic anemia, and osteomalacia**.

Interactions: Being an enzyme inducer, it reduces the effect of many drugs.

Contraindications: Acute intermittent porphyria, **liver and kidney diseases**, obstructive sleep apnea, and pulmonary insufficiency.

Secobarbital

Mechanism of Action: Act at $GABA_A$: BZD receptor-Cl^- Channels

Clinical use: Used for the treatment of insomnia, and for preoperative sedation.

Adverse Effects: Impairs driving skills. Multiple doses produce cumulative effects.

Interactions: Similar to other barbiturates.

Contraindications: Similar to other barbiturates.

Thiopentone

Mechanism of Action: Act at $GABA_A$: BZD receptor-Cl^- Channels

Clinical use: Used as anesthesia because of its rapid action (for induction); however, it has been largely replaced by propofol in medical practice. It can be used for the treatment of refractive cases of **status epilepticus**. It is also used for the treatment of elevated intracranial pressure.

Adverse Effects: Extravasation of the drug from i.v. route can cause intense pain, necrosis, and gangrene of the limb. It produces poor analgesia, significant nausea, very little muscle relaxation, and **laryngospasm**.

Interactions: It should not be mixed with succinylcholine in single syringe, alcohol and CNS depressants, antihypertensive, other barbiturate anesthetics, and ketamine.

Contraindications: Same as other barbiturates.

Benzodiazepines

Flurazepam

Mechanism of Action: Increase the **frequency** of opening of $GABA_A$: BZD receptor-Cl^- Channels

Clinical Use: Useful for patients with frequent nocturnal awakening, generalized anxiety disorders, panic attacks, and the night before surgery.

No rebound insomnia after discontinuation.

Adverse Effects: **Paradoxical stimulation, irritability, and sweating**. Other adverse effects are dizziness, vertigo, disorientation, amnesia, ataxia, and impaired psychomotor skills.

Interactions: Alcohol and other CNS depressants, sodium valproate, cimetidine, isoniazid, oral contraceptives.

Contraindications: Hypersensitivity and pregnancy. Other contraindications are same as other BZDs.

Alprazolam

Mechanism of Action: Increase the **frequency** of opening of $GABA_A$: BZD receptor-Cl^- Channels

Clinical Use: It is a drug of choice for treatment of **panic disorders and agoraphobia**. It is mainly used as **anxiolytic,** but can be used as nighttime hypnotic.

Adverse Effects: Marked withdrawal syndrome after discontinuation. It is more toxic on overdose compared to other BZDs.

Contraindications: Hypersensitivity and pregnancy. Other contraindications are the same as other BZDs.

Triazolam

Mechanism of Action: Increase the **frequency** of opening of $GABA_A$: BZD receptor-Cl^- Channels

It has a rapid onset of action with peak effect in less than 1 hour.

Clinical uses: Good for inducing sleep, but poor for maintaining it.

Adverse Effects: Tolerance and withdrawal syndrome are common (rebound insomnia). Paranoia, psychiatric disorders

Contraindications: Hypersensitivity and pregnancy. Other contraindications are the same as other BZDs.

Lorazepam

Mechanism of Action: Increase the **frequency** of opening of $GABA_A$: BZD receptor-Cl^- Channels

Clinical uses: Second-line choice for treatment of **status epilepticus**. Useful for preventing convulsions (delirium tremens) in alcohol withdrawal, **cocaine toxicity,** and amphetamine overdose. It is also useful before initiating chemotherapy for **cancer** to prevent anxiety.

Other important points:

- It is the only BZD which is recommended for intramuscular use.
- It shows about 90% plasma protein binding.
- It has fewer drug interactions.
- Preferred in **hepatic impairment.**

Diazepam

- It shows about **99% plasma protein binding.**
- It is a potent muscle relaxant. Useful for treatment of tetanus and spinal injuries.
- It can dilate coronary arteries when given intravenously
- Acts as a good analgesic if given intravenously
- Likely to cause rebound insomnia.

Atypical Hypnotics

Zopiclone

Eszopiclone is the enantiomer of Zopiclone.

Mechanism of Action: They act on the same receptor as BZDs. The effect is similar to BZDs but it does not alter REM sleep.

Clinical Uses: They don't have anticonvulsive activity. They can be used for short term treatment of insomnia.

Adverse Effects: Metallic taste, impaired judgment, dry mouth, psychological disturbances

Contraindications: Respiratory insufficiency, sleep apnea, hepatic dysfunction

Zaleplon

- Shortest acting
- Do not prolong sleep
- **Mechanism of Action:** It acts on the same receptor as BZDs
- **Clinical uses:** short-term treatment for insomnia
- Don't have anticonvulsive effect.

- **Interactions**: Alcohol and other CNS depressants

Zolpidem

- **Mechanism of Action:** It acts on the same receptor as BZDs
- **Clinical uses:**
- Shortens sleep latency
- Sleep duration is not prolonged
- No anticonvulsant, anxiolytic and muscle relaxant effect
- No effect on sleep pattern
- Minimal daytime sedation
- No rebound insomnia
- No tolerance, dependence and low abuse potential
- **Adverse Effects**: Dependence liability.
- **Interactions**: Alcohol and other CNS depressants.

Chloral Hydrate

No longer used.

Buspirone

Mechanism of Action: Partial agonist at brain **5-HT$_{1A}$ Receptors** with some affinity to Dopamine D_2 receptor.

Clinical use

- **Generalized anxiety disorder**.
- Selective anxiolytic with no sedative, hypnotic, muscle relaxant activity. It has a **slow onset** of action (10 days).

- Withdrawal doesn't produce rebound anxiety.
- Unsuitable for acute anxiety because it takes about a week to show effect.

Adverse Effects: Tachycardia, palpitation, chest pain, nervousness, tinnitus, dizziness, GI distress, paresthesia, and pupillary constriction

Contraindications: Hypersensitive

Interactions: CYP3A4 inducers and inhibitors

Ramelteon

Mechanism of Action: Agonist at **MT_1 and MT_2 melatonin receptors** at **suprachiasmatic nucleus** in brain.

Clinical use

- For regularizing sleep-wake cycle
- Decreases the time required for falling asleep

Note: No rebound insomnia/ withdrawal syndrome with use of ramelteon

Adverse Effects: Dizziness, somnolence, fatigue, decrease in testosterone and prolactin

Interactions: Alcohol and fluvoxamine

Contraindications: Hypersensitivity

Tasimelteon

Mechanism of Action:

- It is a melatonin receptor (MT_1 & MT_2) agonist.
- More affinity for MT_2

- No withdrawal syndrome, abuse potential or physical dependence observed.

Clinical use: It is used in the treatment of **Non-24-Hour Sleep-Wake Disorder (Non-24).**

Adverse Effects: Headache, nightmares, upper respiratory or urinary tract infections

Interactions: Fluvoxamine, rifampicin

Contraindications: Hepatic impairment and pregnancy.

Suvorexant

Mechanism of Action: Antagonist at orexin receptors

Clinical uses: Useful in sleep onset difficulty and/ or maintenance.

Adverse Effects: Daytime impairment, behavioral changes, sleep paralysis, hallucinations, cataplexy.

Contraindications: Narcolepsy

Interactions: Alcohol