UNIT- II: PHARMACOLOGY OF ANS: DRUGS ACTING ON AUTONOMIC NERVOUS SYSTEM

A. CHOLINERGIC SYSTEM:

1. PARASYMPATHOMIMETIC(CHOLINERGIC) DRUGS

A **parasympathomimetic drug**, sometimes called a **cholinomimetic drug**, is a substance that stimulates the parasympathetic nervous system (PSNS). These chemicals are also called cholinergic drugs because acetylcholine (ACh) is the neurotransmitter used by the PSNS. Chemicals in this family can act either directly by stimulating the nicotinic or muscarinic receptors (thus mimicking acetylcholine), or indirectly by inhibiting cholinesterase, promoting acetylcholine release, or other mechanisms.

Some chemical weapons such as sarin or VX, non-lethal riot control agents such as tear gas, and insecticides such as diazinon fall into this category.

CLASSIFICATION

Direct-acting

These act by stimulating the nicotinic or muscarinic receptors.

- **Choline esters**
  - Acetylcholine (all acetylcholine receptors)
  - Bethanechol (M3 receptors)
  - Carbachol (all muscarinic receptors and some nicotinic receptors)
  - Methacholine (all muscarinic receptors)
- **Plant alkaloids**
  - Arecoline
  - Nicotine
  - Muscarine
  - Pilocarpine (M3 receptors)

Indirect-acting

Indirect acting parasympathomimetic drugs may be either reversible cholinesterase inhibitors, irreversible cholinesterase inhibitors or drugs that promote ACh release or anti-adrenergics. The latter inhibits the antagonistic system, the sympathetic nervous system.

- **Reversible cholinesterase inhibitors**
  - Donepezil
  - Edrophonium
  - Neostigmine
  - Physostigmine
  - Pyridostigmine
  - Rivastigmine
  - Tacrine
  - Caffeine (non-competitive)
  - Huperzine A
- **Irreversible cholinesterase inhibitors**
  - Echothiophate

- Isoflurophate
- Malathion

- **ACh release promoters**
  - Cisapride
  - Droperidol
  - Domperidone
  - Metoclopramide
  - Risperidone
  - Paliperidone
  - Trazodone - via blockade of the α adrenergic receptors

ACETYLCHOLINE RECEPTOR

An **acetylcholine receptor** (abbreviated **AChR**) is an integral membrane protein that responds to the binding of acetylcholine, a neurotransmitter.

Classification

Like other transmembrane receptors, acetylcholine receptors are classified according to their "pharmacology," or according to their relative affinities and sensitivities to different molecules. Although all acetylcholine receptors, by definition, respond to acetylcholine, they respond to other molecules as well.

- Nicotinic acetylcholine receptors (*nAChR*, also known as "ionotropic" acetylcholine receptors) are particularly responsive to nicotine. The nicotine ACh receptor is also a Na+ and K+ ion channel
- Muscarinic acetylcholine receptors (*mAChR*, also known as "metabotropic" acetylcholine receptors) are particularly responsive to muscarine.

Nicotinic and muscarinic are two main kinds of "cholinergic" receptors.

ACh and its receptors

Drug	Nm	Nn	M1	M2	M3
ACh, Carbachol, Methacholine, AChEi (Physostigmine, Galantamine, Neostigmine, Pyridostigmine)	+	+	+	+	+
Nicotine, Varenicline	+	+			
Succinylcholine	+/-				
Atracurium, Vecuronium, Tubocurarine, Pancuronium	-				
Epibatidine, DMPP		+			
Trimethaphan, Mecamylamine,Bupropion, Dextromethophan, Hexamethonium		-			
Muscarine, Oxotremorine, Bethanechol, Pilocarpine			+	+	+
Atropine, Tolterodine, Oxybutynin			-	-	-
Vedaclidine, Talsaclidine, Xanomeline, Ipatropium			+		
Pirenzepine, Telenzepine			-		
Methoctramin				-	
Darifenacin, 4-DAMP, Darifenacin, Solifenacin					-

Nicotinic receptors are of two types: Nm and Nn. Nm is located in the neuromuscular junction which causes the contraction of skeletal muscles by way of end-plate potential (EPPs). Nn causes depolarization in autonomic ganglia resulting in post ganglionic impulse. Nicotinic receptors cause the release of catecholamine from the adrenal medulla, and also site specific excitation or inhibition in brain. Both Nm and Nn are Na^+ and Ca^{++} channel linked but Nn is also linked with an extra K^+ channel.

NAChR: ***Nicotinic acetylcholine receptors***

The nAChRs are ligand-gated ion channels, and, like other members of the "cys-loop" ligand-gated ion channel superfamily, are composed of five protein subunits symmetrically arranged like staves around a barrel. The subunit composition is highly variable across different tissues. Each subunit contains four regions which span the membrane and consist of approximately 20 amino acids.

The nAChR is found at the edges of junctional folds at the neuromuscular junction on the postsynaptic side; it is activated by acetylcholine release across the synapse. The diffusion of Na^+ and K^+ across the receptor causes depolarization, the end-plate potential, that opens voltage-gated sodium channels, which allows for firing of the action potential and potentially muscular contraction.

MAChR: ***Muscarinic acetylcholine receptors***

In contrast, the mAChRs are not ion channels, but belong instead to the superfamily of G-protein-coupled receptors that activate other ionic channels via a second messenger cascade. The muscarine cholinergic receptor activates a G-protein when bound to extracellular ACh. The alpha subunit of the G-protein deactivates adenylate cyclase while the beta-gamma subunit activates the K-channels and therefore hyperpolarize the cell. This causes a decrease in cardiac activity.

Role in health and disease

Nicotinic acetylcholine receptors can be blocked by curare, hexamethonium and toxins present in the venoms of snakesand shellfishes, like α-bungarotoxin. Drugs such as the neuromuscular blocking agents bind reversibly to the nicotinic receptors in the neuromuscular junction and are used routinely in anaesthesia.

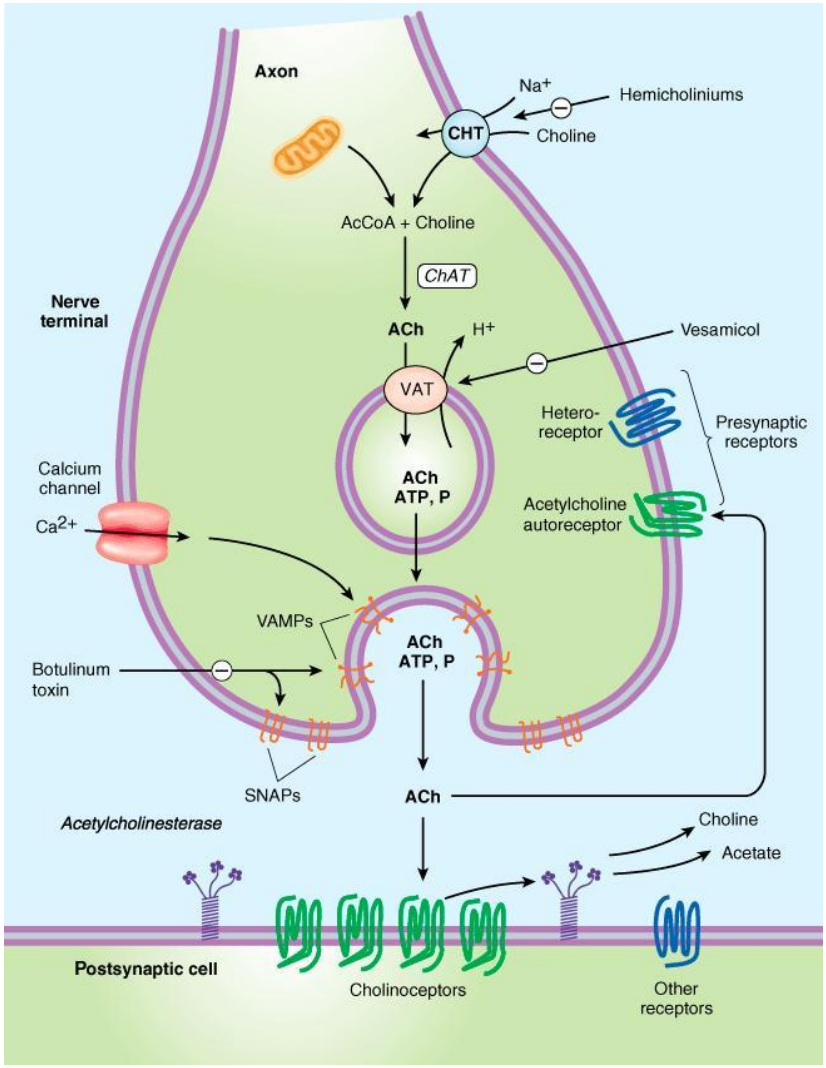
Nicotinic receptors are the primary mediator of the effects of nicotine. In myasthenia gravis, the receptor at the neuromuscular junction is targeted by antibodies, leading to muscle weakness. Muscarinic acetylcholine receptors can be blocked by the drugs atropine and scopolamine.

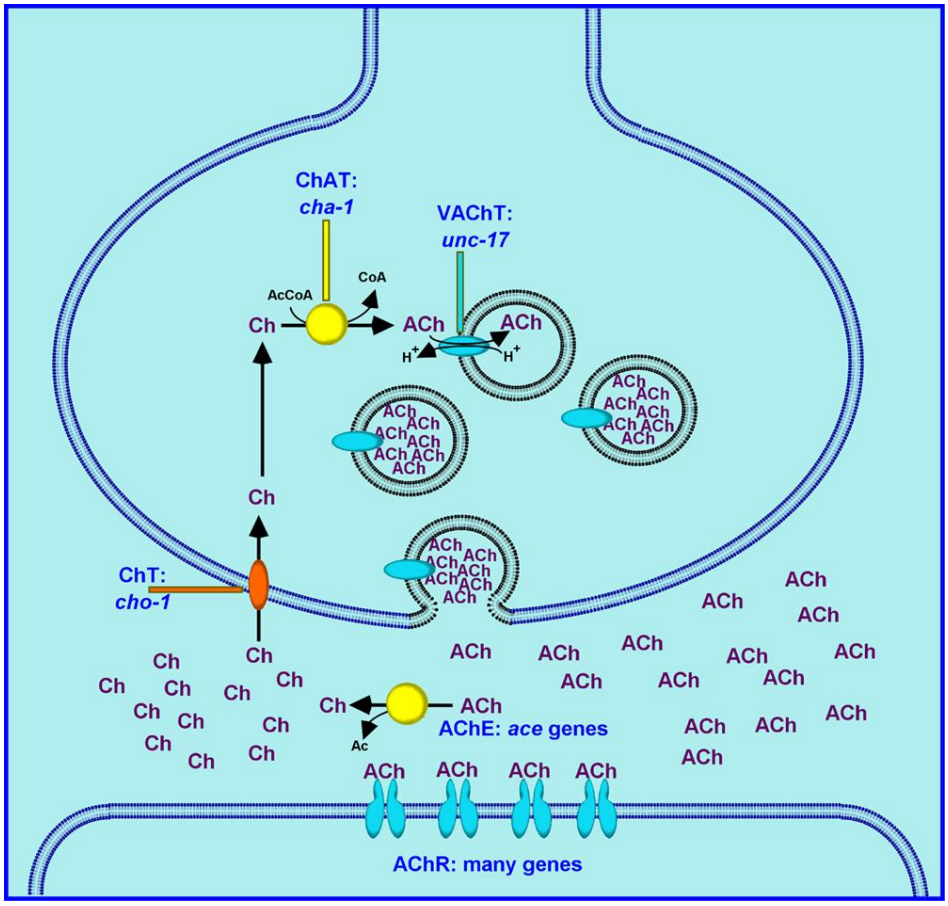
Congenital myasthenic syndrome (CMS) is an inherited neuromuscular disorder caused by defects of several types at the neuromuscular junction. Postsynaptic defects are the most frequent cause of CMS and often result in abnormalities in nicotinic acetylcholine receptors. The majority of mutations causing CMS are found in the AChR subunits genes.

ACETYLCHOLINE-

An ester of choline; synthesized in cell body of neuron by the combination of choline with acetyl group by the enzyme choline acetylase. Synthesis can be blocked by drugs like hemicholinium. After synthesis acetylcholine is transported to membrane bound vesicles; this transport is blocked by vesamicol. Each vesicle contains 1000–50000 molecules of acetylcholine.

• Acetylcholine is released in response to neuronal stimuli; the release of acetylcholine is blocked by botulinium toxin.
• Release of acetylcholine is dependent upon extracellular calcium; and is associated with the release of several other cotransmitters. After its release; acetylcholine may bind and activate postsynaptic receptors.
• Acetylcholine is rapidly hydrolyzed in synaptic cleft by cholinesterase into choline and acetic acid.





SITES OF ACETYLCHOLINE RELEASE CHOLINESTERASE

- Acetyl Cholinesterase OR True Cholinesterase
- Found in synaptic cleft.
- Degrades acetylcholine rapidly.
- Butyryl Cholinesterase OR Pseudocholinesterase
- Found in plasma and liver.
- Degrades acetylcholine, succinylcholine and procaine.

DIRECTLY ACTING CHOLINERGIC DRUGS: PHARMACOLOGICAL ACTIONS:

- Given orally acetylcholine is rapidly destroyed in gut and being quaternary ammonium compound is not well absorbed, when given intravenously.
- Acetylcholine is hydrolyzed by pseudo-cholinesterase present in plasma and the amount that reaches the synaptic cleft is destroyed by true cholinesterase.

ACETYLCHOLINE:

- **PHARMACOLOGICAL ACTIONS:**
- Therefore only extremely large doses of exogenously administered acetylcholine produce effects in body. However, when released by nerve stimulation acetylcholine can produce various effects.
- Following are the important well-recognized effects of acetylcholine released following cholinergic nerve stimulation

MUSCARINIC EFFECTS:

♣ Acetylcholine produces constriction of pupil (MIOSIS), by contracting the circular fibers of sphincter pupillae.

- It also contracts the ciliary muscle, which results in the relaxation of ligament of zonule of the lens.
- This reduces the tension on the lens and allows lens to bulge in the anterior chamber of eye, vision is therefore fixed for short distance, this is known as "Spasm of Accommodation."

• Acetylcholine also increases the drainage of aqueous humor through the canal of schelum by contracting trabecular meshwork (contraction of ciliary muscle); this reduces the intraocular pressure.

CARDIOVASCULAR SYSTEM:

- Acetylcholine reduces the heart rate and force of contraction; it decreases the heart rate by acting on SA node.
- Acetylcholine also decreases the conduction through AV node and purkinji fibers and can produce AV block.
- Acetylcholine produces vasodilatation and reduces the blood pressure.
- It stimulates the release of EDRF from endothelial cells that causes relaxation of vascular smooth muscles, however, vasodilating effect is not well marked.
- When endothelium is damaged, Acetylcholine directly acts on vascular smooth muscles and produces vasoconstriction.
- In Atropinized animals or patients, Acetylcholine produces vasoconstriction and increases BP, by acting on nicotinic receptors at autonomic ganglia that causes release of catecholamines.
- Acetylcholine produces bronchoconstriction, and increases bronchial secretions.

♣ Acetylcholine increases the motility of G.I.T, and decreases the sphincter tone, thus causes the propulsion of food.

- Secretions by salivary, gastric and intestinal glands are increased by acetylcholine

♣ Acetylcholine stimulates the detrusor and relaxes the trigonal muscles of urinary bladder and promotes voiding of urine.

♣ Acetylcholine increases the secretion of salivary, gastric, intestinal, lacrimal, nasopharyngeal, bronchial and sweat glands.

NICOTINIC EFFECTS:

• Acetylcholine by acting on autonomic ganglia stimulates the release of acetylcholine and catecholamines from postganglionic parasympathetic and sympathetic nerve terminals respectively. Acetylcholine causes the release of adrenaline by adrenal medulla.

• Acetylcholine causes the skeletal muscle contraction; sustained contraction by large quantities of acetylcholine can cause paralysis of the muscles.

MECHANISM OF ACTION:

MUSCARINIC EFFECTS:

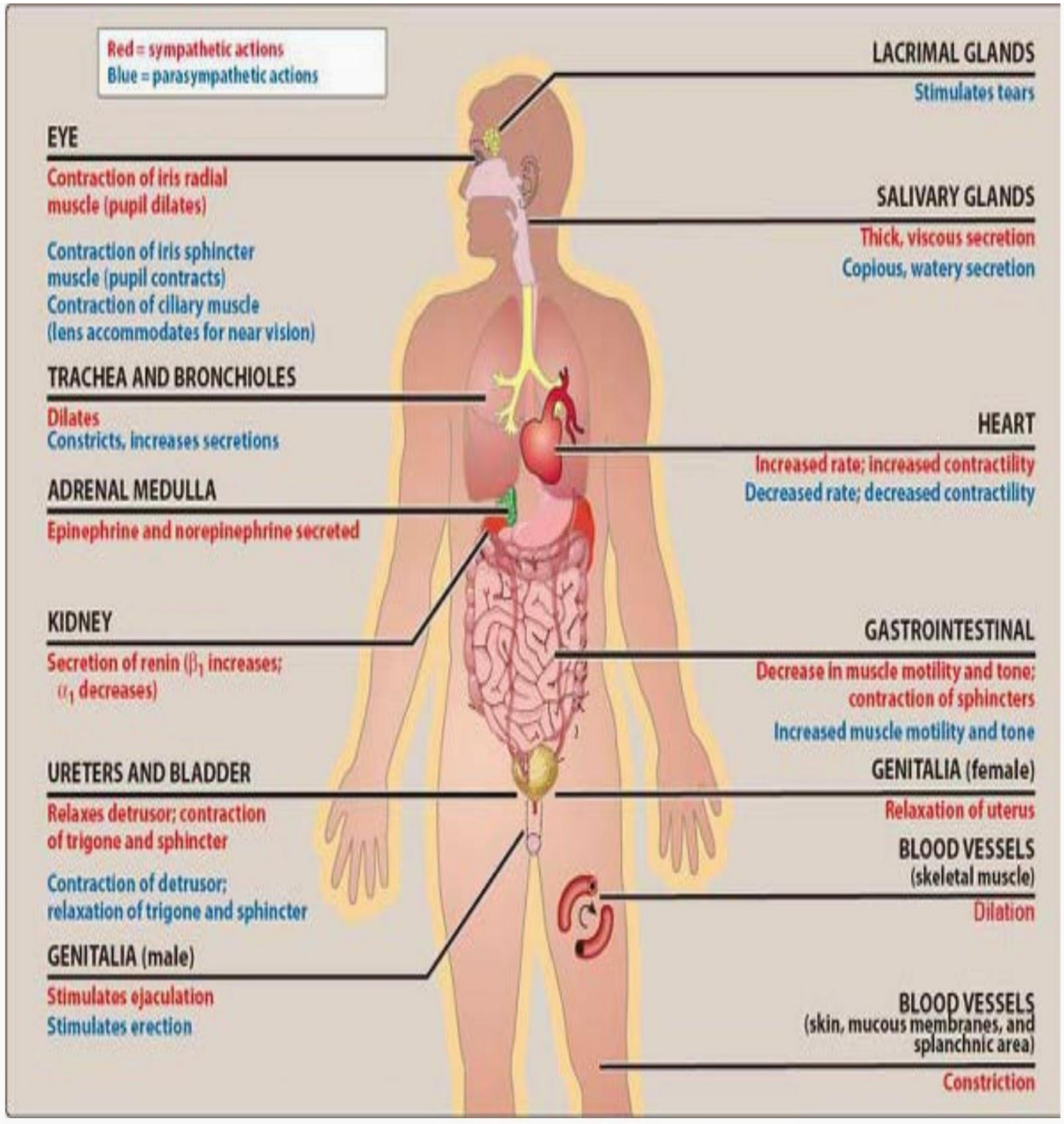
- Acetylcholine after binding to muscarinic receptors stimulates G–Proteins, which in turn causes stimulation of phospholipase C, which leads to the generation of IP3 and DAG.
- DAG opens smooth muscle calcium channels and IP3 elicits the release of calcium ions from sarcoplasmic reticulum.
- Increased intracellular calcium is associated with contractions of smooth muscles and release of glandular secretions.

MUSCARINIC EFFECTS:

- Activation of muscarinic receptors also increases the potassium flux across the cell membranes. This effect is mediated by binding of an activated G protein directly to ion channel.
- In some tissues like heart activation of muscarinic receptors result in inhibition of adenylyl cyclase that leads to decreased formation of cAMP, which may be responsible for decreased heart rate and force of contraction.

NICOTINIC EFFECTS:

- Acetylcholine after binding to nicotinic receptors opens the ionic channels, which in turn regulate the depolarization and repolarization processes.



PHARMACOKINETICS:

- Given orally acetylcholine is rapidly destroyed in gut and being quaternary ammonium compound is not well absorbed.
- When given intravenously, Acetylcholine is hydrolyzed by pseudocholinesterase present in plasma and the amount that reaches the synaptic cleft is destroyed by true cholinesterase.

- **THERAPEUTIC USES:**

• Acetylcholine has no therapeutic utility as a drug as exogenous acetylcholine is rapidly destroyed in the body.

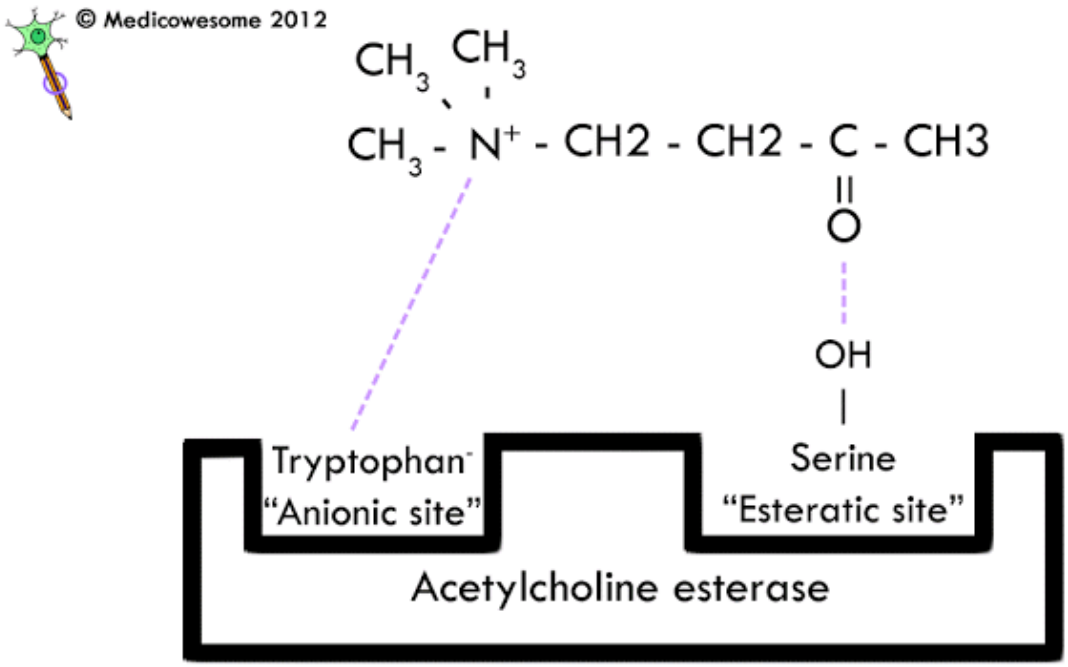
IRREVERSIBLE ANTICHOLINESTERASES: ORGANOPHOSPHORUS COMPOUNDS:

PHARMACOKINETICS:

o Organophosphorus compounds except Ecothiophate are well absorbed from skin, conjunctiva, lungs and gut.
o They are well distributed in the body, cross placenta and blood brain barrier.
o Malathion and parathion are inactive and are converted to active forms in insects and plants. They are metabolized in liver and excreted in urine.

MECHANISM OF ACTION:

o Organophosphorus compounds inhibit the enzymes true and pseudo cholinesterase irreversibly by binding with enzymes covalently.
o Organophosphorus compounds are toxic for human use and are effective insecticides.



CLINICAL FEATURES OF ORGANOPHOSPHORUS COMPOUND POISONING:

o Pinpoint pupil, lacrimation, irritation in eyes, bronchoconstriction, difficulty in breathing, wheezing sounds on auscultation of chest, bradycardia, hypotension, salivation, froth is coming out of mouth, muscular twitching, generalized convulsions, coma, fecal and urinary incontinence, excessive sweating, body is cold and clammy.
o Death results from cardiopulmonary failure.

CLINICAL FEATURES OF ORGANOPHOSPHORUS COMPOUND POISONING:
- In every unconscious patient immediate examination of respiratory & cardiovascular systems and pupil of eye is essential.
- In cases of organophosphorus compound poisoning patient is unconscious with pinpoint pupil.
- Pinpoint pupil is also seen with morphine poisoning.

TREATMENT:
General:
o Gastric lavage (Stomach wash).
o Maintain respiration (Artificial respiration).
o Maintain intravenous line.
o Catheterize the urinary bladder.
o Specific: Atropine: To antagonize the muscarinic effects. Cholinesterase reactivators:
o Pralidoxime, Obidoxime, & Diacetyl monoxime (D.A.M). These agents have high affinity for phosphorus atom and can displace the organophosphorus compounds from cholinesterase enzyme if given within 3–4 hours of poisoning.
o These agents are given parenterally; pralidoxime does not cross the blood brain barrier and can not reverse the effects on CNS.
o They are mainly metabolized in liver and metabolites are eliminated in urine.
o Local irritation, drowsiness, blurring of vision, dipolpia and tachycardia are their side effects.
o In toxic doses pralidoxime can induce neuromuscular weakness.
o Symptomatic:
o For convulsions give diazepam.

ANTICHOLINERGIC (PARASYMPATHOLYTIC) BRONCHODILATORS

The prototype anticholinergic agent is Atropine, which is found naturally in the plants ***Atropa belladonna*** and the Datura species. **Scopalamine** is also extracted from the belladonna plant, and both atropine and scopolamine are called **belladonna alkaloids.**

Clinical Indication for Use

I. Indication for Anticholinergic Bronchodilator
   a. Ipratropium or other anticholinergic agents are indicated as a bronchodilator for maintenance treatment in COPD, including chronic bronchitis and emphysema

II. Indications for Combined Anticholinergic and β-Agonist Bronchodilators
   a. A combination anticholinergic and β-agonist, such as ipratropium and albuterol (Combivent), is indicated for use in patients with COPD on regular treatment who require additional bronchodilation for relief of airflow obstruction

b. Ipratropium is also commonly used in severe asthma in addition to β-agonists, especially in acute bronchoconstriction that does not respond well to β-agonist therapy

III. Anticholinergic Nasal Spray
   a. A nasal spray formulation is indicated for symptomatic relief of allergic and non-allergic perennial rhinitis and the common cold

Clinical Pharmacology

I. Tertiary Ammonium Compounds
   a. Agents
      i. Atropine sulfate
      ii. Scopolamine
   b. Clinical Pharmacodynamics
      i. Easily absorbed into the bloodstream
         1. cause systemic effects
      ii. Cross the blood-brain barrier
         1. cause CNS effects

II. Quaternary Ammonium Compounds
   a. Agents
      i. Ipratropium bromide
      ii. Oxitropium bromide
      iii. Tiotropium bromide
   b. Clinical Pharmacodynamics
      i. Poorly absorbed into the bloodstream
         1. no/minimal systemic effects
      ii. Does not cross the blood-brain barrier
         1. no CNS effects

Pharmacologic Effects of Anticholinergic (Antimuscarinic) Agents

Comparison of cholinergic antagonism to cholinergic effects

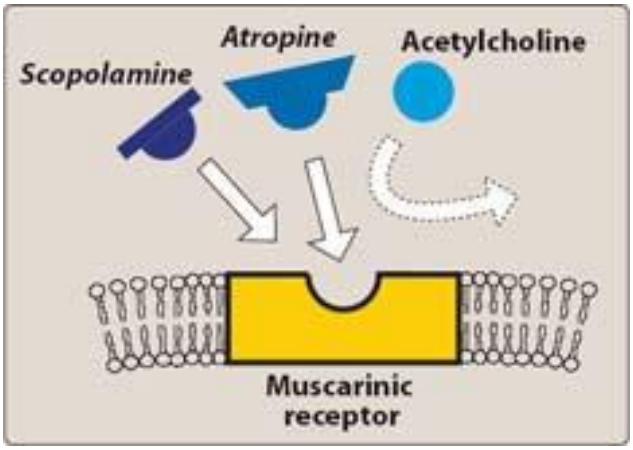
Cholinergic Effect	**Anticholinergic Effect**
Decreased heart rate	Increased heart rate
Miosis (contraction of iris, eye)	Mitosis (pupil dilatation)
Salivation	Drying of the upper airway
Lacrimation	Inhibition of tear formation
Urination	Urinary retention
Defecation	Antidiarrheal or constipation
Secretion of mucus	Mucociliary slowing
Bronchoconstriction	Inhibition of constriction

Pharmacologic Effects of Tertiary versus Quaternary Anticholinergic Agents Given by Inhalation

Organ System	Tertiary	Quaternary
Respiratory Tract	Bronchodilation Decreased mucociliary clearance Blocks hypersecretion	Bronchodilation Little or no change in mucociliary clearance Blocks nasal hypersecretion
Central Nervous System	Altered CNS function	No effect
Eye	Mydriasis Cycloplegia Increased intraocular pressure	Usually no effect*
Cardiac	Minor slowing of heart rate (smaller doses) Increased heart rate (larger doses)	No effect
Gastrointestinal	Dry mouth, dysphagia, dysphonia	Dry mouth
Genitourinary	Urinary retention	Usually no effect**

*Assumes aerosol is not sprayed into eye; use with caution in glaucoma
**Use with caution in prostatic enlargement or urinary retention

Mode of Action and Pharmacologic action



I. Anticholinergic Agents
   a. Cholinergic stimulation of muscarinic receptors on airway smooth muscle and submucosal glands cause bronchoconstriction and increased mucus production
   b. Anticholinergic agents block the action of acetylcholine at parasympathetic postganglionic effector cell receptors
   c. Anticholinergic agents act as antagonists at parasympathetic receptor sites and block cholinergic-induced bronchoconstriction
   d. The effect seen will depend on the degree of tone present that can be blocked
      i. Individuals with normal lungs will have minimal airway dilation – only a resting level of tone to be blocked
      ii. Individuals with COPD may have significant airway dilation due to a higher degree of parasympathetic activity (beyond normal resting level) due to vagally-mediated reflex bronchoconstriction

II. Vagally Mediated Reflex Bronchoconstriction

a. A portion of the bronchoconstriction seen in COPD may be due to a mechanism of vagally mediated reflex innervation of airway smooth muscle
b. Sensory C-fiber nerves respond to a variety of stimuli, such as irritant aerosols, cold air, cigarette smoke, noxious fumes, and mediators of inflammation such as histamine
c. When C-fiber nerves are activated, they produce an afferent nerve impulse to the CNS, which results in a reflex cholinergic efferent impulse
    i. Constriction of airway smooth muscle
    ii. Mucous gland secretion
    iii. Cough

III. Muscarinic Receptor Subtypes
a. Anticholinergic agents are nonselective muscarinic receptor antagonists

Receptor	Location	Effect
M_1	Postganglionic neuron	Facilitate cholinergic nerve transmission causing the release of ACH
M_2	Postganglionic neuron	Inhibits further ACH release
M_3	Airway smooth muscle Submucosal glands	Causes contraction of smooth muscle Increased secretion

Adverse Effects

Side Effects Seen with Anticholinergic Aerosol (Ipratropium)

1. Dry mouth
2. Cough
3. Nervousness
4. Irritation
5. Dizziness
6. Headache
7. Palpitation
8. Rash
9. Pharyngitis
10. Dyspnea
11. Flu-like symptoms
12. Bronchitis
13. Upper respiratory infections
14. Nausea
15. Occasional bronchoconstriction
16. Eye pain
17. Urinary retention (<3%)

Precautions: Use with caution in patients with narrow-angle glaucoma, prostatic hypertrophy, bladder neck obstruction, constipation, bowel obstruction, or tachycardia

I. Use in Chronic Obstructive Pulmonary Disease
a. Anticholinergic agents were found to be more potent bronchodilators than β-adrenergic agents in bronchitis-emphysema

II. Use in Asthma
a. Anticholinergic agents not proven superior to β-adrenergic agents
b. They offer an additional avenue of management

c. They are especially useful for
    i. Nocturnal asthma
    ii. Psychogenic asthma (vagally mediated)
    iii. Patients on beta blockers (angina, HTN, glaucoma)
    iv. Patients with notable side effects from theophylline
    v. Acute, severe episodes of asthma not responding well to β-adrenergic agents

III. Combination Therapy: β-adrenergic and Anticholinergic Agents in COPD
a. Theoretically useful
    i. Complementary sites of action
    ii. Mechanism of action separate and complimentary
    iii. Pharmacokinetics somewhat complementary (onset, peak, duration)
    iv. Possible additive effects – results conflicting
    v. Combivent Study: 462 patients at 24 centers

IV. Sequence of Administration
a. Frequently debated
    i. Anticholinergic bronchodilator acts in the central, larger airways
        1. some argue it should be given before the β-adrenergic
    ii. β-adrenergic often given first
        1. have more rapid onset and beta-2 receptors are distributed in the large and small airways

DRUGS ACTING ON AUTONOMIC GANGLIA:

Drugs acting on autonomic ganglia act on both sympathetic and parasympathetic ganglia without specificity and either (stimulate or inhibit discharges from post ganglionic fibres). These are classified into

1. Autonomic ganglionic stimulating drugs
2. Autonomic ganglionic blocking drugs

Autonomic Ganglionic Stimulating Drugs

These are further divided into
Natural alkaloids.
Eg. Nicotine, Lobeline

Synthetic drugs.
Eg.Tetramethyl ammonium (TMA),
Dimethyl Phenyl Piperazinium (DMPP)

Autonomic ganglionic blocking drugs

These are subdivided into

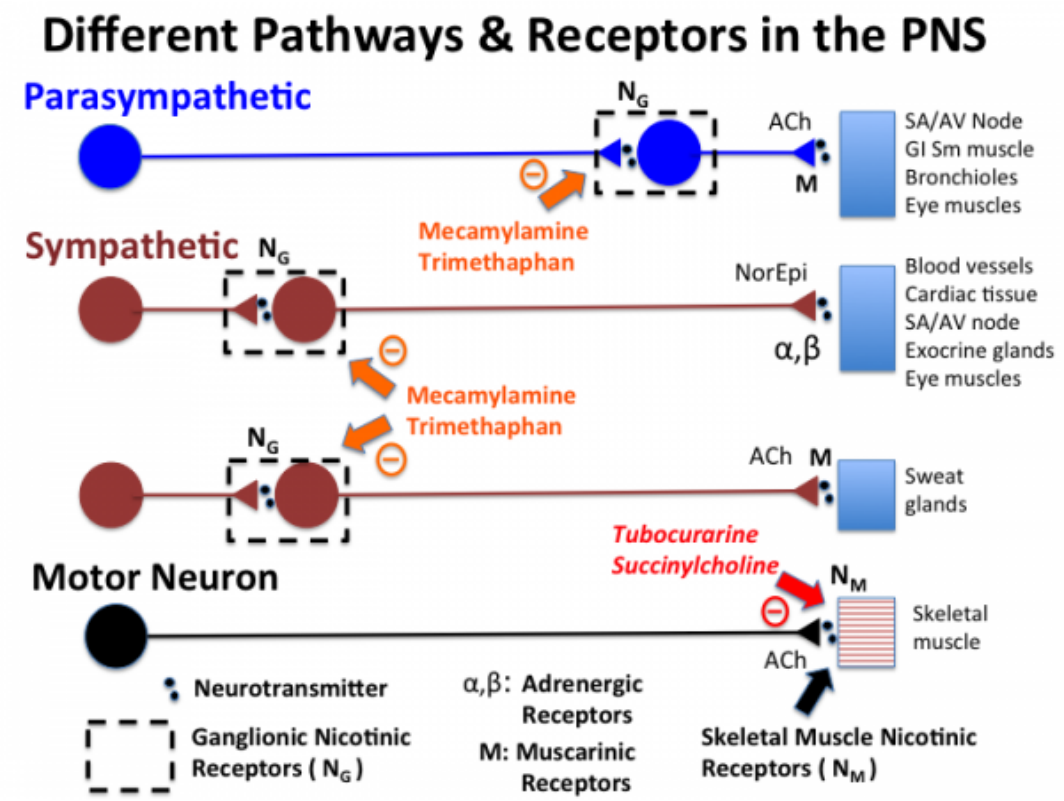
Persisting depolarizing ganglionic blocking drugs.
Eg. Nicotine (large doses)

Non-depolarizing ganglionic blocking drugs.

Eg. Hexamethonium, Pentalinium, Pentamethonium, Mecamylamine, pempidine, Trimethaphan

Since drugs acting on autonomic ganglia affect both sympathetic and parasympathetic postganglionic fibers, the overall effects of these agents on various functions are depended upon the predominance of sympathetic or parasympathetic tone in particular structure as detailed below

Organ	**Predominant tone**	**Effect of ganglionic stimulation**	**Effect of ganglionic blockade**
Cardiovascular system & blood vessels	Sympathetic	Vasoconstriction, hypertension , decreased peripheral blood flow	Vasodilation, hypotension , increased peripheral blood flow, decrease venous return,, pooling of blood
Heart	Parasympathetic	Bradycardia	Tachycardia
GI tract	Parasympathetic	Increased tone and motility, increased secretion , defecation	Increased tone and motility, constipation
Eye	Parasympathetic	Miosis	Mydriasis
Iris Ciliary muscle	Parasympathetic	-	Cycloplegia
Urinary bladder	Parasympathetic	Urination	Urine retention
Salivary glands	Parasympathetic	Watery salivation	Dry mouth
Sweat glands	Sympathetic (Adrenergic)	Increased sweating	Anhydrosis



PHARMACOLOGICAL ACTIONS OF GANGLIONIC STIMULANTS

CENTRAL NERVOUS SYSTEM

1. Nicotine is an extremely toxic substance that transiently stimulates and then depresses the CNS.
2. Death is from respiratory paralysis of the diaphragm and chest muscles resulting from descending paralysis.

3. Nicotine is absorbed through the chitinous shell of insects after a direct spraying or after contacting a sprayed surface and kills the insect by paralysis.

CARDIOVASCULAR SYSTEM

1. Small doses of nicotine activate both caridoaccelerator and cardioinhibitory nerves. Since cardioinhibitory nerve is more predominant, decreased pulse rate is noticed.

2. Due to paralysis of the autonomic ganglia after a large dose of nicotine, the heart rate returns towards normal.

3. Small doses of nicotine can cause a pressor response due to the sympathetic stimulation.

4. Peripheral vasodilatation results after a large dose due to autonomic ganglionic blockade.

GASTROINTESTINAL SYSTEM

1. Activates both the smooth muscles and secretory glands of the digestive tract and produce excessive salivation, increased gastric secretion, vomiting, increased peristalsis and defecation.

SKELETAL MUSCLE

1. Initially stimulates nicotinic receptors of the motor end plate and in large doses produces a depolarising muscle paralysis.

ACUTE NICOTINE POISONING

1. Excitement, hyperapnea, salivation, pulse rate irregularities, diarrhoea and emesis. After this transient stimulatory phase, a depressed state characterised by incoordination, tachycardia, dyspnoea, coma and death from respiratory paralysis.

PHARMACOLOGICAL ACTIONS OF GANGLIONIC BLOCKERS

Organ	**Predominant tone**	**Effects of ganglionic blockade**
Cardiovascular	-	Overall depression
Arterioles	Sympathetic	Vasodilatation, increased peripheral blood flow, hypotension
Veins	Sympathetic	Vasodilatation, pooling of blood, decreased venous return
Heart	Parasympathetic	Tachycardia
Gastrointestinal tract	Parasympathetic	Decreased tone and motility, constipation
Eye	-	-
Iris	Parasympathetic	Mydriasis
Ciliary muscle	Parasympathetic	Cycloplegia
Urinary bladder	Parasympathetic	Urinary retention
Salivary glands	Parasympathetic	Dry mouth
Sweat glands	Sympathetic	Anhydrosis
Bronchioles	Parasympathetic	Relaxation, decreased secretion

B. ADRENERGIC SYSTEM:

- Adrenergic neurons in the periphery are postganglionic sympathetic neurons whose cell bodies lie in sympathetic ganglia.
- They generally have long axons which end in a series of varicosities strung along the branching terminal network.
- These varicosities contain numerous synaptic vesicles, which are absent in other parts of the neuron and they represent the sites of synthesis and release of nerepinephrine.
- The synaptic vesicles of adrenergic neurons are larger and more granular than in other neurons, and these large electron-dense core vesicles are the storage organelles for catecholamines, which are released by exocytosis.

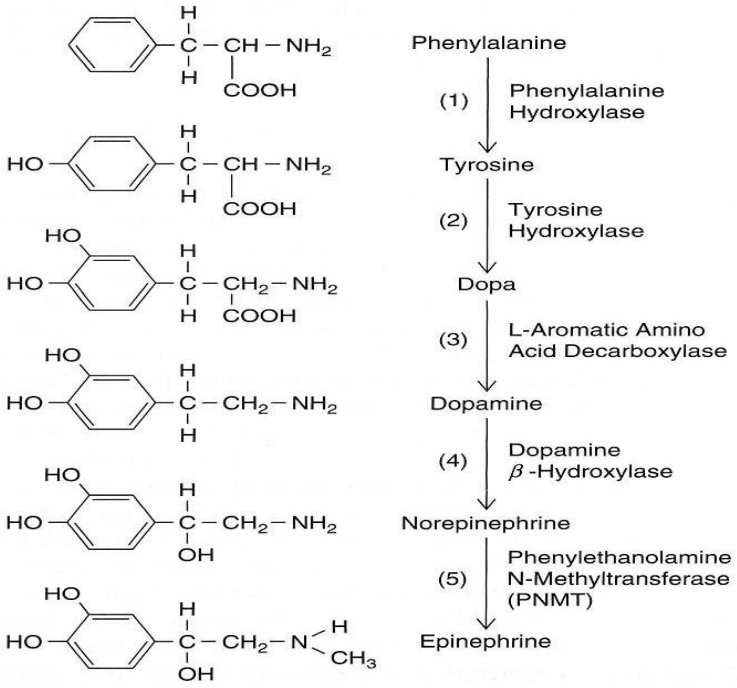
	NE	**EPI**	**ISO**
Alpha effects	Potent alpha stimulant (usually less than EPI)	Most potent alpha stimulant	least potent
Beta effects	Weak stimulant of blood vessel β2 receptor	Potent β stimulant	Most potent β stimulant
	Weak to moderate stimulant of smooth muscle β2 receptor outside the blood vessels		
	Potent stimulant of heart (β1 stimulant)		

CATECHOLAMINES

- 3, 4, dihydroxybenzene is called catechol and hence the drugs that have this structure are called catecholamines.
- Epinephrine, norepinephrine and dopamine are known as endogenous catecholamines.
- Isoproterenol is a synthetic catecholamine.
- Epinephrine (EPI), norepinephrine (NE) and isproterenol exhibit varying agonistic actions on the adrenoceptors.
- The effect of alpha adrenergic action of catechoamines (contraction of smooth muscle)is in the order of : EPI ≥ NE >> ISO
- and the beta adrenergic effect (relaxation of smooth muscle) is in the order of : ISO > EPI

SYNTHESIS OF CATECHOLAMINES

Figure 14.3 Pathway of catecholamine biosynthesis.



1. The precursor for catecholamine synthesis is tyrosine
2. Conversion of phenylalanine to tyrosine takes place in the liver.
3. Conversion of tyrosine to DOPA and DOPA to dopamine takes place in the adrenergic neuronal cytoplasm.
4. Dopamine gets converted to norepinephrine in the granules and norepinephrine to epinephrine in the adrenal medulla.
5. Tyrosine hydroxylase is the rate limiting enzyme and its inhibition by alpha methyl-ρ-tyrosine results in depletion of catecholamines. All enzymes of catecholamine synthesis are rather non-specific and can act on closely related substrates. Tyrosine hydroxylase is activated by cAMP dependent protein kinases and inhibited by catecholamines.
6. *Storage* within the granular vesicles is accomplished by complexation of the catecholamines with adenosine triphosphate and a specific protein, chromogranin. This complexation makes the amines inactive until their release. The vesicles also contain ascorbic acid and dopamine beta hydroxylase. Catecholamines are taken up from the cytoplasm into the granules by an active transport system that is ATP and Mg^{++} dependent. This intragranular pool of norepinephrine is believed to be the principal source of the neurotransmitter that is released upon nerve stimulation.
7. *Release* from the storage vesicles is calcium dependent exocytosis induced by depolarisation of the nerve ending. Drugs can also induce release by destruction of storage vesicles or displacement of catecholamines from the storage vesicles.
8. Amines within, the cytoplasm may be taken up by the granules for storage or, they may be inactivated by a deaminating enzyme monoamine oxidase (MAO) that is located in the neuronal mitochondria. Intracytoplasmic dopamine may also be deaminated by MAO.
9. *Fate* -The action of nerepinephrine may be terminated by (in descending order of importance)

a. active reuptake into the nerve across the axoplasmic membrane accounting for removal of NE upto 65% from the synaptic cleft. (uptake I)
b. diffusion from the cleft space via the extracellular fluid accounting for 15% of removal of NE (uptake II)
c. metabolic breakdown by enzymes accounting for 20% of metabolism.

10. Norepinephrine that has been taken back into the nerve may be restored in granules or it may be deaminated by MAO. Reuptake is an active mechanism and requires energy.
11. Norepinephrine termination of action by enzymatic conversion accounts for 20 per cent of released norepinephrine. Initial inactivation involves two enzymes.
    a. *Monoamine oxidase* (MAO) inactivates amines by conversion to aldehydes, which can subsequently be metabolized to carboxylic acids and alcohols. MAO is localised on the outer surface of the mitochondria and is present in neuronal and non-neuronal tissues. The reaction requires oxygen.
    b. *Catechol-O-methyl transferase* (COMT) methylates *m*-hydroxyl group of catechols. COMT an extraneuronal enzyme that has a wide tissue distribution and broad substrate specificity.
12. Catecholamines in the blood are metabolized in the liver by COMT and MAO. Aldehyde reductase and aldehyde dehydrogenase further metabolise the aldehydes formed by the deamination by MAO. Aldehyde reductase catalyses the formation of alcohol products and aldehyde derhydrogenase catalyse the formation of acid products. Products of the above enzymatic reactions can subserve as substrates for others. The major final products are 3-methyl-4-hydroxymandelic acid (VMA) or 3-methoxy-4-hydroxy-phenylethyleneglycol (MOPEG).

EFFECTS OF CATECHOLAMINES

- Epinephrine (EPI), norepinephrine (NE) and isproterenol exhibit varying agonistic actions on the adrenoceptors.
- The effect of alpha adrenergic action of catechoamines (contraction of smooth muscle)is in the order of : EPI ≥ NE >> ISOand the beta adrenergic effect (relaxation of smooth muscle) is in the order of : ISO > EPI

Effects of catecholamines

	NE	**EPI**	**ISO**
Alpha effects	Potent alpha stimulant (usually less than EPI)	Most potent alpha stimulant	least potent
Beta effects	Weak stimulant of blood vessel β2 receptor	Potent β stimulant	Most potent β stimulant
	Weak to moderate stimulant of smooth muscle β2 receptor outside the blood vessels		
	Potent stimulant of heart (β1 stimulant)		

DIFFERENCE BETWEEN CATECHOLAMINES AND NON CATECHOLAMINES

Adrenergic drugs are divided into catecholamines and non catecholamines. The difference between catecholamine and non catecholamines is follows:

Catecholamines	Non catecholamines
Contain hydroxyl groups at position 3 and 4 on the benzene ring	Lack one or both hydroxyl groups on benzene ring
Mainly have direct action. Few compounds may have mixed action (like dopamine)	Mainly have indirect or mixed actions and few may have direct action (like phenylephrine)
Have high affinity for α and/or β receptors	Have moderate to poor affinity for adrenoceptors
Usually have shorter half life because of their rapid metabolism	Have moderate to longer half life as these are degraded slowly
Metabolised mainly by MAO or COMT	Poor substrates for MAO and resistant to COMT
Usually not effective by oral route and are given parenterally	Most of the drugs are effective orally
Being polar drugs, poorly penetrate the CNS and hence have minimal effect on CNS	Easily pass blood brain barrier and produce significant CNS effects
Effects are produced even after adrenergic denervation	Loose activity following adrenergic denervation
No development of tolerance	Tolerance develops following repeated administration

CATECHOLAMINES - ADRENALINE

Adrenaline: (Epinephrine)

- It is an endogenous catecholamine and major hormone secreted by adrenal medulla. Commercial preparation is white to off white micro crystalline powder or granules which on exposure to light turns reddish (due to oxidation) with loss of activity.
- Both endogenous and commercial adrenaline is in levo form which is 15 times more potent than dextro isomer.

- *Pharmacological effects*
  - Adrenaline is a potent directly acting drug that interacts with all subtypes (α_1, α_2, β_1, β_2 and β_3) of adrenergic receptors.

Cardiovascular system

- *Blood vessels*
  - The main action of adrenaline is exerted on smaller arterioles and pre-capillary sphincter. Vasoconstriction predominates in cutaneous, mucous membrane, mesenteric and renal beds and occurs primarily through α_1-receptors. There is marked reduction in blood flow to these structures when adrenaline is injected.
  - On the other hand, vasodilatation predominates in skeletal muscles, liver and coronary blood vessels. Vasodilatation is mediated by β_2 receptor. Skeletal muscles blood vessels have both α and β_2 receptors, but β_2 are more sensitive to adrenaline than α receptors.
  - Large doses of adrenaline however causes vasoconstriction in skeletal muscles because α mediated action overrides β_2 mediated relaxation.
- *Blood pressure*
  - Effect of adrenaline on BP depends on dose, route and rate of administration.
  - Adrenaline given by slow IV infusion, SC injection or in slow doses (0.1µg/kg) causes fall in BP.
  - If a pharmacological dose of (1-3µg/kg) of adrenaline is given by rapid IV route, it produces a characteristic biphasic response on BP because the initial rise due to α_1 activity followed by β2 activity.
  - The immediate raise in BP is mediated by myocardial stimulation and peripheral vasoconstriction.
- *Heart*
  - Adrenaline is a powerful cardiac stimulant.
  - Both the heart rate and force of contraction are increased, resulting in a marked increase in cardiac output and cardiac oxygen consumption. These effects are mediated by β_1 receptors.
- *Smooth muscles*
  - Effects of adrenaline on smooth muscles of different organs and systems depend on the type of adrenergic receptors available in them.
  - Activation of α_1 receptors produces contraction of all smooth muscles except GI tract, mainly from release of intracellular calcium through the action of second messenger IP_3. Relaxation of smooth muscles is mediated by $\beta_2$receptors which increase intracellular cAMP concentration.
- *GI tract*
  - In general adrenaline relaxes the smooth muscles of the GI tract, mediated by the activation of both the α and β receptors.
  - Frequency and amplitude of peristaltic movements is decreased. However, the sphincters are contracted. Gastric juice secretion is decreased and the saliva produced is thick and scanty.

- *Uterus*
  - Response varies depending on the species and stage of gestation. In human adrenaline contracts gravid and non-gravid uterus when examined in vitro.
  - In situ, however, adrenaline relaxes the uterus in non-gravid stage, but contracts uterus during late pregnancy. Contraction of uterus is mediated through α receptors and relaxation is mediated via β_2 receptors.

Species	Non-gravid uterus	Gravid uterus
Rat	Relaxation	Relaxation
Rabbit	Contraction	Contraction
Cat	Relaxation	Contraction
Sheep	Contraction	Relaxation

- *Urinary bladder*
  - Relaxes detrusor muscle of bladder through receptors and contracts trigone and sphincter muscle via α receptor activation.
  - Net effect is retention of urine.
- *Respiratory tract*
  - Adrenaline causes broncho dilatation by relaxing bronchial smooth muscles through activation of β2 receptors. However, only the contracted bronchioles are dilated and normal bronchioles are not affected.
  - Adrenaline also decreases bronchial secretions and produce decongestion via α receptors.
  - High doses of adrenaline cause pulmonary oedema by shifting blood from system pulmonary tree.
- *Eye*
  - Adrenaline causes mydriasis due to contraction of radial muscle of the iris (α1 action).
  - However, this action is minimal when applied topically as adrenaline penetrates cornea very poorly.

Metabolic effects

- Produces significant hyperglycaemic effect, which result from
  - increased glycogenolysis in liver (β2 action)
  - increased release of glucagon (β2 action)
  - decreased release of insulin (α2 action)
- Increases concentration of free fatty acids in blood by stimulating β receptors in adipose tissues.
- In general adrenaline causes conversion of energy sources of glycogen and fat to glucose and free fatty acids, which acts as readily available energy sources.
- *Other effects*
  - Adrenaline contracts smooth muscles of spleen capsule (α effect), this discharges more blood into circulation.
  - Causes contraction of piloerector muscles, so hair become erect (α1 effect)
  - Adrenaline has little effect on the brain as it penetrates the blood brain barrier poorly.

- **Pharmacokinetics**
  - Adrenaline is not effective orally as it is metabolised rapidly by MAO and COMT present in intestinal wall and liver. Absorption from IM injection site is rapid, but is relatively slower following SC injection. In emergency adrenaline can be given by IV.
  - In general adrenaline parenterally has rapid action, but a brief duration of action. Most of the absorbed adrenaline is metabolised by the hepatic COMT and MAO into an inactive metabolites an excreted in urine. Adrenaline does not cross blood brain barrier, but crosses the placenta an is distributed in milk.
- *Side/adverse effects*
  - Adrenaline can induce a feeling of fear or anxiety, tremors, excitability, vomiting, pallor and lactic acidosis.
  - Large doses may cause cerebral haemorrhage, cardiac arrhythmias, pulmonary oedema, dyspnoea, renal failure, metabolic acidosis and cold skin.
- *Contraindications*
  - Adrenaline is contraindicated in narrow-angle glaucoma, general anaesthesia with halogenated hydrocarbons, coronary insufficiency, hypertension, hyperthyroidism and along with non-sedative β receptor blocking drugs.

Clinical uses

- Drug of choice in anaphylaxis
- Adrenaline restores cardiac rhythm in cardiac arrest (asystole)
- Added with local anaesthetics (1:100,000) to decrease their absorption from the injection site.
- Adrenaline relieves bronchospasm in acute asthma.
- Adrenaline reduces intraocular pressure in open-angle glaucoma when applied topically as 2% solution. It reduces formation of aqueous humour by vasoconstriction of the ciliary blood vessels.

NOREPINEPHRINE

Noradrenaline (Norepinephrine)

- It is the neurotransmitter released by the post ganglionic sympathetic neurons.
- It also constitutes 10-20% of the catecholamines content of adrenal medulla.
- Pharmacological effects:
  - Noradrenaline primarily acts on α_1, α_2 and β_1 receptors and has little action on β_2 receptors. Nor adrenaline and adrenaline are equipotent on β_1 receptors.
  - However noradrenaline is 2-10 times less potent than adrenaline on α receptors.

Cardiovascular system

- *Blood vessels*
  - Causes intensive vasoconstriction (α receptor mediated) and peripheral resistance in most vascular beds including cutaneous, mucosal splanchnic, hepatic, renal and skeletal muscle.
  - Unlike adrenaline, nor adrenaline decreases blood flow to skeletal muscles, because of predominal α action, rather than β_2 action.

- *Blood pressure*
  - Noradrenaline given either by slow infusion or bolus injection, causes dose related increase in blood pressure.
  - Unlike adrenaline, noradrenaline does not produce the biphasic response.
- *Heart*
  - Noradrenaline is a potent myocardial stimulant causes both positive inotropic and positive chronotropic effects ($\beta_1$action).
  - Cardiac output is, however, unaffected or decreased due to decreased venous return as a result of predominant vasoconstriction.
  - In intact animals, there is reflex bradycardia due to stimulation of vagus through baroreceptor mechanism.
- *Smooth muscles*
  - Noradrenaline causes relaxation of intestinal smooth muscles (α action) which is lesser than that produced by adrenaline.
  - It has a negligible effect on bronchial smooth muscle (due to lack of action on β_2 receptors). It contracts radial muscle of eye (α_1 action) and produces mydriasis.

Metabolic effects

Noradrenaline produces hyperglycaemia and other metabolic effects similar to adrenaline, but these are less pronounced.

- *Pharmacokinetics*
  - Noradrenaline is ineffective when given orally due to rapid distribution in GI epithelium and liver. Absorbed noradrenaline is metabolised by MAO and COMT.
- *Side/Adverse effects*
  - Similar to adrenaline, but less intensive in nature. Reduced blood flow to vital organs is the major danger with the neither use of nor adrenaline.
- *Contraindications*
  - Should not be used during general anaesthesia with halogenated hydrocarbons.

Clinical uses

- Has only limited therapeutic value.
- It may be given as slow drip in haemorrhagic or burn shock, as it increases vascular resistance and blood pressure.
- However, decreased blood supply to the kidney is a limitation.

DOPAMINE

Dopamine: (3, 4-dihydroxyphenylethylamine)

- It is an endogenous catecholamine and immediate precursor of nor adrenaline.
- Dopamine is a unique catecholamine which has both direct (α and β actions) and indirect (release of nor adrenaline) actions. In addition it also has dopaminergic ($D_1$and D_2 receptor actions.
- The cardiovascular effects of dopamine are mediated by different receptors that vary in either affinity for the dopamine.

- At very low IV doses (0.5-2µg/kg/min) dopamine acs predominantly on vascular D_1, dopaminergic receptors and dilates the renal, mesenteric and coronary vascular beds. This results in increase in renal blood flow, glomerular filtration rate and Sodium excretion.
- At somewhat higher IV doses (2-10µg/kg/min) dopamine also stimulates β_1 receptors on heart and releases noradrenaline from sympathetic nerve terminals. This exerts a positive inotropic but little chronotropic effects on heart. It increases the blood pressure, but the vascular resistance is unaffected.
- At high dose (10µg/kg/min) dopamine activate vascular α1 effects leading to vasoconstriction, which counters the useful effects of dopamine.
- Dopamine has no effect on non vascular α and β receptors. Exogenous dopamine has no central effects as it cannot cross the BBB.
- Dopamine is useful in the treatment of cardiogenic or septic shock, oliguria and severe congestive heart failure.

ISOPRENALINE

Isoprenaline (Isoproterenol/Isopropylarterenol)

- It is a direct acting synthetic catecholamine which predominantly stimulatesβ1 and β2 receptors. Its main actions are seen on the heart, blood vessels of skeletal muscles and smooth muscles of bronchi and GI tract.
- Isoprenaline decreases the peripheral resistance and increased blood flow to skeletal muscles, with little effect on cutaneous, mucosal and renal blood vessels. Overall, it lowers the blood pressure.
- On the heart, isoprenaline has positive inotropic and positive chronotropic effects with increased COP and in this respect it is more potent than adrenaline and noradrenaline.
- Isoprenaline relaxes all smooth muscles. Metabolic effects are similar to adrenaline.

PHARMACOLOGICAL ACTIONS

- Pharmacological actions of catecholamines can be studied under four major categories.
  - *Excitatory*
    - Blood vessels - constriction (including veins, increased venous return to heart).
    - Iris - contraction of the radial muscle with mydriasis .
    - GI & Urinary - contraction of the sphincters.
    - Sweat glands - secretion in horse.
    - Salivary glands - viscous secretion .
    - Male genetalia - ejaculation .
  - *Inhibitory*
    - Bronchioles - dilatation.
    - Blood vessels - dilatation.
    - GI Tract - relaxation of smooth muscle.
    - Urinary bladder - relaxation of detrusor.

- *Cardioexcitatory effects*
  - SA node - increased heart rate
  - Atria & Ventricles - increased force of contraction, conduction velocity.
  - AV node & His Purkinje System - increased automaticity, conduction velocity.
- *Metabolic effects*
  - Liver - glycogenolysis and gluconeogenesis, hyperglycemia.
  - Pancreas decrease (α) and increased (β) secretion.
  - Fat cells - lipolysis, increased plasma free fatty acids.
  - Skeletal - Muscle glycogenolysis, increased blood lactate.
- In addition to these effects, some CNS effects are also noticed.

THERAPEUTIC USES

- *Acute anaphylactic reaction* – to counter hypotension (α) and bronchospasm (β), epinephrine is the drug of choice.
- *Allergic disorders, asthma* – Objective is to produce brnchodilatation via β_2 receptors. Isoproterenol or epinephrine can be used by inhalation or by intramuscular or intravenous injection. They are short acting and also produce marked cardiac stimulation via the β1 receptors. Ephedrine can also be used. Though it is long acting, it produces marked CNS stimulation.
- *Cardiac arrest/heart block* – intracardiac injections of epinephrine or isoproterenol followed by IV infusion or subcutaneous and intramuscular injections are useful.
- *In combination with local anaesthetics* – to produce local vasoconstriction and retard the removal of the anaesthetic thereby, increasing the duration of anaesthetic action. Epinephrine is preferred for this use.
- *Control of bleeding* – epinephrine when applied locally arrests bleeding from arterioles and capillaries.
- *Decongestion of mucous membrane* – phenylephrine and pseudoephedrine are used in rhinitis, sinusitis and hay fever as decongestant.
- *Ophthalmology* – ephedrine or phenylephrine can be used to examine the eye as they induce mydriasis without cyclopegia.
- *Shock* – Use of α agonists to maintain blood pressure in shock may be harmful by reducing the perfusion to the kidney and brain, which are already affected. But dopamine is useful in the treatment of cardiogenic, traumatic and hypovolemic shock because it selectively dilates the kidney blood vessels, increasing glomerular filtration and increasing urine production. In addition dopamine increases blood supply to abdominal organs.
- *Hypertension* – clonidine is effective in hypertension and its effect is primarily central. It may partially activate peripheral presynaptic α_2 receptors.
- *Uterine relaxants* – isoxuprine can be used to produce uterine relaxation (tocolytic).

ADRENERGIC DRUGS (sympathomimetics)

Drugs acting on adrenergic nervous system

- Two groups:
  - Adrenergic agonists (sympathomimetic)
  - Adrenergic antagonists (sympatholytic)
- Adrenergic agonists- Produce actions similar to that of adrenaline and noradrenaline and hence their pharmacological effects are similar to those observed when sympathetic nerve is stimulated. These are also called sympathomimetic drugs.
- Anti adrenergic drugs are those drugs that interfere with the actions of sympathetic nervous system stimulation. These drugs are also called sympatholytic drugs.

ADRENOCEPTORS

- Pharmacological effects of adrenergic drugs are mediated by activation of adrenergic receptors.
- Two types of adrenergic receptors were proposed to explain the dissimilar effects of sympathomimetic agents in different tissues.
- They are α and β receptors.
- The α and β receptors are differentiated pharmacologically, initially based on the relative properties of catecholaminesnamely epinephrine, norepinephrine and isoproterenol.

Effects of adrenoceptors

- Released catecholamines interact with the α-adrenergic or β-adrenergic receptors on the postjunctional membrane to produce specific effects in the postjunctional cell through activation of specific G-proteins.
- In some systems released catecholamines interact with a α_2-adrenergic receptors, which are on the prejunctional nerve cell. These receptors mediate an inhibition of the release of norepinephrine thus allowing the neurotransmitter to modulate its own release. This has been termed as auto-inhibitory feedback mechanism and may play an important role in the regulation of catecholamine release.
- In general, α receptors mediate excitatory/contractile response and β receptors mediate stimulation of the heart, relaxation of smooth muscles and metabolic effects.
- In addition to these receptors, dopamine receptors are available in periphery, which mediate vasodilatation in the kidney, heart, mesentry and increase the force of contraction of the heart. Dopamine also has a weak agonistic activity on the α adrenergic receptors.

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ADRENERGIC RECEPTORS AND ADRENERGIC RESPONSES

α actions	**β actions**
Constriction of arterioles and veins – rise in BP	Dilatation of arterioles and veins – fall in BP
Heart – little action, arrhythmia in high doses	Cardiac stimulation, increased heart rate, force and conduction velocity
-	Bronchodilatation
Contraction of radial muscles of the eye – mydriasis, decreased aqueous secretion	No effect on iris and ciliary muscles, enhanced aqueous secretion
Intestinal relaxation, contraction of sphincters	Intestinal relaxation
Bladder trigone – contraction	Detrusor - relaxation
Uterus – contraction	Relaxation
Splenic capsule – contraction	Relaxation
Neuromuscular transmission facilitated – increased Ach	Active state – prolonged in fast contracting muscle, abbreviated in slow contracting muscle

Insulin secretion inhibited (œ$_2$ dominant)	Augmented insulin (mild)
Liver – glycogenolysis	-
-	Renin release from the kidney
Male sex organs – ejaculation	-
Salivary glands – K^+ and H_2O secretion	Ptylin secretion
-	ADH secretion from posterior pituitary
Nictitating membrane – contraction in some species	-

ALPHA RECEPTOR SUB TYPES

	a $_1$	**a $_2$**
Location	Postjunctional effector organs	Prejunctional nerve ending, postjunctional in brain, pancreatic β cells, platelets and extrajunctional in blood vessels
Function subserved	Smooth muscle – contraction Blood vessels - Vasoconstriction Glands – decreased secretion Gut – relaxation Heart – arrhythmia	Inhibitors of transmitter release Blood vessels-Vasoconstriction Decreased central sympathetic flow Decreased insulin release Platelet aggregation
Selective agonist	Phenylephrine, methoxamine	Clonidine
Selective antagonist	Prazosin	Yohimbine

BETA RECEPTOR SUB TYPES

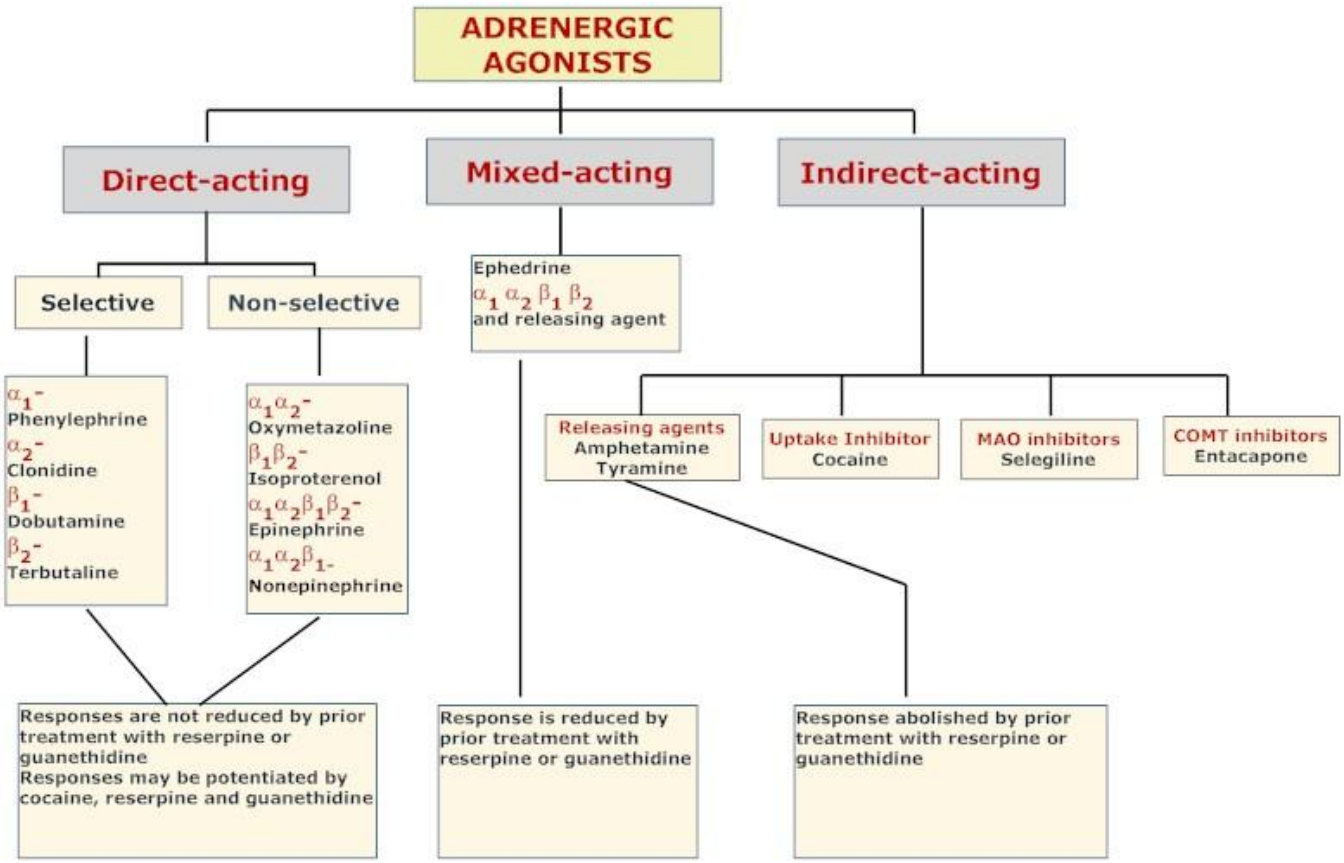
	β_1	**β_2**	**β_3**
Location and function subserved	Heart – increased heart rate, increased force of contraction, increased AV nodal conduction velocity Juxtaglomerular cells in kidney – increased renin secretion	Bronchi – relaxation Blood vessels – Vasodilatation Uterus – relaxation	Adipose tissue - lipolysis

		GI tract – relaxation Urinary tract – relaxation Skeletal muscle – glycogenolysis Liver – glycogenolysis	
Selective agonist	Dobutamine	Salbutamol	
Selective antagonist	Atenolol	Butoxamine	

CLASSIFICATION OF SYMPATHOMIMETIC DRUGS

Sympathomimetic drugs are classified as follows

- Direct acting (Adrenergic agonists)
  - *These are agents that act directly either on alpha (alpha1 and alpha 2) or beta (beta1 and 2) adrenoceptors.*
  - Drugs having equal potency at α and β receptors. Eg. Epinephrine, Ephedrine, Dopamine
  - Drugs having higher potency at α receptors. Eg. Norepinephrine
  - Selective α receptor agonists. Eg. Phenylephrine and Methoxamine (alpha 1), Clonidine (alpha 2)
  - Nonselective β receptor agonist. Eg. Isoproterenol
  - Selective β1 agonist. Eg. Dobutamine
  - Selective β2 agonists. Eg. Metaproterenol, Terbutaline, Salbutamol
- Indirect acting
  - Drugs inducing release of neurotransmitter. Eg. Amphetamine, Tramine, Ephedrine
  - Drugs inhibiting reuptake of neurotransmitter. Eg. Cocaine, Imipramine
  - Drugs inhibiting monoamine oxidases. Eg. Pargyline, Clorgyline
  - Drugs inhibiting catechol-o-methyl transferase. Eg. Pyragallol



α_1 - ADRENERGIC RECEPTOR AGONIST

Acts predominantly on α_1 adrenergic receptors.

- Phenylephrine
  - It is a direct acting non-catecholamine with powerful α_1 adrenergic agonistic activity.
  - It has negligible β agonistic and CNS actions.
  - Chemically phenylephrine differs from adrenaline in lacking 4-OH group on the benzene ring.
  - It is less potent than nor adrenaline on α_1, but has long duration of action.
- Pharmacological effects
  - It produces peripheral vasoconstriction with resulting increase in BP and small decrease in COP.
  - Trough phenylephrine has no direct effect on myocardium, it produces reflex bradycardia.
  - It decreases cutaneous, renal splanchnic blood flow, but increases the coronary blood flow.
  - It causes mydriasis and reduces intraocular pressure.
- Pharmacokinetics
  - Given orally is rapidly metabolized in the GI tract and does not produce any response. Hence, given parenterally by IV or IM routes.
  - It is mainly metabolized in the liver and partly its action is terminated by uptake into tissue.
- Methoxamine

- It is a directly acting sympathomimmetic with relatively selective α receptor action. But unlike phenylephrine, methoxmine slightly higher doses has some β receptor blocking action. This β- receptor blocking effect makes it less prone to induce cardiac arrhythmias.
- Methoxamine is primarily used in the treatment of hypotensive states. In contrast, to other adrenergic drugs, methoxamine can be used during general anesthesia with halogenated hydrocarbons.
- Some selective α-adrenergic receptor agonists: Oxymetazoline, Xylometazoline, Naptazoline.

α_2 - ADRENERGIC RECEPTOR AGONIST

Clonidine

- Is a partial α_2 - adrenergic receptor agonist. Rapid IV injection causes a transient increase in BP due to activation of post junctional α_2 receptors in peripheral vascular smooth muscles. However, this effect is followed by a more sustained hypotensive responsive mediated through activation of presynaptic α_2 adrenoceptors in the lower brain stem (vasomotor centre in medulla oblongata), that causes decrease in central sympathetic outflow.
- In CNS α_2 receptors regulate the neuronal release of noradrenaline and several other transmitters and involved in the modulation of sympathetic outflow and cardiovascular and endocrine functions. In addition to central effects clonidine activates the prejunctional α_2 receptors that suppress release of noradrenaline from peripheral nerve endings. Clonidine also stimulates parasympathetic outflow, which produces the bradycardia.
- In addition to the CVS effect, clonidine produces other effects like: central sedative and analgesic effect, contraction of pregnant uterus leading to premature labour, inhibition of insulin and rennin secretion, stimulation of growth hormone, elevation of blood glucose level and activation of salt absorption from gut mucosa.

Clinical use

- Widely used in humans for treatment of hypertension. Also used for treating persons addicted to narcotics, alcohol and tobacco.

Xylazine

- It is structurally related to clonidine and is a α_2- receptor agonist.
- It is primarily used as a central sedative- analgesic with muscle relaxant properties.

Mechanism of action

- α_2-receptor activation produces analgesia and sedation similar to the of opioid receptor stimulation in the CNS. Both the receptors are found in similar region of the brain and on some of the same neurons.
- Even though the receptors are different, both α_2 and opioid receptors are connected to the same signal transducer and both types use the same effector mechanism. Hence when xylazine binds to α_2 receptors, it causes activation of membrane associated G-proteins. This inturn opens potassium channels in the neuronal membrane , making the cell membrane hyperpolarized. Thus the neuronal cells become insensitive to exciting input and, the transmission pathway blocked. This finally results in sedation and analgesia .

- Xylazine like clonidine also stimulates the prejunctional α_2 receptors in peripheral synopsis and decrease the release of nor adrenaline.

Pharmacological effect

- CNS: it produces sedation, analgesia, muscle relaxation and anxiolysis. in cats it causes emesis. Xylazine depresses thermoregulatory mechanisms and may produce either hypothermia or hyperthermia depending on the ambient temperature.
- CVS: It produces transient hypertension, followed by longer lasting hypotension and decreased COP.
- Clinical uses: Sedative, preanesthetic sedative prior to general anesthesia, inhalation or injectable) local anesthesia, as a general anesthetic in combination with ketamine, as emetic in cats.

Other selective α_2-receptor agonists

- Detomidine, Medetomidine, Romifidine. (These are mostly in veterinary practice as anaesthetics, analgesics like xylazine.)

β_1 - ADRENERGIC RECEPTOR AGONIST

Dobutamine

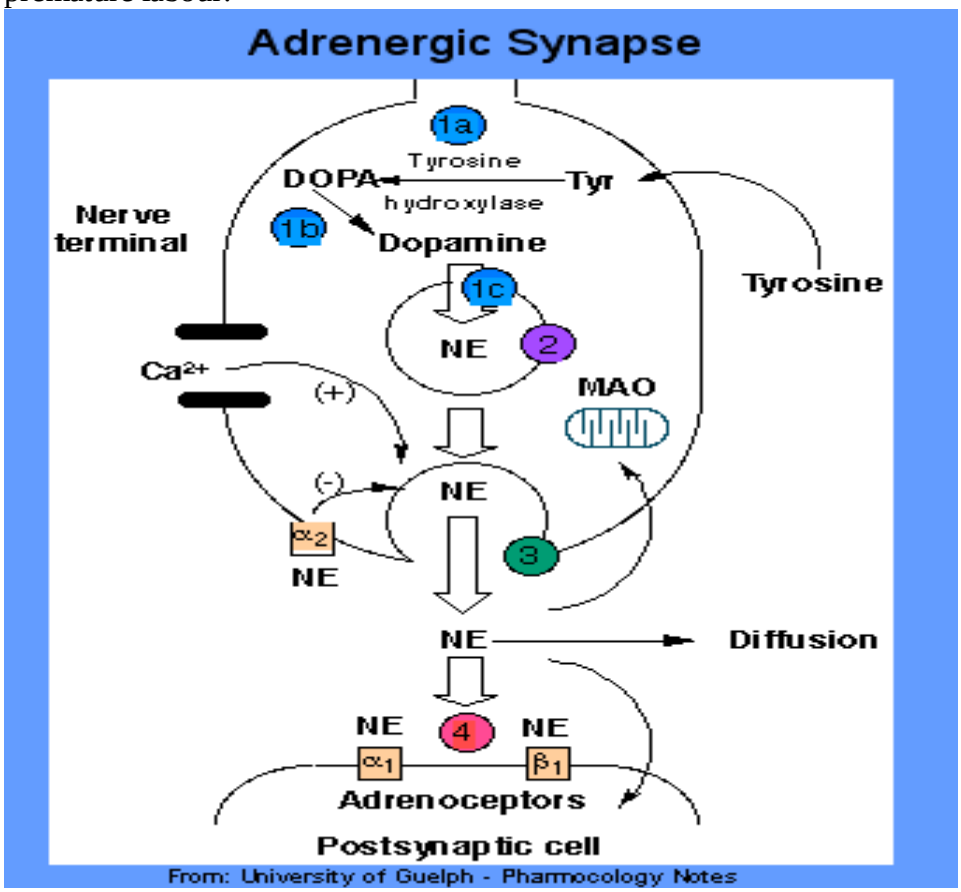
Dobutamine is a synthetic direct acting catecholamine with relatively selective β_1 receptor agonistic action. Dobutamine resembles dopamine structurally, but does not cause release noradrenaline. Hence, dobutamine produces only β_1 agonistic activity.

- Pharmacological effects
  - Intravenous infusion of dobutamine increase cardiac contractility and cardiac output, without significant change in heart rate, peripheral resistance and blood pressure. Increased myocardial contractility may increase oxygen demand and coronary blood flow. Overall, dobutamine is a more effective positive inotropic than dopamine, but it does not dilate the renal vascular bed.
- Pharmacokinetics
  - Being catecholamine, not active when given orally and is given by IV route. As it is rapidly metabolized in the liver and other tissue. Its half life is too brief. Hence, it is given by continuous IV infusion.
- Clinical use
  - Primarily used as an inotropic agent in severe congestive heart failure.

β_2 - ADRENERGIC RECEPTOR AGONIST

- In general, β_2 receptor agonists relax smooth muscles of bronchi and uterus and blood vessels of skeletal muscles. At high doses, however, may exhibit β_1 action on heart.
- Tachycardia is common after systemic administration which is due to the agonistic action of β_1 receptors.
- Long term use of β_2 receptor agonists, may result in their down regulation with subsequent decreased pharmacological response.
- Important selective β_2- adrenoceptor stimulant include clenbuterol, terbutaline, isoxuprine, salbutamol (albuterol) and orciprenaline (metaproterenol). Salbutamol has highest ratio of β_2: $\beta_1$action (about 10 times)

- These are primarily used as bronchodilators and as uterine relaxants to delay premature labour.



ANTIADRENERGIC DRUGS / ADRENERGIC ANTAGONISTS

- These are drugs that interfere with the functions of the sympathetic nervous system either by blocking the adrenergic receptors or by interfering the synthesis, storage or release of nor adrenaline in sympathetic nerve terminals.
- Accordingly these drugs are divided into two groups:
  - Adrenergic receptor antagonists
  - Adrenergic neuron blocking drugs

Differences between two are

Adrenergic receptor antagonists	**Adrenergic neuron blocking drugs**
Act on post junctional or pre junctional Receptors	Act on adrenergic neuron membrane (pre junctional)
Act by blocking adrenoceptors (alpha and beta)	Act by inhibiting synthesis, storage or release of nor adrenaline
Effects of exogenous adrenergic drugs is blocked	Not blocked

ADRENERGIC RECEPTOR ANTAGONISTS

- These drugs interact with adrenergic receptors (α and / or β) on effector cells (post junctional) or on adrenergic neurons (pre junctional) and prevent their access to either endogenous catecholamines or exogenous adrenergic drugs, except phenoxybenzamine, almost all these drugs act as competitive antagonists.
- These are further divided into three groups, based on the type of receptors they antagonize:
  - α receptor antagonists (selective and non selective)
  - β receptor antagonists (selective and non selective)
  - α and β receptor antagonists

α - RECEPTOR ANTAGONIST

- Inhibit all responses mediated through α adrenergic receptors without affecting those mediated by β adrenergic receptors.
- Based on α-receptors subtypes these drug antagonize. These are further divided into
  - Non-selective α adrenergic receptor antagonists (block both alpha1 and alpha2 adrenoceptors)
    - Haloalkylamine derivatives Eg: Phenoxybenzamine, Dibenamine
    - Imidazoline derivatives: Eg: Tolazoline, Phentolamine
    - Ergot derivatives Eg: Ergotmine, Dihydroergotamine, Dihydroergotoxine
    - Miscellaneous drugs
      - Neuroleptics- Chlorpromazine, Haloperidol
      - Benzodioxan derivatives- Piperoxane, Dibozane
      - Dibenzepine derivatives- Azapetine
  - Selective α - adrenergic receptor antagonists
    - Selective α1 adrenergic receptor antagonists
      - Quinazoline derivatives- Prazosin, Terazosin, Doxazosin, Trimazosin
      - Indole derivatives- Indoramin
      - Miscellaneous drugs- Ketanserin, Urapidil
    - Selective α_2- adrenergic receptor antagonists- Yohimbine, Atipamazole

NON- SELECTIVE α - ADRENERGIC RECEPTOR ANTAGONIST (Blocks both alpha1 and alpha2 adrenoceptors)

Phenoxybenzamine

It is a non competitive antagonists of both α_1 and α_2 receptors.

- *Pharmacological effects*
  - CVS: causes progressive decrease in peripheral resistance. It causes a fall in blood pressure following release of adrenaline during fight and flight.
  - Due to the non availability of α receptors, the released adrenaline acts only β – sub population.

- Phenoxybenzamine causes cutaneous blood flow to increase, but little effects are observed in skeletal or cerebral blood flow. The decreased peripheral resistance increased the COP and reflex tachycardia. The tachycardia is accentuated by neither enhanced release of nor adrenaline (because of pre junctional α_2 - receptor blockade) and its decreased inactivation (because of inhibition of neuronal and extraneuronal uptake by phenoxybenzamine).
- Phenoxybenzamine and other α- receptor antagonist block the α-agonistic actions of exogenously administered adrenaline or noradrenaline. In the presence of these antagonists, the pressor response of adrenaline is converted to a depressor response and this phenomenon is called "Dale's adrenaline reversal". This is because of action adrenaline only on β- receptors (as the α-receptors are blocked) that dilate the blood vessels. However, the action of nor adrenaline is not reversed, but is either diminished or blocked (nor adrenaline has no action of β_2 – receptors.)
- *Other effects*
  - Causes relaxation of nictitating membrane and blocks pupillary dilation. Urinary incontinence is observed due to relaxation of sphincter of urethra and relaxation of base of bladder. There is also failure of ejaculation in males.
  - Antagonises the hyperglycaemic effect of adrenaline, as it increases insulin secretion by pancreas (due to blockade of α-receptors in pancreas).
- *Side/Adverse effects:* Important side effect and adverse effects include: loss of vasomotor tone, hypotension, miosis, tachycardia, nasal congestion and inhibition of ejaculation. High doses may cause postural hypotension and shock.
- *Clinical uses:* Used in small animals for treatment of urinary retention and in treatment of hypertesion associated wit phaechromocytoma.

Tolazoline

- It is a weak to modest α_1 and α_2 receptor antagonist. Unlike phenoxybenzamine it is a reversible antagonist. In addition to α_1 and α_2 receptor blockade effects, it has also direct vasodilator and cardiac stimulant actions. It also blocks 5HT receptors and has histamine like gastric secretagogue effect and acetylcholine like motor action on intestine.
- Tolazoline is primarily used as an antidote to xylazine over dosage and to increase blood flow in peripheral vasospastic conditions like frost bite.

Phentolamine

- It is a close congener of tolazoline.
- It is more potent in blocking α-receptors compared to tolazoline, but other actions are less pronounced.

Ergot alkaloids

- Ergot is a fungus (*Claviceps purpurea*) that parasitizes rye and other grains. Ergot contains about 12 alkaloids (six isomeric pairs) and the naturally occurring l-forms are much more active than the d- forms. These alkaloids act as partial agonists or antagonists at α- adrenergic, tryptaminergic and dopaminergic receptors. Different groups of ergot alkaloids are:
  - Ergotamine group: These cause adrenergic blockade but have little effect on non vascular smooth muscles. Eg: Ergotamine, Ergosine

- Ergotaxine group: This group of alkaloids have alpha blocking activity and in addition stimulate vascular smooth muscle and uterus. Eg: Ergocrytpine, Ergocristine, Ergocornine.
- Ergometrine group: Have a weak adrenoceptor blocking activity, but are powerful stimulants of uterus (myometrium). Eg: Ergometrine (Ergonovine).

- *Pharmacological effects:* Most important effects are seen on cardiovascular system and uterine smooth muscle.
- *Cardiovascular system:* Initially cause direct peripheral vasoconstriction and pressor response that may persist for longer duration. Larger doses may cause blockade of α- receptors and can reverse the pressor response of adrenaline to depressor action. Still larger doses cause intense and persistant peripheral vasoconstriction leading to stasis of blood, thrombosis and obliterative endoarterities causing gangrene and sloughing of extremities (ergotism).
- *Other effects:* Initially stimulate the central nervous system followed by depression. Stimulates the chemoreceptor trigger zone and produce vomition. It also stimulates gastrointestinal tract and uterine smooth muscles.
- *Clinical uses:* Ergometrine is primarily used for contraction of the uterus post-partum.
- *Other drugs:* Although neuroleptic drugs like chlorpromazine and haloperidol produce significant α- receptor blockade effect , these are not clinically used for α – receptor blockade because of their many other pharmacological actions.

SELECTIVE α - ADRENERGIC RECEPTOR ANTAGONIST

Quinazoline derivative

- *Prazosin*
  - Prazosin is extremely potent highly selective α_1 adrenoceptor blocking drug with no action on α_2 receptors. It has 1000 times more greater affinity to α_1 receptors than for α_2 receptors.
  - It decreases peripheral vascular resistance and lowers blood pressure, by relaxing both arterial and venous smooth muscle. It also decreases venous return to the heart.
  - Unlike other non-specific α- receptor blockers, prazosin does not cause reflex tachycardia. This is because prazosin decrease cardiac pre-load and also does not cause release of nor adrenaline from sympathetic nerve endings in myocardium due to its no action on the pre junctional α_2- receptors. There are minimum changes in cardiac output, renal blood flow and glomerular filtation rate.
- *Clinical uses:* Treatment of systemic hypertension or pulmonary hypertension.

Selective α_2-adrenoceptor antagonists

- *Yohimbine*
  - It is a competitive antagonist with selective action on α_2- receptors. It is an alkaloid with structural resemblance to reserpine obtained from *Pausinystalia yohimbe.*
  - Yohimbine produces a short duration competitive blockade of α2 adrenergic receptor and 5-HT receptors.

- By blocking central α_2 –adrenergic receptors releases nor adrenaline and increases sympathetic outflow. This results in increased heart rate and blood pressure. However, as it also blocks the peripheral post-junctional $\alpha_2$receptors. It causes vasodilatation and hypotension usually predominate. The vasodilator effect of yohimbine in male genetalia causes penile erection.
- Yohimbine crosses readily the blood brain barrier and produces central nervous excitation, motor activity, ADH release, nausea and vomiting. It also antagonizes the effects of xylazine.

- *Clinical uses:* Yohimbine is used to antagonize the over dosage effects of xylazine.

β - ADRENERGIC RECEPTOR ANTAGONIST

- Depending on the selectivity for β-receptor blockade, these are grouped as follows:
  - Non selective β-adrenergic receptor antagonists (beta 1 and 2). Eg: Propranolol, Nadolol, Pindolol, Timolol, Sotalol.
  - Selective β-adrenergic receptor antagonists
    - Selective β_1-adrenergic receptor antagonists. Eg: Metoprolol, Atenolol, and Esmolol
    - Selective β_2-adrenergic receptor antagonist. Eg: Butoxamine.

NON SELECTIVE β - ADRENERGIC RECEPTOR ANTAGONIST

Propranolol

It interacts with both β_1 and β_2 receptors and blocks them competitively. It has powerful local anesthetic effect also.

- Cardiovascular effects
  - Blockade of β_1 –receptors produces decrease in heart rate, force of contraction and cardiac output. These are more evident during stress or exercise.
  - Cardiac work and oxygen demand are reduced. The AV conduction time is slowed, ectopic pacemaker activity is reduced and automaticity is suppressed.
  - Propranolol blocks cardiac stimulant action of adrenergic agonistic drugs, but not that of digitalis, Ca^{++} or methylxanthines.
- Propranolol increases peripheral vascular resistance as a result of blockade of vascular β_2- receptors. Hence, blood flow to all organs, except heart decreases. Propranolol blocks vasodilatation and fall in blood pressure caused by adrenaline. Pressor response of noradrenaline is slightly reduced due to blockade of cardiac $\beta_1$response.
- Propranolol blocks β_2- adrenergic receptors in bronchial smooth muscle leading to increased airway resistance. This bronchoconstriction is more marked in asthmatic patients.
- Propranolol blocks adrenaline induced lipolysis and glycogenolysis.
- Clinically used as an anti arrhythmic drug.

SELECTIVE β - ADRENERGIC RECEPTOR ANTAGONIST

Selective β_1 – receptor antagonists

- Metoprolol is the prototype of cardioselective β_1- receptor blockers. Its potency to block β_1- receptors equals that of propranolol, but about 50-100 times higher dose is required to block β_2-receptors.
- Cardiovascular effects secondary to metoprolol's negative inotropic and chronotropic actions include decreased sinus heart rate, slow AV conduction, decreased cardiac output, myocardial oxygen demand and reduced blood pressure. It reduces plasma renin activity in hypertensive patients. Unlike propranolol, metaprolol as relatively little effect on pulmonary function, peripheral resistance and carbohydrate metabolism.
- *Clinical uses:* It is used in arrhythmias, systemic hypertension, ventricular hypertrophy.
- *Atenolol*
  - Unlike propranolol and metoprolol, atenolol has very low lipid solubility, so it penetrates the brain only to a very limited extent.
- *Esmolol*
  - It is an ultra short acting β_1-rceptor blocker. It is given IV when β_1-receptor blockade is required for short duration. It is very useful for the investigation and immediate therapy of tachycardia.

Selective β_2-adrenergic receptor antagonists

- *Butoxamine*
  - It is relatively β_2-adrenergic receptor antagonist.
  - It is not used clinically as blockade of β2- adrenergic receptors has no therapeutic applications and on the other hand causes bronchoconstriction.

α AND β - ADRENERGIC RECEPTOR ANTAGONIST

Labetolol

- Labetolol at lower doses blocks only β receptors but at higher doses blocks both α and β receptors.
- Though it non selectively blocks β_1 and β_2 receptors, its α- receptor blockade is limited to only α_1-receptors.
- Labetolol produces fall in blood pressure without producing peripheral vasoconstriction.
- Used for treating hypertension. It is also an important experimental tool.

THERAPEUTIC USES

- Cardiovascular shock – These drugs can be used to overcome compensatory vasoconstriction. They must be used in conjunction with adequate fluid therapy to increase tissue perfusion.

- Pheochromocytoma – Can be used to overcome hypertensive attacks and to counteract effects of manipulation of tumor during surgical removal. (These drugs are used in combination with β blockers).
- Hypertension – Prazosin is used in hypertension.
- Epinephrine reversal (Dale's vasomotor reversal): Epinephrine acts both on α and β receptors. When given in high doses the vasoconstrictor effect and a rise in blood pressure are observed. But, when the a receptors are blocked using ergot like drugs / alpha 1 blockers and then the same dose of epinephrine is repeated, the a action on blood pressure is blocked and only the β receptors are free to act. Hence a fall in blood pressure is noticed instead of a rise. This is known as epinephrine reversal.

β-adrenergic antagnoists

- Non-selective antagnoists (Interact with β1 and β2 with equal potency)
- Dichloroisoproterenol was the first β -blocker to be synthesized. It is not used clinically, however, because it initially stimulates receptors (partial agonist).
- Propranolol (Inderal) as well as several others including Timolol Alprenolol, Pindolol, Nadolol, Sotalol are non-selective β-receptor antagonists and block β1 and β2 receptors with equal potency.

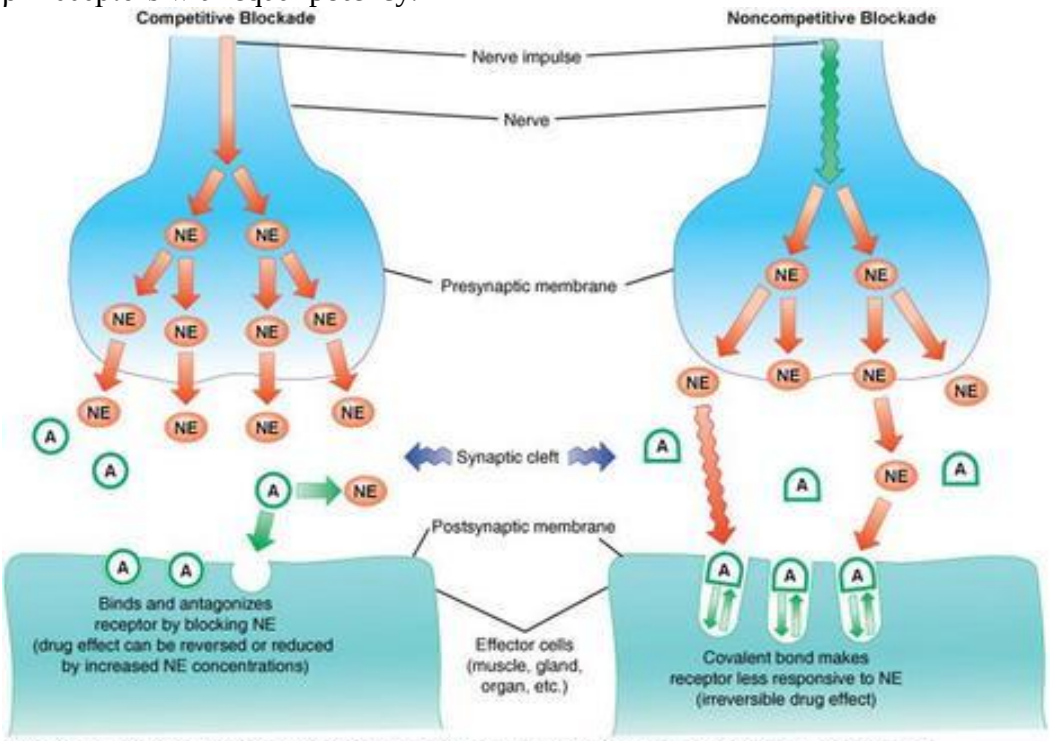


Fig. 18-1. Mechanisms for α-adrenergic competitive and noncompetitive blockade by a-blockers. *A*, α-blocker; *NE*, norepinephrine.

Pharmacological Actions

- Heart
  - Decrease in heart rate and force of contraction and cardiac output (minimal under resting conditions). Maximum exercise tolerance is reduced, partly because of the limited cardiac response but also because the β mediated vasodilatation in skeletal muscle is reduced. Coronary flow is reduced, but relatively less than myocardial oxygen consumption, so oxygenation of the myocardium is improved. β -Adrenergic receptor blockers can aggravate heart failure.

- Bronchioles
  - Slight increase in airway resistance due to bronchonconstriction and should therefore be avoided in bronchoconstrictor disorders such as asthma and allergic reactions. In these disorders non-selective β antagonists by themselves can cause severe bronchoconstriction, which is unresponsive to b agonists.
- Metabolic Effects
  - Can cause hypoglycemia by inhibiting β -receptor mediated adrenergic responses and should be used with caution in patients prone to hypoglycemia or in diabetes with insulin treatment.

Therapeutic Uses

- Cardiac arrhythmias - Can be used for supraventricular and ventricular arrhythmias, and are especially valuable in anesthetic and digitalis-induced arrhythmias. They have been shown to reduce the incidence of death from ventricular fibrillation during heart attacks.
- Post-myocardial infarction - Prophylactically reduces incidence of recurrent myocardial infarction in individuals with recent history of infarction.
- Glaucoma - Production of aqueous humor is reduced, lowering intraocular pressure. The mechanism of this effect is not clear. The advantage over cholinergic agonists is that accommodation and pupillary reactions are unaffected.
- Pheochromocytoma (adrenal medullary tumour) - Can be useful for managing tachycardia and arrhythmias and during surgery (in combination with a blockers).
- Hypertension - Usually used in combination with a diuretic. This is a common use in human medicine. Patients with hypertension show a gradual fall in arterial pressure that takes several days to develop fully.
- Angina pectoris - Used prophylactically in human medicine because of improved oxygenation of myocardium.
- Hyperthyroidism - Can be used to control many of the symptoms .

UNIT-III : DRUG ACTING ON PNS

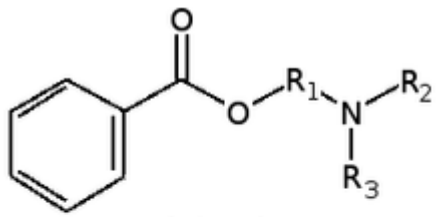
LOCAL ANESTHETICS

A **local anesthetic** (LA) is a medication that causes reversible absence of painsensation, although other senses are often affected, as well. Also, when it is used on specific nerve pathways (local anesthetic nerve block), paralysis (loss of musclepower) also can be achieved.

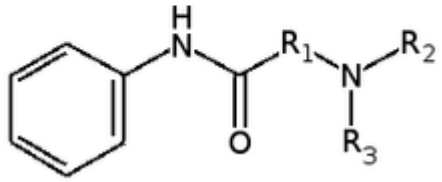
Clinical LAs belong to one of two classes: aminoamide and aminoester local anesthetics. Synthetic LAs are structurally related to cocaine. They differ from cocaine mainly in that they have a very low abuse potential and do not produce hypertension or (with few exceptions) vasoconstriction.

They are used in various techniques of local anesthesia such as:

- Topical anesthesia (surface)
- Topical administration of cream, gel, ointment, liquid, or spray of anaesthetic dissolved in DMSO or other solvents/carriers for deeper absorption
- Infiltration
- Brachial plexus block
- Epidural (extradural) block
- Spinal anesthesia (subarachnoid block)
- Iontophoresis



Aminoester



Aminoamide

Medical uses

Acute pain

Acute pain may occur due to trauma, surgery, infection, disruption of blood circulation, or many other conditions in which tissue injury occurs. In a medical setting, pain alleviation is desired when its warning function is no longer needed. Besides improving patient comfort, pain therapy can also reduce harmful physiological consequences of untreated pain.

Acute pain can often be managed using analgesics. However, conduction anesthesia may be preferable because of superior pain control and fewer side effects. For purposes of

pain therapy, LA drugs are often given by repeated injection or continuous infusion through a catheter. Low doses of LA drugs can be sufficient so that muscle weakness does not occur and patients may be mobilized.

Some typical uses of conduction anesthesia for acute pain are:

- Labor pain (epidural anesthesia, pudendal nerve blocks)
- Postoperative pain (peripheral nerve blocks, epidural anesthesia)
- Trauma (peripheral nerve blocks, intravenous regional anesthesia, epidural anesthesia)

Chronic pain

Chronic pain is a complex and often serious condition that requires diagnosis and treatment by an expert in pain medicine. LAs can be applied repeatedly or continuously for prolonged periods to relieve chronic pain, usually in combination with medication such as opioids, NSAIDs, and anticonvulsants.

Surgery

Virtually every part of the body can be anesthetized using conduction anesthesia. However, only a limited number of techniques are in common clinical use. Sometimes, conduction anesthesia is combined with general anesthesia or sedation for the patient's comfort and ease of surgery. Typical operations performed under conduction anesthesia include:

- Dentistry (surface anesthesia, infiltration anesthesia or intraligamentary anesthesia during restorative operations or extractions, and regional nerve blocks during extractions and surgeries)
- Podiatry (cutaneous, nail avulsions, matricectomy, and various other podiatric procedures)
- Eye surgery (surface anesthesia with topical anesthetics or retrobulbar block)
- ENT operations, head and neck surgery (infiltration anesthesia, field blocks, or peripheral nerve blocks, plexus anesthesia)
- Shoulder and arm surgery (plexus anesthesia or intravenous regional anesthesia)
- Heart and lung surgery (epidural anesthesia combined with general anesthesia)
- Abdominal surgery (epidural anesthesia/spinal anesthesia, often combined with general anesthesia)
- Gynecological, obstetrical, and urological operations (spinal/epidural anesthesia)
- Bone and joint surgery of the pelvis, hip, and leg (spinal/epidural anesthesia, peripheral nerve blocks, or intravenous regional anesthesia)
- Surgery of skin and peripheral blood vessels (topical anesthesia, field blocks, peripheral nerve blocks, or spinal/epidural anesthesia)

Other uses

Topical anesthesia, in the form of lidocaine/prilocaine (EMLA) is most commonly used to enable relatively painless venipuncture (blood collection) and placement of intravenous cannulae. It may also be suitable for other kinds of punctures such as ascites drainage and amniocentesis.

Surface anesthesia also facilitates some endoscopic procedures such as bronchoscopy (visualization of the lower airways) or cystoscopy (visualization of the inner surface of the bladder).

Side effects

Localized side effects

The local adverse effects of anesthetic agents include neurovascular manifestations such as prolonged anesthesia(numbness) and paresthesia (tingling, feeling of "pins and needles", or strange sensations). These are symptoms of localized nerve impairment or nerve damage. Of particular note, the use of topical anesthetics for relief of eye pain can result in severe corneal damage.

Risks

The risk of temporary or permanent nerve damage varies between different locations and types of nerve blocks.

Recovery

Permanent nerve damage after a peripheral nerve block is rare. Symptoms are likely to resolve within a few weeks. The vast majority of those affected (92%–97%) recover within four to six weeks; 99% of these people have recovered within a year. An estimated one in 5,000 to 30,000 nerve blocks results in some degree of permanent persistent nerve damage.[2]

Symptoms may continue to improve for up to 18 months following injury.

Causes

Causes of localized symptoms include:

1. neurotoxicity due to allergenic reaction
2. excessive fluid pressure in a confined space
3. severing of nerve fibers or support tissue with the needle/catheter
4. injection-site hematoma that puts pressure on the nerve
5. injection-site infection that produces inflammatory pressure on the nerve and/or necrosis

General side effects

General systemic adverse effects are due to the pharmacological effects of the anesthetic agents used. The conduction of electric impulses follows a similar mechanism in peripheral nerves, the central nervous system, and the heart. The effects of local anesthetics are, therefore, not specific for the signal conduction in peripheral nerves. Side effects on the central nervous system and the heart may be severe and potentially fatal. However, toxicity usually occurs only at plasma levels which are rarely reached if proper anesthetic techniques are adhered to. High plasma levels might arise, for example, when doses intended for epidural or intrasupport tissue administration are accidentally delivered as intravascular injection.[3]

Mechanism of action

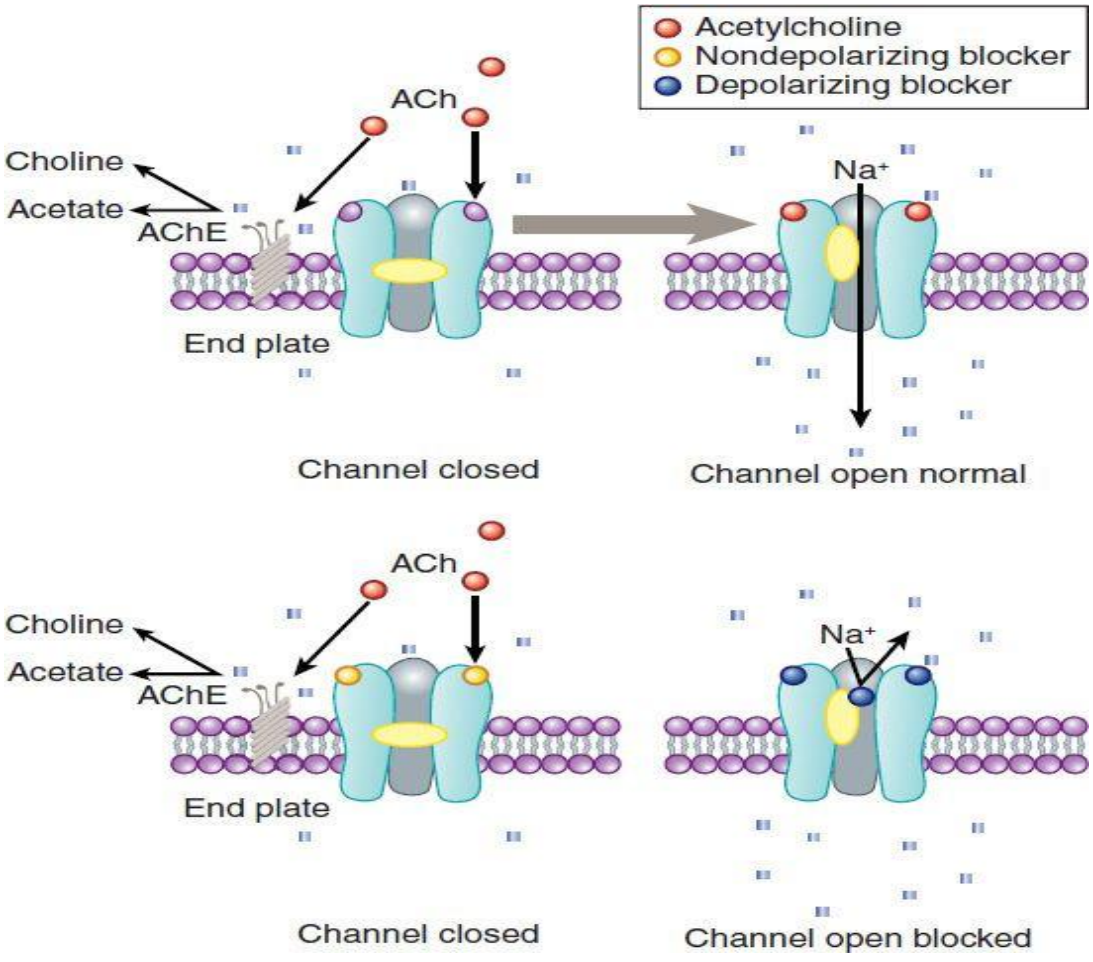
All LAs are membrane-stabilizing drugs; they reversibly decrease the rate of depolarization and repolarization of excitable membranes (like nociceptors). Though many other drugs also have membrane-stabilizing properties, not all are used as LAs (propranolol, for example). LA drugs act mainly by inhibiting sodium influx through sodium-specific ion channels in the neuronal cell membrane, in particular the so-called voltage-gated sodium channels. When the influx of sodium is interrupted, an action potential cannot arise and signal

conduction is inhibited. The receptor site is thought to be located at the cytoplasmic (inner) portion of the sodium channel. Local anesthetic drugs bind more readily to sodium channels in an activated state, thus onset of neuronal blockade is faster in rapidly firing neurons. This is referred to as state-dependent blockade.

LAs are weak bases and are usually formulated as the hydrochloride salt to render them water soluble. At a pH equal to the protonated base's pKa, the protonated (ionized) and unprotonated (unionized) forms of the molecule exist in equimolar amounts, but only the unprotonated base diffuses readily across cell membranes. Once inside the cell, the local anesthetic will be in equilibrium, with the formation of the protonated (ionized form), which does not readily pass back out of the cell. This is referred to as "ion-trapping". In the protonated form, the molecule binds to the LA binding site on the inside of the ion channel near the cytoplasmic end. Most LAs work on the internal surface of the membrane - the drug has to penetrate the cell membrane, which is achieved best in the nonionised form.

Acidosis such as caused by inflammation at a wound partly reduces the action of LAs. This is partly because most of the anesthetic is ionized and therefore unable to cross the cell membrane to reach its cytoplasmic-facing site of action on the sodium channel.

All nerve fibers are sensitive to LAs, but due to a combination of diameter and myelination, fibers have different sensitivities to LA blockade, termed differential blockade. Type B fibers (sympathetic tone) are the most sensitive followed by type C (pain), type A delta (temperature), type A gamma (proprioception), type A beta (sensory touch and pressure), and type A alpha (motor). Although type B fibers are thicker than type C fibers, they are myelinated, thus are blocked before the unmyelinated, thin C fiber.



Techniques

Local anesthetics can block almost every nerve between the peripheral nerve endings and the central nervous system. The most peripheral technique is topical anesthesia to the skin or other body surface. Small and large peripheral nerves can be anesthetized individually (peripheral nerve block) or in anatomic nerve bundles (plexus anesthesia). Spinal anesthesia and epidural anesthesia merge into the central nervous system.

Injection of LAs is often painful. A number of methods can be used to decrease this pain, including buffering of the solution with bicarbonate and warming.

Clinical techniques include:

- Surface anesthesia is the application of an LA spray, solution, or cream to the skin or a mucous membrane; the effect is short lasting and is limited to the area of contact.
- Infiltration anesthesia is infiltration of LA into the tissue to be anesthetized; surface and infiltration anesthesia are collectively topical anesthesia
- Field block is subcutaneous injection of an LA in an area bordering on the field to be anesthetized.
- Peripheral nerve block is injection of LA in the vicinity of a peripheral nerve to anesthetize that nerve's area of innervation.
- Plexus anesthesia is injection of LA in the vicinity of a nerve plexus, often inside a tissue compartment that limits the diffusion of the drug away from the intended site of action. The anesthetic effect extends to the innervation areas of several or all nerves stemming from the plexus.
- Epidural anesthesia is an LA injected into the epidural space, where it acts primarily on the spinal nerve roots; depending on the site of injection and the volume injected, the anesthetized area varies from limited areas of the abdomen or chest to large regions of the body.
- Spinal anesthesia is an LA injected into the cerebrospinal fluid, usually at the lumbar spine (in the lower back), where it acts on spinal nerve roots and part of the spinal cord; the resulting anesthesia usually extends from the legs to the abdomen or chest.
- Intravenous regional anesthesia (Bier's block) is when blood circulation of a limb is interrupted using a tourniquet (a device similar to a blood-pressure cuff), then a large volume of LA is injected into a peripheral vein. The drug fills the limb's venous system and diffuses into tissues, where peripheral nerves and nerve endings are anesthetized. The anesthetic effect is limited to the area that is excluded from blood circulation and resolves quickly once circulation is restored.
- Local anesthesia of body cavities includes intrapleural anesthesia and intra-articular anesthesia.

- Transincision (or transwound) catheter anesthesia uses a multilumen catheter inserted through an insicion or wound and aligned across it on the inside as the incision or wound is closed, providing continuous administration of local anesthetic along the incision or wound.

This LA system is designed to prevent needlestick injury. A cartridge of LA fits into the disposable needle, which can be locked when not in use and can be separated from the handle.

Local anesthetic solutions for injection typically consist of:

- The local anesthetic agent itself
- A vehicle, which is usually water-based or just sterile water
- Vasoconstrictor possibly (see below)
- Reducing agent (antioxidant), e.g. if epinephrine is used, then sodium metabisulfite is used as a reducing agent
- Preservative, e.g. methylparaben
- Buffer

Esters are prone to producing allergic reactions, which may necessitate the use of an amide. The names of each locally clinical anesthetic have the suffix "-caine". Most ester LAs are metabolized by pseudocholinesterase, while amide LAs are metabolized in the liver. This can be a factor in choosing an agent in patients with liver failure, although since cholinesterases are produced in the liver, physiologically (e.g. very young or very old individual) or pathologically (e.g. cirrhosis) impaired hepatic metabolism is also a consideration when using amides.

Sometimes, LAs are combined, e.g.:

- Lidocaine/prilocaine (EMLA, eutectic mixture of local anesthetic)
- Lidocaine/tetracaine (Rapydan)
- TAC

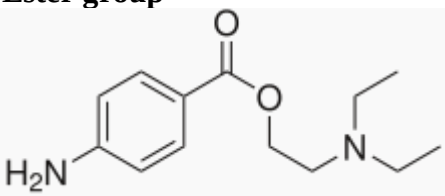
LA solutions for injection are sometimes mixed with vasoconstrictors (combination drug) to increase the duration of local anesthesia by constricting the blood vessels, thereby safely concentrating the anesthetic agent for an extended duration, as well as reducing hemorrhage. Because the vasoconstrictor temporarily reduces the rate at which the systemic circulation removes the local anesthetic from the area of the injection, the maximum doses of LAs when combined with a vasoconstrictor is higher compared to the same LA without any vasoconstrictor. Occasionally, cocaine is administered for this purpose. Examples include:

- Prilocaine hydrochloride and epinephrine (trade name Citanest Forte)
- Lidocaine, bupivacaine, and epinephrine (recommended final concentrations of 0.5, 0.25, and 0.5%, respectively)
- Iontocaine, consisting of lidocaine and epinephrine
- Septocaine (trade name Septodont), a combination of articaine and epinephrine

One combination product of this type is used topically for surface anaesthesia, TAC (5-12% tetracaine, $^{1}/_{2000}$ (0.05%, 500 ppm, ½ per mille) adrenaline, 4 or 10% cocaine).

Using LA with vasoconstrictor is safe in regions supplied by end arteries. The commonly held belief that LA with vasoconstrictor can cause necrosis in extremities such as the nose, ears, fingers, and toes due to constriction of end arteries], is invalidated, since no case of necrosis has been reported since the introduction of commercial lidocaine with epinephrine in 1948.

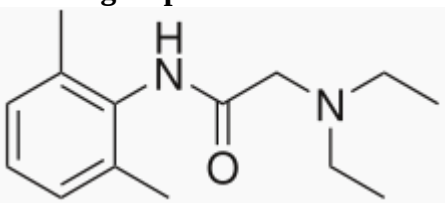
Ester group



Procaine

- Benzocaine
- Chloroprocaine
- Cocaine
- Cyclomethycaine
- Dimethocaine/Larocaine
- Piperocaine
- Propoxycaine
- Procaine/Novocaine
- Proparacaine
- Tetracaine/Amethocaine

Amide group



Lidocaine

- Articaine
- Bupivacaine
- Cinchocaine/Dibucaine
- Etidocaine
- Levobupivacaine
- Lidocaine/Lignocaine
- Mepivacaine
- Prilocaine
- Ropivacaine
- Trimecaine

Naturally derived

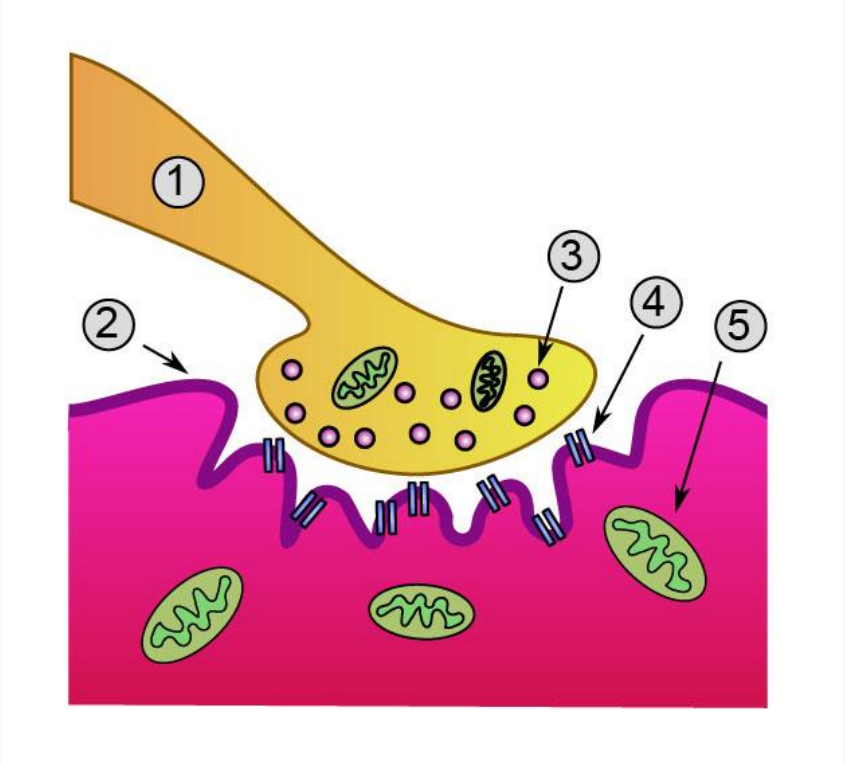
- Saxitoxin
- Neosaxitoxin
- Tetrodotoxin
- Menthol
- Eugenol
- Cocaine

Naturally occurring local anesthetics not derived from cocaine are usually neurotoxins, and have the suffix -toxin in their names. Unlike cocaine produced local anesthetics which are intracellular in effect, saxitoxin, neosaxitoxin & tetrodotoxin bind to the extracellular side of sodium channels.

SKELETAL MUSCLE RELAXANTS

PERIPHERALLY ACTING SKELETAL MUSCLE RELAXANTS

A **muscle relaxant** is a drug that affects skeletal muscle function and decreases the muscle tone. It may be used to alleviate symptoms such as muscle spasms, pain, and hyperreflexia. The term "muscle relaxant" is used to refer to two major therapeutic groups: neuromuscular blockers and spasmolytics. Neuromuscular blockers act by interfering with transmission at the neuromuscular end plate and have no central nervous system (CNS) activity. They are often used during surgical procedures and in intensive care and emergency medicine to cause temporary paralysis. Spasmolytics, also known as "centrally acting" muscle relaxants, are used to alleviate musculoskeletal pain and spasms and to reduce spasticity in a variety of neurological conditions. While both neuromuscular blockers and spasmolytics are often grouped together as muscle relaxants, the term is commonly used to refer to spasmolytics only.



Detailed view of a neuromuscular junction:
1. Presynaptic terminal
2. Sarcolemma
3. Synaptic vesicle
4. Nicotinic acetylcholine receptor
5. Mitochondrion

Neuromuscular-blocking drugs block neuromuscular transmission at the neuromuscular junction, causing paralysis of the affected skeletal muscles. This is accomplished either by acting presynaptically via the inhibition of acetylcholine(ACh) synthesis or release or by acting postsynaptically at the acetylcholine receptors of the motor nerve end-plate. While some drugs act presynaptically (such as botulinum toxin and tetanus toxin), those of current clinical importance work postsynaptically.

In clinical use, neuromuscular block is used adjunctively to anesthesia to produce paralysis, firstly to paralyze the vocal cords, and permit intubation of the trachea, and secondly to optimize the surgical field by inhibiting spontaneous ventilation, and causing relaxation of skeletal muscles. Because the appropriate dose of neuromuscular-blocking drug may paralyze muscles required for breathing (i.e., the diaphragm), mechanical ventilation should be available to maintain adequate respiration.

Patients are still aware of pain even after full conduction block has occurred; hence, general anesthetics and/or analgesics must also be given to prevent anesthesia awareness.

Quaternary ammonium muscle relaxants are quaternary ammonium salts used as drugs for muscle relaxation, most commonly in anesthesia. It is necessary to prevent spontaneous movement of muscle during surgical operations. Muscle relaxants inhibit neuron transmission to muscle by blocking the nicotinic acetylcholine receptor. What they have in common, and is necessary for their effect, is the structural presence of quaternary ammonium groups, usually two. Some of them are found in nature and others are synthesized molecules.

Neuromuscular blocking drugs are often classified into two broad classes:

- Pachycurares, which are bulky molecules with nondepolarizing activity
- Leptocurares, which are thin and flexible molecules that tend to have depolarizing activity.

It is also common to classify them based on their chemical structure.

- **Acetylcholine, succinylcholine, and decamethonium**

Succinylcholine was synthesised by connecting two acetylcholine molecules and has the same number of heavy atomsbetween methonium heads as decamethonium. Just like acetylcholine, succinylcholine, decamethonium and other polymethylene chains, of the appropriate length and with two methonium, heads have small trimethyl onium heads and flexible links. They all exhibit a depolarizing block.

- **Aminosteroids**

Pancuronium, vecuronium, rocuronium, rapacuronium, dacuronium, malouètine, duador, dipy randium, pipecuronium, chandonium (HS-310), HS-342 and other HS- compounds are aminosteroidal agents. They have in common the steroidstructural base, which provides a rigid and bulky body. Most of the agents in this category would also be classified as non-depolarizing.

- **Tetrahydroisoquinoline derivatives**

Compounds based on the tetrahydroisoquinoline moiety such as atracurium, mivacurium, and doxacurium would fall in this category. They have a long and flexible chain between

the onium heads, except for the double bond of mivacurium. D-tubocurarine and dimethyltubocurarine are also in this category. Most of the agents in this category would be classified as non-depolarizing.

- **Gallamine and other chemical classes**

Gallamine is a trisquaternary ether with three ethonium heads attached to a phenyl ring through an ether linkage. Many other different structures have been used for their muscle relaxant effect such as alcuronium (alloferin), anatruxonium, diadonium, fazadinium (AH8165) and tropeinium.

- **Novel NMB agents**

In recent years much research has been devoted to new types of quaternary ammonium muscle relaxants. These are asymmetrical diester isoquinolinium compounds and bis-benzyltropinium compounds that are bistropinium salts of various diacids. These classes have been developed to create muscle relaxants that are faster and shorter acting. Both the asymmetric structure of diester isoquinolinium compounds and the acyloxylated benzyl groups on the bisbenzyltropiniums destabilizes them and can lead to spontaneous breakdown and therefore possibly a shorter duration of action.[4]

Classification

These drugs fall into two groups:

- **Non-depolarizing blocking agents**: These agents constitute the majority of the clinically relevant neuromuscular blockers. They act by competitively blocking the binding of ACh to its receptors, and in some cases, they also directly block the ionotropic activity of the ACh receptors.[5]
- **Depolarizing blocking agents**: These agents act by depolarizing the sarcolemma of the skeletal muscle fiber. This persistent depolarization makes the muscle fiber resistant to further stimulation by ACh.

Non-depolarizing blocking agents

A **neuromuscular non-depolarizing agent** is a form of neuromuscular blocker that does not depolarize the motor end plate.

The quaternary ammonium muscle relaxants belong to this class.

Below are some more common agents that act as competitive antagonists against acetylcholine at the site of postsynaptic acetylcholine receptors.

Tubocurarine, found in curare of the South American plant Pareira, *Chondrodendron tomentosum*, is the prototypical non-depolarizing neuromuscular blocker. It has a slow onset (>5 min) and a long duration of action (30 mins). Side-effects include hypotension, which is partially explained by its effect of increasing histamine release, a vasodilator, as well as its effect of blocking autonomic ganglia. It is excreted in the urine.

This drug needs to block about 70–80% of the ACh receptors for neuromuscular conduction to fail, and hence for effective blockade to occur. At this stage, end-plate potentials (EPPs) can still be detected, but are too small to reach the threshold potential needed for activation of muscle fiber contraction.

Comparison of non-depolarizing neuromuscular blocking agents

Agent	**Time to onset** (seconds)	**Duration** (minutes)	**Side effects**	**Clinical use**	Storage
Rapacuronium (Raplon)					
Mivacurium (Mivacron)	90	12–18	• hypotension (transiently), by release of histamine	No longer manufactured secondary to marketing, manufacturing, and financial concerns	refrigerated
Atracurium (Tracrium)	90	30 min or less	• hypotension, transiently, by release of histamine • Toxic metabolite called laudanosine, greater accumulation in individuals with renal failure	widely	refrigerated
Doxacurim (Nuromax)		long	• hypotension, transiently, by release of histamine • Toxic metabolite called laudanosine, greater accumulation in individuals with renal failure		
Cisatracurium (Nimbex)	90	60–80	does not cause release of histamine		refrigerated
Vecuronium (Norcuron)	60	30–40[9]	Few, may cause prolonged paralysis and promote muscarinic block	widely	non-refrigerated

Comparison of non-depolarizing neuromuscular blocking agents

Agent	**Time to onset** (seconds)	**Duration** (minutes)	**Side effects**	**Clinical use**	Storage
Rocuronium (Zemuron)	75	45–70	may promote muscarinic block		non-refrigerated
Pancuronium (Pavulon)	90	180 or more	tachycardia (slight) (no hypotension)	widely	non-refrigerated
Tubocurarine (Jexin)	300 or more	60–120	• hypotension (by ganglion-block and histamine release)[9] • Bronchoconstriction (by histamine release)	rarely	
gallamine (Flaxedil)	300 or more	60–120	• tachycardia		
Pipecuronium	90	180 or more	• tachycardia (slight) (no hypotension)		non-refrigerated

Depolarizing blocking agents

A **depolarizing neuromuscular blocking agent** is a form of neuromuscular blocker that depolarizes the motor end plate.[10]

An example is succinylcholine.

Depolarizing blocking agents work by depolarizing the plasma membrane of the muscle fiber, similar to acetylcholine. However, these agents are more resistant to degradation by acetylcholinesterase, the enzyme responsible for degrading acetylcholine, and can thus more persistently depolarize the muscle fibers. This differs from acetylcholine, which is rapidly degraded and only transiently depolarizes the muscle.

There are two phases to the depolarizing block. During phase I (*depolarizing phase*), they cause muscular fasciculations (muscle twitches) while they are depolarizing the muscle fibers. Eventually, after sufficient depolarization has occurred, phase II (*desensitizing phase*) sets in and the muscle is no longer responsive to acetylcholine released by the motoneurons. At this point, full neuromuscular block has been achieved.

The prototypical depolarizing blocking drug is succinylcholine (suxamethonium). It is the only such drug used clinically. It has a rapid onset (30 seconds) but very short duration of action (5–10 minutes) because of hydrolysis by various cholinesterases (such

as butyrylcholinesterase in the blood). Succinylcholine was originally known as diacetylcholine because structurally it is composed of two acetylcholine molecules joined with a methyl group. Decamethonium is sometimes, but rarely, used in clinical practice.

Comparison of drugs

The main difference is in the reversal of these two types of neuromuscular-blocking drugs.

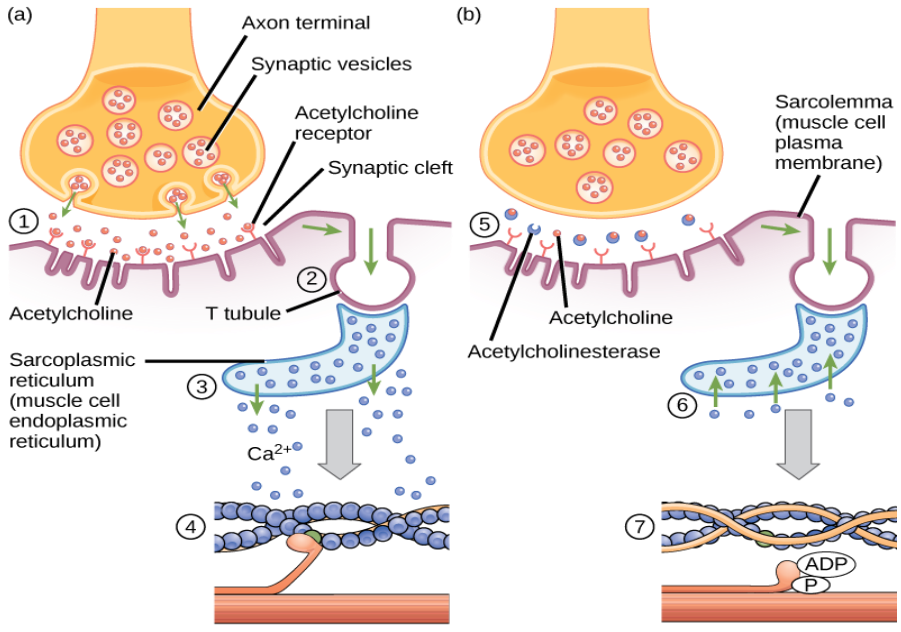
- Non-depolarizing blockers are reversed by acetylcholinesterase inhibitor drugs since non-depolarizing blockers are competitive antagonists at the ACh receptor so can be reversed by increases in ACh.
- The depolarizing blockers already have ACh-like actions, so these agents have prolonged effect under the influence of acetylcholinesterase inhibitors. Administration of depolarizing blockers initially produces *fasciculations* (a sudden twitch just before paralysis occurs). This is due to depolarization of the muscle. Also, post-operative pain is associated with depolarizing blockers.

The *tetanic fade* is the failure of muscles to maintain a fused tetany at sufficiently high frequencies of electrical stimulation.

- Non-depolarizing blockers have this effect on patients, probably by an effect on presynaptic receptors.
- Depolarizing blockers do not cause the tetanic fade. However, a clinically similar manifestation called Phase II block occurs with repeated doses of suxamethonium.

This discrepancy is diagnostically useful in case of intoxication of an unknown neuromuscular-blocking drug.

<u>Mechanism of action</u>



1. Acetylcholine released from the axon terminal binds to receptors on the sarcolemma.
2. An action potential is generated and travels down the T tubule.
3. Ca^{2+} is released from the sarcoplasmic reticulum in response to the change in voltage.
4. Ca^{2+} binds troponin; Cross-bridges form between actin and myosin.
5. Acetylcholinesterase removes acetylcholine from the synaptic cleft.
6. Ca^{2+} is transported back into the sarcoplasmic reticulum.
7. Tropomyosin binds active sites on actin causing the cross-bridge to detach.

Quaternary muscle relaxants bind to the nicotinic acetylcholine receptor and inhibit or interfere with the binding and effect of ACh to the receptor. Each ACh-receptor has two receptive sites and activation of the receptor requires binding to both of them. Each receptor site is located at one of the two α-subunits of the receptor. Each receptive site has two subsites, an anionic site that binds to the cationic ammonium head and a site that binds to the blocking agent by donating a hydrogen bond.

Non-depolarizing agents A decrease in binding of acetylcholine leads to a decrease in its effect and neuron transmission to the muscle is less likely to occur. It is generally accepted that non-depolarizing agents block by acting as reversible competitive inhibitors. That is, they bind to the receptor as antagonists and that leaves fewer receptors available for acetylcholine to bind.

Depolarizing agents Depolarizing agents produce their block by binding to and activating the ACh receptor, at first causing muscle contraction, then paralysis. They bind to the receptor and cause depolarization by opening channels just like acetylcholine does. This causes repetitive excitation that lasts longer than a normal acetylcholine excitation and is most likely explained by the resistance of depolarizing agents to the enzyme acetylcholinesterase. The constant depolarization and triggering of the receptors keeps the endplate resistant to activation by acetylcholine. Therefore, a normal neuron transmission to muscle cannot cause contraction of the muscle because the endplate is depolarized and thereby the muscle paralysed.

Binding to the nicotinic receptor Shorter molecules like acetylcholine need two molecules to activate the receptor, one at each receptive site. Decamethonium congeners, which prefer straight line conformations (their lowest energy state), usually span the two receptive sites with one molecule (binding inter-site). Longer congeners must bend when fitting receptive sites.

The greater energy a molecule needs to bend and fit usually results in lower potency.

CENTRALLY ACTING SKELETAL MUSCLE RELAXANT

Spasmolytics: ***Antispasmodic***

The generation of the neuronal signals in motor neurons that cause muscle contractions are dependent on the balance of synaptic excitation and inhibition the motor neuron receives. Spasmolytic agents generally work by either enhancing the level of inhibition, or reducing the level of excitation. Inhibition is enhanced by mimicking or enhancing the actions of endogenous inhibitory substances, such as GABA.

Terminology

Because they may act at the level of the cortex, brain stem or spinal cord, or all three areas, they have traditionally been referred to as "centrally acting" muscle relaxants. However, it is now known not every agent in this class has CNS activity (e.g. dantrolene), so this name is inaccurate.

Most sources still use the term "centrally acting muscle relaxant". According to MeSH, dantrolene is usually classified as a centrally acting muscle relaxant. The World Health Organization, in its ATC, uses the term "centrally acting agents", but adds a distinct category of "directly acting agents", for dantrolene. Use of this terminology dates back to at least 1973.

The term "spasmolytic" is also considered a synonym for antispasmodic.

Clinical use

Spasmolytics such as carisoprodol, cyclobenzaprine, metaxalone, and methocarbamol are commonly prescribed for low back pain or neck pain, fibromyalgia, tension headaches and myofascial pain syndrome. However, they are not recommended as first-line agents; in acute low back pain, they are not more effective than paracetamol or nonsteroidal anti-inflammatory drugs (NSAIDs), and in fibromyalgia they are not more effective than antidepressants. Nevertheless, some (low-quality) evidence suggests muscle relaxants can add benefit to treatment with NSAIDs. In general, no high-quality evidence supports their use. No drug has been shown to be better than another, and all of them have adverse effects, particularly dizziness and drowsiness. Concerns about possible abuse and interaction with other drugs, especially if increased sedation is a risk, further limit their use. A muscle relaxant is chosen based on its adverse-effect profile, tolerability, and cost.

Muscle relaxants (according to one study) were not advised for orthopedic conditions, but rather for neurological conditions such as spasticity in cerebral palsy and multiple sclerosis. Dantrolene, although thought of primarily as a peripherally acting agent, is associated with CNS effects, whereas baclofen activity is strictly associated with the CNS.

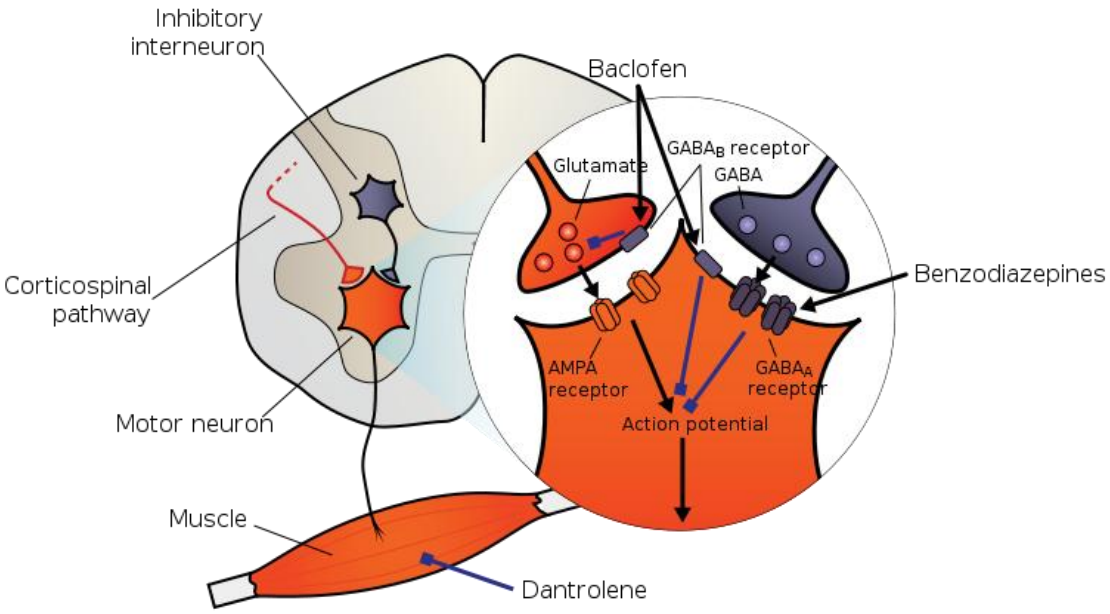
Muscle relaxants are thought to be useful in painful disorders based on the theory that pain induces spasm and spasm causes pain. However, considerable evidence contradicts this theory.

In general, muscle relaxants are not approved by FDA for long-term use. However, rheumatologists often prescribe cyclobenzaprine nightly on a daily basis to increase stage 4 sleep. By increasing this sleep stage, patients feel more refreshed in the morning. Improving sleep is also beneficial for patients who have fibromyalgia.

Muscle relaxants such as tizanidine are prescribed in the treatment of tension headaches.

Diazepam and carisoprodol are not recommended for older adults, pregnant women, or people who suffer depression or for those with a history of drug or alcohol addiction.

Mechanism of action



A view of the spinal cord and skeletal muscle showing the action of various muscle relaxants – black lines ending in arrow heads represent chemicals or actions that enhance the target of the lines, blue lines ending in squares represent chemicals or actions that inhibition the target of the line

Because of the enhancement of inhibition in the CNS, most spasmolytic agents have the side effects of sedation, drowsiness and may cause dependence with long-term use. Several of these agents also have abuse potential, and their prescription is strictly controlled.

The benzodiazepines, such as diazepam, interact with the $GABA_A$ receptor in the central nervous system. While it can be used in patients with muscle spasm of almost any origin, it produces sedation in most individuals at the doses required to reduce muscle tone.[5]

Baclofen is considered to be at least as effective as diazepam in reducing spasticity, and causes much less sedation. It acts as a GABA agonist at $GABA_B$ receptors in the brain and spinal cord, resulting in hyperpolarization of neurons expressing this receptor, most likely due to increased potassium ion conductance. Baclofen also inhibits neural function presynaptically, by reducing calcium ion influx, and thereby reducing the release of excitatory neurotransmitters in both the brain and spinal cord. It may also reduce pain in patients by inhibiting the release of substance P in the spinal cord, as well.

Clonidine and other imidazoline compounds have also been shown to reduce muscle spasms by their central nervous system activity. Tizanidine is perhaps the most thoroughly studied clonidine analog, and is an agonist at α_2-adrenergic receptors, but reduces spasticity at doses that result in significantly less hypotension than clonidine. Neurophysiologic studies show that it depresses excitatory feedback from muscles that would normally increase muscle tone, therefore minimizing spasticity. Furthermore, several clinical trials indicate that tizanidine has a similar efficacy to other spasmolytic agents, such as diazepam and baclofen, with a different spectrum of adverse effects.

The hydantoin derivative dantrolene is a spasmolytic agent with a unique mechanism of action outside of the CNS. It reduces skeletal muscle strength by inhibiting the excitation-contraction coupling in the muscle fiber. In normal muscle contraction, calcium is released from the sarcoplasmic reticulum through the ryanodine receptor channel, which causes the tension-generating interaction of actin and myosin. Dantrolene interferes with the release of calcium by binding to the ryanodine receptor and blocking the endogenous ligand ryanodine by competitive inhibition. Muscle that contracts more rapidly is more sensitive to dantrolene than muscle that contracts slowly, although cardiac muscle and smooth muscle are depressed only slightly, most likely because the release of calcium by their sarcoplasmic reticulum involves a slightly different process. Major adverse effects of dantrolene include general muscle weakness, sedation, and occasionally hepatitis.

Side effects

Muscle relaxants are very powerful drugs which may produce negative effects, including heart failure and paralysis. Patients most commonly report sedation as the main adverse effect of muscle relaxants. Usually, people become less alert when they are under the effects of muscle relaxant drugs. People are normally advised not to drive vehicles or operate heavy machinery while under muscle relaxants' effects.

Cyclobenzaprine produces confusion and lethargy, as well as anticholinergic side effects. When taken in excess or in combination with other substances, it may also be toxic. While the body adjusts to this medication, it is possible for patients to experience dry

mouth, fatigue, lightheadedness, constipation or blurred vision. Some serious but unlikely side effects may be experienced, including mental or mood changes, possible confusion and hallucinations, and difficulty urinating. In a very few cases, very serious but rare side effects may be experienced: irregular heartbeat, yellowing of eyes or skin, fainting, abdominal pain including stomachache, nausea or vomiting, lack of appetite, seizures, dark urine, or loss of coordination.

Patients taking carisoprodol for a prolonged time have reported dependence, withdrawal and abuse, although most of these cases were reported by patients who had had a history of addiction. These effects were also reported by patients who took it in combination with other drugs with abuse potential, and in fewer cases, there were reports of carisoprodol-associated abuse when used without other drugs with abuse potential.

Common side effects eventually caused by metaxalone include dizziness, headache, drowsiness, nausea, irritability, nervousness, upset stomach and vomiting. Severe side effects may be experienced when consuming metaxalone, such as severe allergic reactions (rash, hives, itching, difficulty breathing, tightness in the chest, swelling of the mouth, face, lips, or tongue), chills, fever, and sore throat, may require medical attention. Other severe side effects include unusual or severe tiredness or weakness, as well as yellowing of the skin or the eyes. When baclofen is administered intrathecally, it may cause CNS depression accompanied with cardiovascular collapse and respiratory failure. Tizanidine may lower blood pressure. This effect can be controlled by administering a low dose at the beginning and increasing it gradually.

Adverse effects

Since these drugs may cause paralysis of the diaphragm, mechanical ventilation should be at hand to provide respiration. In addition, these drugs may exhibit cardiovascular effects, since they are not fully selective for the nicotinic receptor and hence may have effects on muscarinic receptors. If nicotinic receptors of the autonomic ganglia or adrenal medulla are blocked, these drugs may cause autonomic symptoms. Also, neuromuscular blockers may facilitate histamine release, which causes hypotension, flushing, and tachycardia.

In depolarizing the musculature, suxamethonium may trigger a transient release of large amounts of potassium from muscle fibers. This puts the patient at risk for life-threatening complications, such as hyperkalemia and cardiac arrhythmias.

Certain drugs such as aminoglycoside antibiotics and polymyxin and some fluoroquinolones also have neuromuscular blocking action as their side-effect.

UNIT-IV: PHARMACOLOGY OF CNS

GENERAL ANAESTHETICS

A **general anaesthetic** (or **anesthetic**, see spelling differences) is a drug that can bring about a reversible loss of consciousness. Anaesthetists, physician assistants or nurse anaesthetists administer these drugs to induce or maintain general anaesthesia to facilitate surgery. Some of these drugs are also used in lower dosages for pain management. The biological mechanisms of the action of general anaesthetics are not well understood.

Mode of administration

Drugs given to induce general anaesthesia can be either as gases or vapours (inhalational anaesthetics), or as injections (intravenous anaesthetics or even intramuscular). It is possible to deliver anaesthesia solely by inhalation or injection, but most commonly the two forms are combined, with an injection given to induce anaesthesia and a gas used to maintain it.

Inhalation

Inhalational anaesthetic substances are either volatile liquids or gases, and are usually delivered using an anaesthesia machine. An anaesthesia machine allows composing a mixture of oxygen, anaesthetics and ambient air, delivering it to the patient and monitoring patient and machine parameters. Liquid anaesthetics are vapourised in the machine. All of these agents share the property of being quite hydrophobic (i.e., as liquids, they are not freely miscible—or mixable—in water, and as gases they dissolve in oils better than in water).

Many compounds have been used for inhalation anaesthesia, but only a few are still in widespread use. Desflurane, isoflurane and sevoflurane are the most widely used volatile anaesthetics today. They are often combined with nitrous oxide. Older, less popular, volatile anaesthetics, include halothane, enflurane, and methoxyflurane. Researchers are also actively exploring the use of xenon as an anaesthetic.

Injection

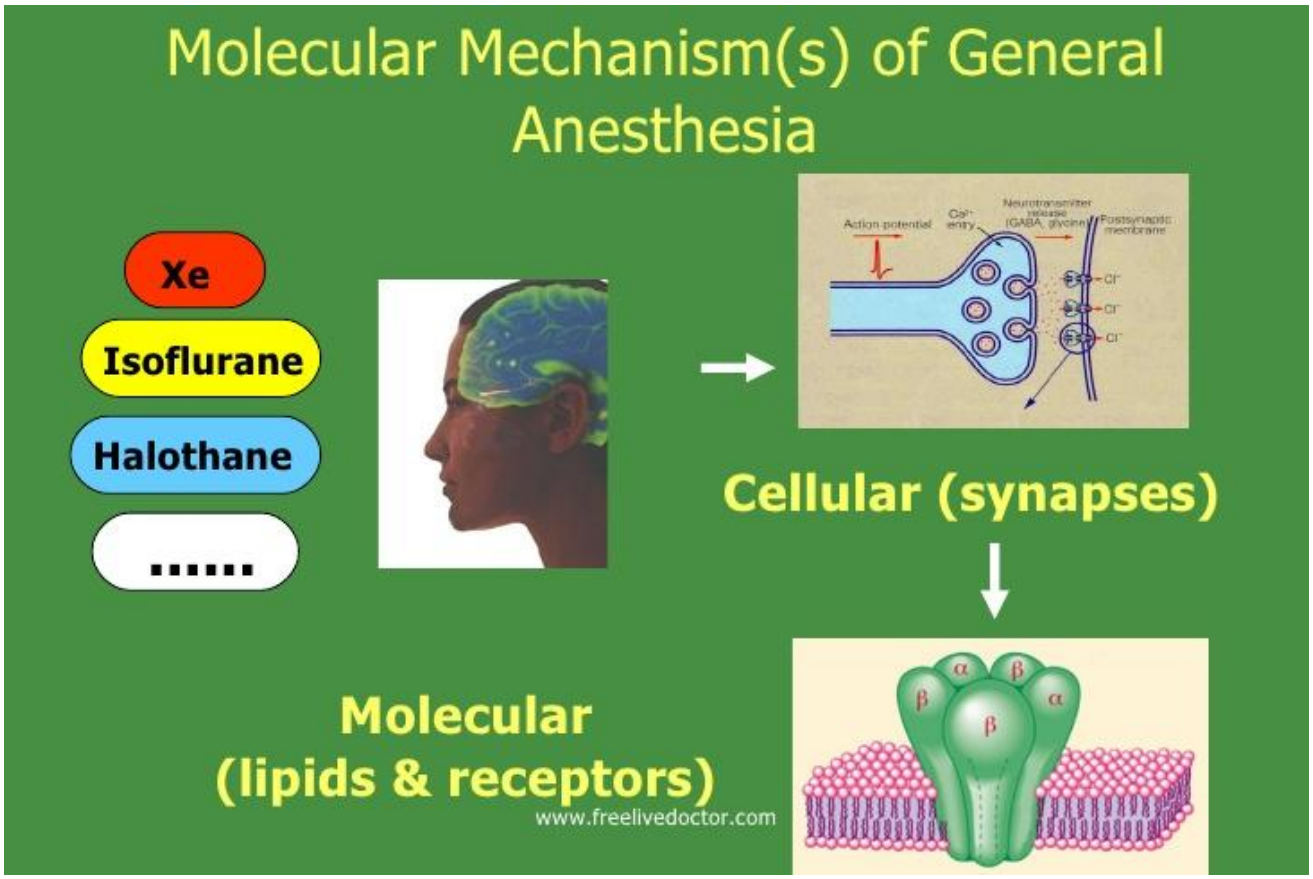
Injectable anaesthetics are used for the induction and maintenance of a state of unconsciousness. Anaesthetists prefer to use intravenous injections, as they are faster, generally less painful and more reliable than intramuscular or subcutaneous injections. Among the most widely used drugs are:

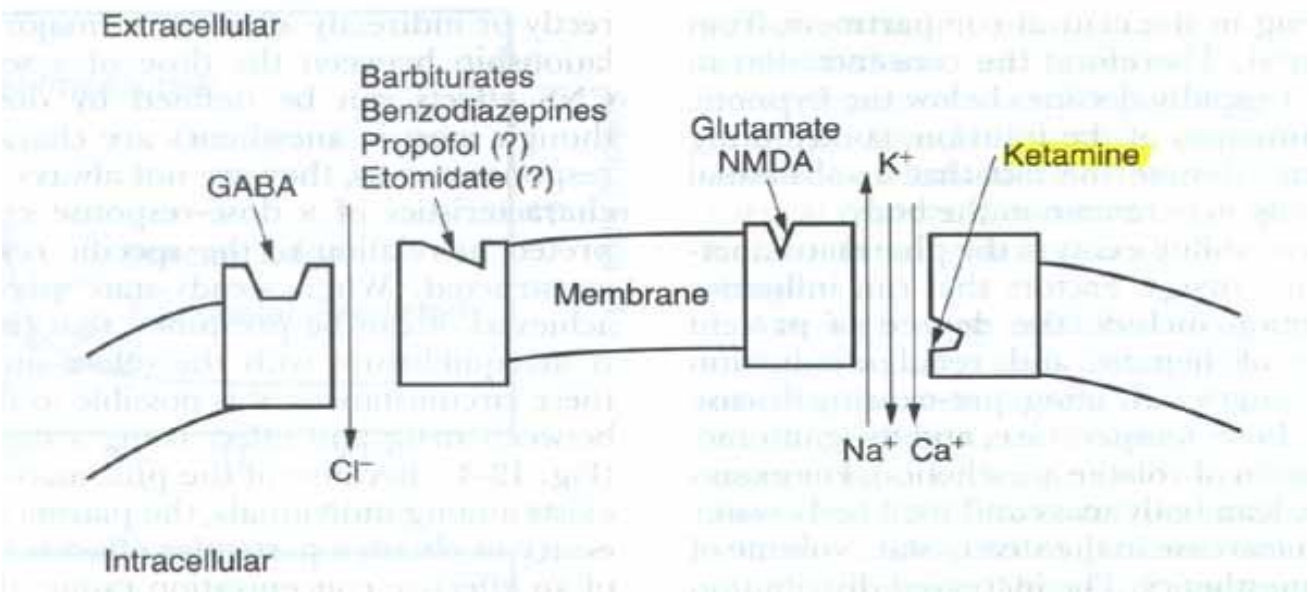
- Propofol
- Etomidate
- Barbiturates such as methohexital and thiopentone/thiopental
- Benzodiazepines such as midazolam
- Ketamine is used in the UK as "field anaesthesia", for instance at a road traffic incidents or similar situations where an operation must be conducted at the scene or when there is not enough time to move to an operating room, while preferring other anaesthetics where conditions allow their use. It is more frequently used in the operative setting in the US.

Benzodiazepines are sedatives and are used in combinations with other general anaesthetics.

Method of action

General anaesthetics are often defined as compounds that induce a reversible loss of consciousness in humans or loss of righting reflex in animals. Clinical definitions are also extended to include the lack of awareness to painful stimuli, sufficient to facilitate surgical applications in clinical and veterinary practice. General anaesthetics do not act as analgesics and should also not be confused with sedatives. General anaesthetics are a structurally diverse group of compounds whose mechanisms encompasses multiple biological targets involved in the control of neuronal pathways. The precise workings are the subject of some debate and ongoing research.





Pharmacokinetics

Induction

Induction is a term that refers to the first stage of anaesthesia, Stage 1, prior to reaching a depth suitable for surgery, i.e. Stage 3. The speed of induction depends on the time taken for the drug to reach an effective concentration in the brain. Different compounds partition to different compartments of the body, such as fatty tissue, at different rates. Hence, different compounds have different rates of induction. Intravenous anaesthetics like Thiopental have been used for induction and it is common for aneasthesia to be maintained by inhalational anaesthetics such as Isoflurane. Propofol is now the most widely used intravenous general anaesethetic.

Elimination

Volatile anaesthetics are eliminated in the terminal phase via the lungs. A low blood:gas partition coefficient is therefore necessary for quick removal of the anaesthetic. When the oil:water coefficient is high, there will be little anaesthetic in the blood, so elimination will be slow, giving a prolonged hangover effect.

Intravenous and intramuscular drugs are eliminated by metabolic pathways in the liver. It is not uncommon to produce toxic metabolites (e.g. chloroform).

A **preanesthetic agent** (or **preanaesthetic agent**) is a drug that is given before the administration of an anesthetic.

Examples

Examples of preanesthetic agents are:

- Acepromazine

- atropine
- diazepam
- Scopolamine

These are the drugs used prior to the administration of an anesthetic agent, with the important object of making anesthesia safe and more agreeable to the patient. The reasons for such medication are

1) For sedation, to reduce anxiety and apprehension 2) To obtain an additive or synergistic effect so that induction could be smooth and rapid 3) To counteract certain adverse effects of the anesthetic drug 4) to relieve from pain. Common drugs used are 1) Opioid analgesic : morphine, pethidine and buprenorphine.

Stages of Anesthesia

Stage I (stage of analgesia or disorientation): from beginning of induction of general anesthesia to loss of consciousness.

Stage II (stage of excitement or delirium): from loss of consciousness to onset of automatic breathing. Eyelash reflex disappear but other reflexes remain intact and coughing, vomiting and struggling may occur; respiration can be irregular with breath-holding.

Stage III (stage of surgical anesthesia): from onset of automatic respiration to respiratory paralysis. It is divided into four planes:

- *Plane I* - from onset of automatic respiration to cessation of eyeball movements. Eyelid reflex is lost, swallowing reflex disappears, marked eyeball movement may occur but conjunctival reflex is lost at the bottom of the plane
- *Plane II* - from cessation of eyeball movements to beginning of paralysis of intercostal muscles. Laryngeal reflex is lost although inflammation of the upper respiratory tract increases reflex irritability, corneal reflex disappears, secretion of tears increases (a useful sign of light anesthesia), respiration is automatic and regular, movement and deep breathing as a response to skin stimulation disappears.
- *Plane III* - from beginning to completion of intercostal muscle paralysis. Diaphragmatic respiration persists but there is progressive intercostal paralysis, pupils dilated and light reflex is abolished. The laryngeal reflex lost in plane II can still be initiated by painful stimuli arising from the dilatation of anus or cervix. This was the desired plane for surgery when muscle relaxants were not used.
- *Plane IV* - from complete intercostal paralysis to diaphragmatic paralysis (apnea).

Stage IV: from stoppage of respiration till death. Anesthetic overdose cause medullary paralysis with respiratory arrest and vasomotor collapse. Pupils are widely dilated and muscles are relaxed.

In 1954, Joseph F. Artusio further divided the first stage in Guedel's classification into three planes.

- 1st plane The patient does not experience amnesia or analgesia
- 2nd plane The patient is completely amnesic but experiences only partial analgesia

- 3rd plane The patient has complete analgesia and amnesia

ALCOHOL AND DISULFIRAM

Alcoholism, also known as **alcohol use disorder** (**AUD**), is a broad term for any drinking of alcohol that results in problems. It was previously divided into two types: alcohol abuse and alcohol dependence. In a medical context, alcoholism is said to exist when two or more of the following conditions is present: a person drinks large amounts over a long time period, has difficulty cutting down, acquiring and drinking alcohol takes up a great deal of time, alcohol is strongly desired, usage results in not fulfilling responsibilities, usage results in social problems, usage results in health problems, usage results in risky situations, withdrawal occurs when stopping, and alcohol tolerance has occurred with use.

As with similar substances with a sedative-hypnotic mechanism, such as barbiturates and benzodiazepines, withdrawal from alcohol dependence can be fatal if it is not properly managed. Alcohol's primary effect is the increase in stimulation of the $GABA_A$ receptor, promoting central nervous system depression. With repeated heavy consumption of alcohol, these receptors are desensitized and reduced in number, resulting in tolerance and physical dependence. When alcohol consumption is stopped too abruptly, the person's nervous system suffers from uncontrolled synapse firing. This can result in symptoms that include anxiety, life-threatening seizures, delirium tremens, hallucinations, shakes and possible heart failure. Other neurotransmitter systems are also involved, especially dopamine, NMDA and glutamate.

DISULFIRAM

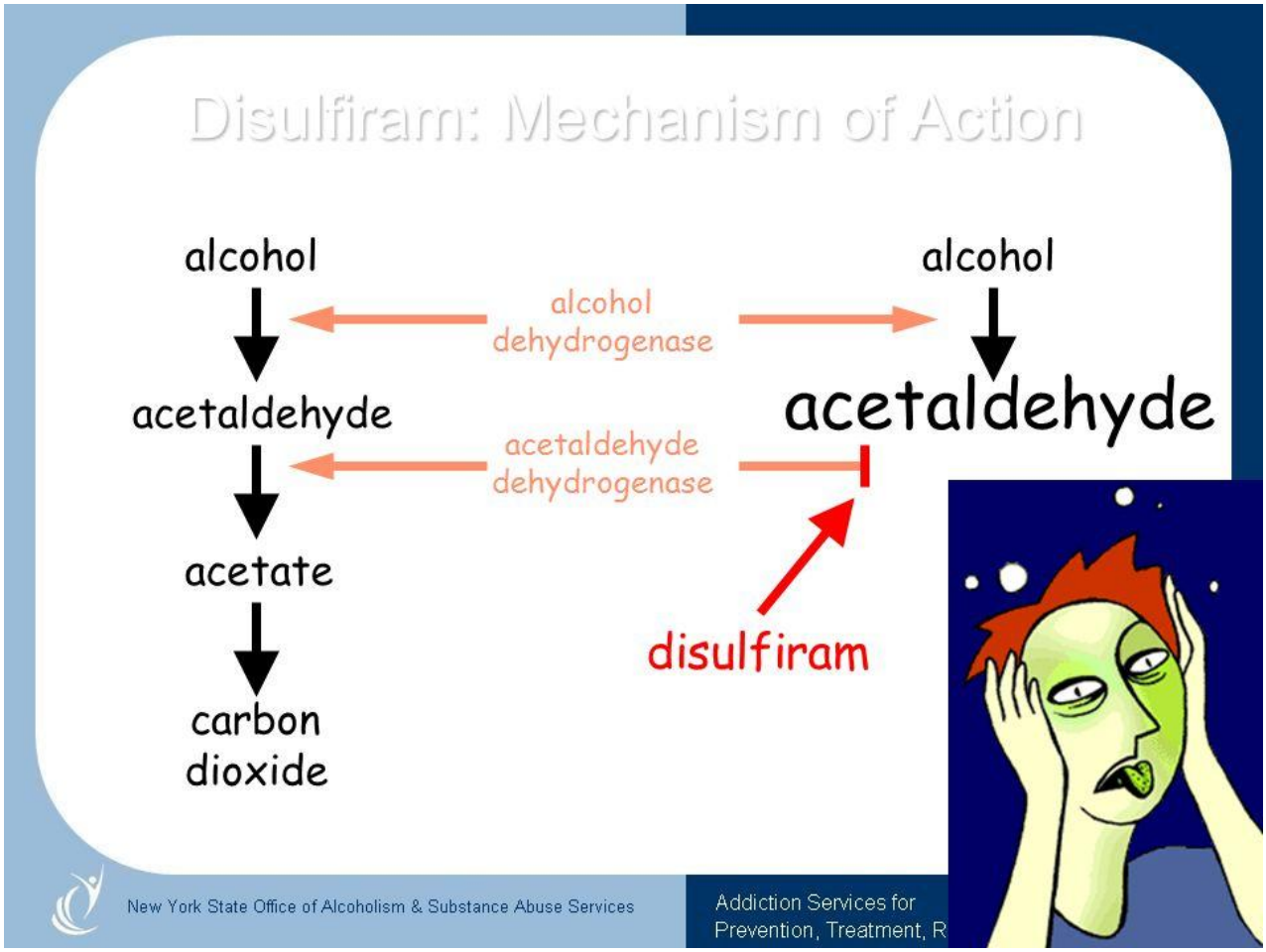
Disulfiram (sold under the trade names **Antabuse** and **Antabus**) is a drug discovered in the 1920s that is used to support the treatment of chronic alcoholism by producing an acute sensitivity to ethanol (alcohol). Disulfiram works by inhibiting the enzyme acetaldehyde dehydrogenase, which means many of the effects of a "hangover" are felt immediately after alcohol is consumed. "Disulfiram plus alcohol, even small amounts, produce flushing, throbbing in head and neck, throbbing headache, respiratory difficulty, nausea, copious vomiting, sweating, thirst, chest pain, palpitation, dyspnea, hyperventilation, tachycardia, hypotension, syncope, marked uneasiness, weakness, vertigo, blurred vision, and confusion. In severe reactions there may be respiratory depression, cardiovascular collapse, arrhythmias, myocardial infarction, acute congestive heart failure, unconsciousness, convulsions, and death"

In the body, alcohol is converted to acetaldehyde, which is then broken down by aldehyde dehydrogenase. If the dehydrogenase enzyme is inhibited, acetaldehyde builds up and causes unpleasant effects. Disulfiram should be used in conjunction with counseling and support.

Side effects in absence of alcohol

The most common side effects in the absence of alcohol are headache, and a metallic or garlic taste in the mouth, though more severe side effects may occur. Tryptophol, a chemical compound that induces sleep in humans, is formed in the liver after disulfiram treatment.

Cases of disulfiram neurotoxicity have also occurred, causing extrapyramidal and other symptoms. Disulfiram disrupts metabolism of several other compounds, including paracetamol (acetaminophen), theophylline and caffeine. However, in most cases, this disruption is mild and presents itself as a 20-40% increase in the half-life of the compound at typical dosages of disulfiram.



SEDATIVE AND HYPNOTICS

A **sedative** or **tranquilliser** is a substance that induces sedation by reducing irritability or excitement.

At higher doses it may result in slurred speech, staggering gait, poor judgment, and slow, uncertain reflexes. Doses of sedatives such as benzodiazepines, when used as a hypnotic to induce sleep, tend to be higher than amounts used to relieve anxiety, whereas only low doses are needed to provide a peaceful effect.

Sedatives can be misused to produce an overly-calming effect (alcohol being the classic and most common sedating drug). In the event of an overdose or if combined with another sedative, many of these drugs can cause unconsciousness (see hypnotic) and even death.

Types of sedatives

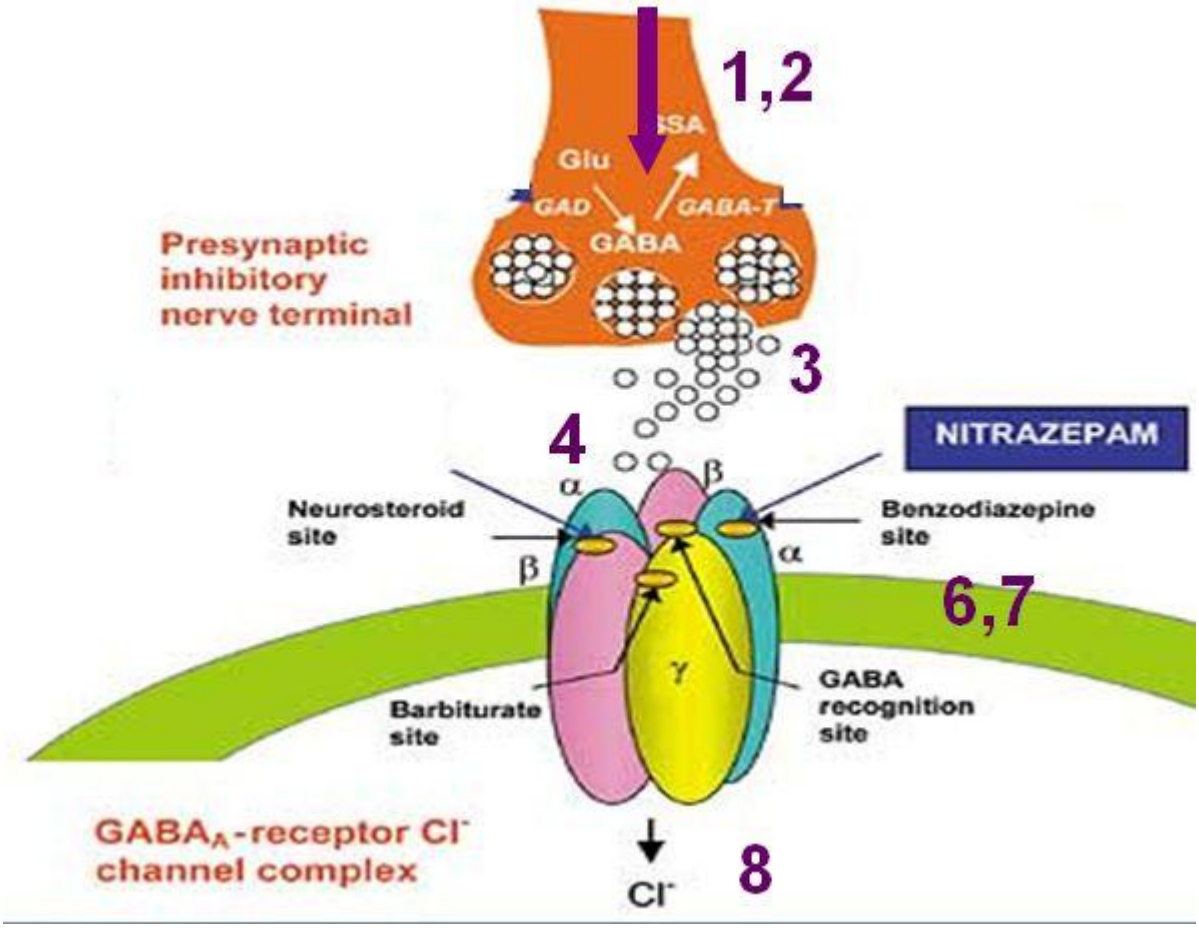
- **Barbiturates**
  - Benzylbutylbarbiturate (designer drug)
  - amobarbital (Amytal)
  - pentobarbital (Nembutal)
  - secobarbital (Seconal)
  - phenobarbital (Luminal)
- **Benzodiazepines** (trade names)
  - clonazepam (Klonopin North America; Rivotril Europe, Asia)
  - diazepam (Valium)
  - estazolam (Prosom)
  - flunitrazepam (Rohypnol)
  - lorazepam (Ativan)
  - midazolam (Versed)
  - nitrazepam (Mogadon)
  - oxazepam (Serax)
  - triazolam (Halcion)
  - temazepam (Restoril, Normison, Planum, Tenox, and Temaze)
  - chlordiazepoxide (Librium)
  - alprazolam (Xanax)
- **Nonbenzodiazepine "Z-drugs" sedatives**
  - eszopiclone (Lunesta)
  - zaleplon (Sonata)
  - zolpidem (Ambien)
  - zopiclone (Imovane, Zimovane)
- **Orexin antagonist**
  - Suvorexant
- **Antihistamines**
  - diphenhydramine
  - dimenhydrinate
  - doxylamine
  - mirtazapine
  - promethazine
  - hydroxyzine
- **Herbal sedatives**
  - Duboisia hopwoodii
  - Chamomile
  - Prostanthera striatiflora
  - catnip
  - Kava (Piper methysticum)
  - valerian
  - cannabis
  - passiflora spp.(passiflora incarnata)
  - Validol
- **Methaqualone and analogues**
  - Afloqualone
  - Cloroqualone
  - Diproqualone
  - Etaqualone

    - Methaqualone (Quaalude)
    - Methaqualone
    - Methylmethaqualone
    - Mebroqualone
    - Mecloqualone
    - Nitromethaqualone
- **Other**
    - 2-methyl-2-butanol (2M2B)
    - chloral hydrate
    - chlorobutanol
    - etizolam (benzodiazepine analog)
    - alcohol
    - pregabalin
    - gabapentin
    - trazodone
    - opiates and opioids
    - glutethimide
    - GHB

- **Hypnotic** (from Greek *Hypnos*, sleep) or **soporific** drugs, commonly known as **sleeping pills**, are a class of psychoactive drugs whose primary function is to induce sleep and to be used in the treatment of insomnia (sleeplessness), or surgical anesthesia.
- This group is related to **sedatives**. Whereas the term *sedative* describes drugs that serve to calm or relieve anxiety, the term *hypnotic* generally describes drugs whose main purpose is to initiate, sustain, or lengthen sleep. Because these two functions frequently overlap, and because drugs in this class generally produce dose-dependent effects (ranging from anxiolysis to loss of consciousness) they are often referred to collectively as **sedative-hypnotic** drugs.

MODE OF ACTION

The GABA system is the predominant inhibitory neurotransmitter system in the CNS. Almost all sedative-hypnotics in clinical use exert their primary pharmacodynamics effects in the GABA system, although recent studies have revealed important differences in the activity on GABA and the glutamate system



Pharmacokinetics

1. The rates of oral absorption of sedative-hypnotics differ depending on a number of factors, including lipophilicity.

For example, the absorption of triazolam is extremely rapid, and that of diazepam and the active metabolite of clorazepate is more rapid than other commonly used benzodiazepines.

Clorazepate, a prodrug, is converted to its active form, desmethyldiazepam (nordiazepam), by acid hydrolysis in the stomach. Most of the barbiturates and other older sedative-hypnotics, as well as the newer hypnotics (eszopiclone, zaleplon, zolpidem), are absorbed rapidly into the blood following oral administration.

2. Lipid solubility plays a major role in determining the rate at which a particular sedative-hypnotic enters the central nervous system.

2. All sedative-hypnotics cross the placental barrier during pregnancy. If sedative-hypnotics are given during the predelivery period, they may contribute to the depression of neonatal vital functions. Sedative-hypnotics are also detectable in breast milk and may exert depressant effects in the nursing infant.

Absorption and distribution Sedative-Hypnotic Drugs

Pharmacokinetics- Metabolic transformation to more water-soluble metabolites is necessary for clearance of sedative-hypnotics from the body. The microsomal drug-metabolizing

enzyme systems of the liver are most important in this regard, so elimination half-life of these drugs depends mainly on the rate of their metabolic transformation.

Biotransformation Sedative-Hypnotic Drugs

Biotransformation
(1) Benzodiazepines Most benzodiazepines undergo microsomal oxidation (phase I reactions), including Ndealkylation and aliphatic hydroxylation catalyzed by cytochrome P450 isozymes, especially CYP3A4.

The metabolites are subsequently conjugated (phase II reactions) to form glucuronides that are excreted in the urine.

They vary greatly in duration of action, and can be roughly divided into z Short-acting compounds: triazolam (Tmax 1h, t1/2 2-3 h) (favors its use as a hypnotic rather than as a sedative drug) z Medium-acting compounds: estazolam (Tmax 1h, t1/2 6 h) z Long-acting compounds: diazepam, flurazepam (50h)

Benzodiazepines appear to increase the efficiency of GABAergic synaptic inhibition. The benzodiazepines do not substitute for GABA but appear to enhance GABA's effects allosterically without directly activating GABAA receptors or opening the associated chloride channels. The enhancement in chloride ion conductance induced by the interaction of benzodiazepines with GABA takes the form of an increase in the frequency of channel-opening events.

2. Barbiturates also facilitate the actions of GABA at multiple sites in the central nervous system, but—in contrast to benzodiazepines— they appear to increase the duration of the GABA-gated chloride channel openings. At high concentrations, the barbiturates may also be GABA-mimetic, directly activating chloride channels. Barbiturates are less selective, because they also depress the actions of the excitatory neurotransmitter glutamic acid via binding to the AMPA receptor. Barbiturates also exert nonsynaptic membrane effects in parallel with their effects on GABA and glutamate neurotransmission. This multiplicity of sites of action of barbiturates may be the basis for their ability to induce full surgical anesthesia and for their more pronounced central depressant effects (which result in their low margin of safety) compared with benzodiazepines and the newer hypnotics.

Pharmacodynamics | Organ Level Effects Sedation Hypnosis

The use of sedative-hypnotics for more than 1–2 weeks leads to some tolerance to their effects on sleep patterns.

Anesthesia high doses of certain sedative-hypnotics depress the central nervous system to the point known as stage III of general anesthesia Anticonvulsant effects Many sedative-hypnotics are capable of inhibiting the development and spread of epileptiform electrical activity in the central nervous system in association with their selectivity.

Muscle Relaxation Drugs at high doses may also depress transmission at the skeletal neuromuscular junction Effects on Respiration and Cardiovascular To produce significant respiratory depression in patients with pulmonary disease. Effects on respiration are dose-related, and depression of the medullary respiratory center is the usual cause of death due to overdose of sedative-hypnotics.

In hypovolemic states, heart failure, and other diseases that impair cardiovascular function, normal doses of sedative-hypnotics may cause cardiovascular depression.

At toxic doses, myocardial contractility and vascular tone may both be depressed by central and peripheral effects, leading to circulatory collapse.

ANTIEPILEPTIC DRUGS

Anticonvulsants (also commonly known as **antiepileptic drugs** or as **antiseizure drugs**) are a diverse group of pharmacological agents used in the treatment of epileptic seizures. Anticonvulsants are also increasingly being used in the treatment of bipolar disorder and borderline personality disorder, since many seem to act as mood stabilizers, and for the treatment of neuropathic pain.[1] Anticonvulsants suppress the rapid and excessive firing of neurons during seizures. Anticonvulsants also prevent the spread of the seizure within the brain.[5] Some investigators have observed that anticonvulsants themselves may cause reduced IQ in children. However these adverse effects must be balanced against the significant risk epileptic seizures pose to children and the distinct possibility of death and devastating neurological sequelae secondary to seizures. Anticonvulsants are more accurately called **antiepileptic drugs** (abbreviated "AEDs"), and are often referred to as **antiseizure drugs** because they provide symptomatic treatment only and have not been demonstrated to alter the course of epilepsy.

Conventional antiepileptic drugs may block sodium channels or enhance γ-aminobutyric acid (GABA) function. Several antiepileptic drugs have multiple or uncertain mechanisms of action.

Next to the voltage-gated sodium channels and components of the GABA system, their targets include $GABA_A$ receptors, the GAT-1 GABA transporter, and GABA transaminase.

Additional targets include voltage-gated calcium channels, SV2A, and α2δ.[9][10] By blocking sodium or calcium channels, antiepileptic drugs reduce the release of excitatory glutamate, whose release is considered to be elevated in epilepsy, but also that of GABA.

Some anticonvulsants have shown antiepileptogenic effects in animal models of epilepsy. That is, they either prevent the development of epilepsy or can halt or reverse the progression of epilepsy. However, no drug has been shown in human trials to prevent epileptogenesis (the development of epilepsy in an individual at risk, such as after a head injury).

DRUGS

1. Aldehydes
2. Aromatic allylic alcohols
3. Barbiturates
4. Benzodiazepines
5. Bromides
6. Carbamates
7. Carboxamides
8. Fatty acids
9. Fructose derivatives
10. GABA analogs

11. Hydantoins
12. Oxazolidinediones
13. Propionates
14. Pyrimidinediones
15. Pyrrolidines
16. Succinimides
17. Sulfonamides
18. Triazines
19. Ureas
20. Valproylamides (amide derivatives of valproate)
21. Other

Antiepileptic Drugs

How They Work: Neuronal Targets and Mechanisms of Action

AEDs decrease excitation and enhance inhibition by various mechanisms. AEDs act on specific neuronal targets (Table 1), and many of them block voltage-sensitive sodium channels. This action decreases the frequency of action potentials, raises the threshold for repetitive action-potential generation, and prevents burst firing of neurons.[1] In the treatment of epilepsy, this mechanism is thought to prevent the spread of the electrical discharge from an epileptic seizure focus, thereby preventing the spread and generalization of epileptic discharge into a tonic-clonic or grand mal seizure. In the case of neuropathic pain, prevention of repetitive discharge may prevent the windup phenomenon thought to be characteristic of the development of changes in lamina II of the dorsal horn of the spinal cord, which may be important in the development of neuropathic pain.

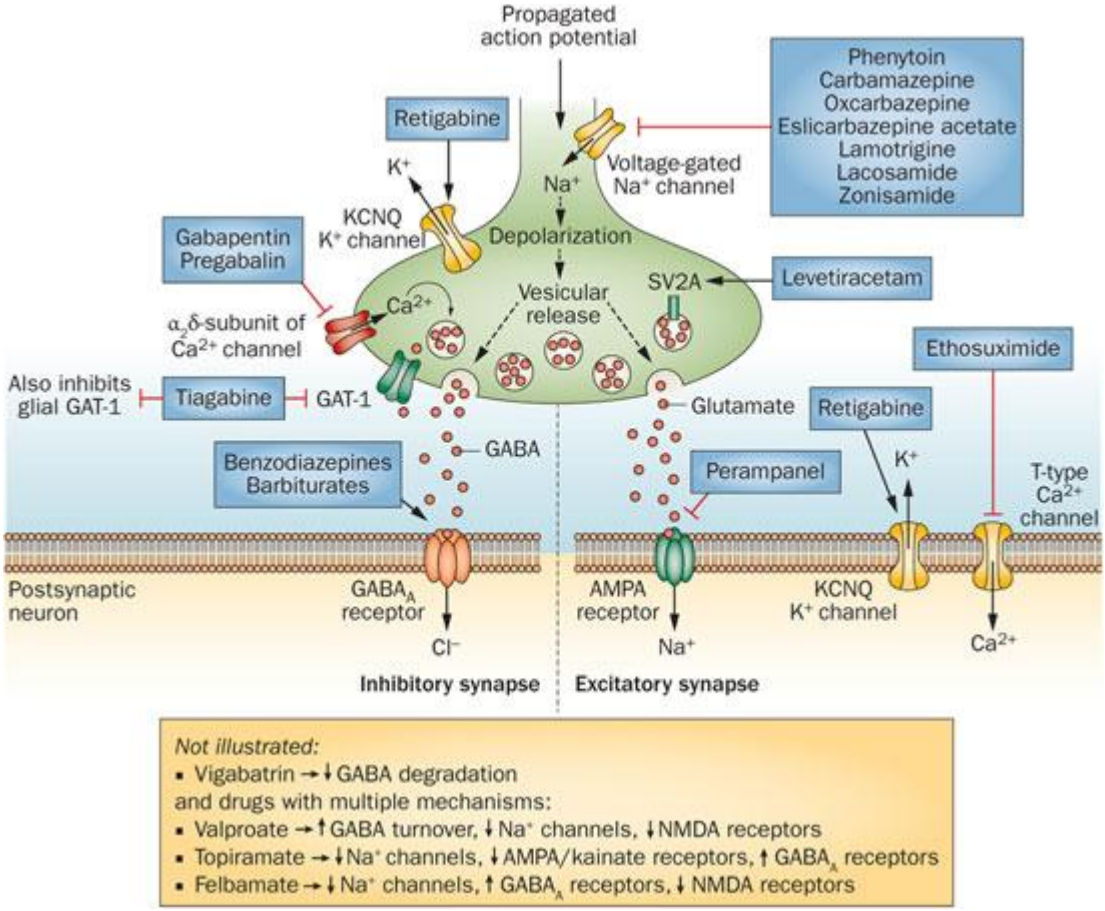
Table 1

Antiepileptic Drug Targets for the Control of Neuronal Excitation and Inhibition

Target	Effect
1. A. Na^{+} channels	▼ action-potential frequency
B. Ca^{++} channels	
T type	▼ excitation of thalamocortical circuits
L type	▼ neuronal excitation
N type	▼ neurotransmitter release
2. GABA-ergic transmission	
Enhance $GABA_A$ receptor activity	▲ inhibition
Increase GABA synthesis/release	▲ inhibition
Block GABA reuptake	▲ inhibition
Reverse GABA uptake	▲ inhibition
Effect serotonin release	▲ inhibition
3. Glutamatergic transmission	
Inhibition of glutamate receptors	▼ excitation
4. Inhibition of glutamate synthesis and release	▼ excitation

Na^{+}=sodium; Ca^{++}=calcium; GABA=γ-aminobutyric acid; ▼=decreased; ▲=increased.

Wilder BJ. Primary Psychiatry. Vol 9, No 1. 2002.



Pharmacological action of phenytoin

Heart and blood vessels

Severe low blood pressure and abnormal heart rhythms can be seen with rapid infusion of IV phenytoin. IV infusion should not exceed 50 mg/min in adults or 1–3 mg/kg/min (or 50 mg/min, whichever is slower) in children. Heart monitoring should occur during and after IV infusion. Due to these risks, oral phenytoin should be used if possible.

Neurological

At therapeutic doses, phenytoin may produce nystagmus on lateral gaze. At toxic doses, patients experience vertical nystagmus, double vision, sedation, slurred speech, cerebellar ataxia, and tremor. If phenytoin is stopped abruptly, this may result in increased seizure frequency, including status epilepticus.

Phenytoin may accumulate in the cerebral cortex over long periods of time which can cause atrophy of the cerebellum. The degree of atrophy is related to the duration of phenytoin treatment and is not related to dosage of the medication.

Abrupt discontinuation of phenytoin can precipitate status epilepticus. Phenytoin is known to be a causal factor in the development of peripheral neuropathy.

Blood

It has been suggested that phenytoin causes a reduction in folic acid levels, predisposing patients to megaloblastic anemia. Folate is presented in foods as polyglutamate, which is then converted into monoglutamates by intestinal conjugase. Phenytoin acts by inhibiting this enzyme, thereby causing folate deficiency. Other side effects may include: agranulocytosis, aplastic anemia, decreased white blood cell count, and a low platelet count.

Pregnancy

Phenytoin is a known teratogen. The syndrome consists of craniofacial anomalies (broad nasal bridge, cleft lip and palate, smaller than normal head) and a mild form of mental retardation (average IQ=71). This syndrome resembles the well-described Fetal Alcohol Syndrome and has also been called the "fetal hydantoin syndrome". Some recommend avoiding polytherapy and maintaining the minimal dose possible during pregnancy, but acknowledge that current data do not provide clear answers. Data now being collected by the Epilepsy and Antiepileptic Drug Pregnancy Registry may one day answer this question definitively.

Cancer

There is no good evidence that phenytoin is a human carcinogen.

Mouth

Phenytoin has been associated with drug-induced gingival enlargement (overgrowth of the gums), probably due to above-mentioned folate deficiency; indeed, evidence from a randomized controlled trial suggests that folic acid supplementation can prevent gingival enlargement in children who take phenytoin. Plasma concentrations needed to induce gingival lesions have not been clearly defined. Effects consist of the following: bleeding upon probing, increased gingival exudate, pronounced gingival inflammatory response to plaque levels, associated in some instances with bone loss but without tooth detachment.

Skin

Hypertrichosis, Stevens-Johnson syndrome, purple glove syndrome, rash, exfoliative dermatitis, itching, excessive hairiness, and coarsening of facial features can be seen in those taking phenytoin.

Phenytoin therapy has been linked to the life-threatening skin reactions Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN). These conditions are significantly more common in patients with a particular HLA-B allele, HLA-B*1502. This allele occurs almost exclusively in patients with ancestry across broad areas of Asia, including South Asian Indians.

Phenytoin is primarily metabolized to its inactive form by the enzyme CYP2C9. Variations within the CYP2C9 gene that result in decreased enzymatic activity have been associated with increased phenytoin concentrations, as well as reports of drug toxicities due to these increased concentrations. The U.S. Food and Drug Administration (FDA) notes on the phenytoin drug label that since strong evidence exists linking HLA-B*1502 with the risk

of developing SJS or TEN in patients taking carbamazepine, consideration should be given to avoiding phenytoin as an alternative to carbamazepine in patients carrying this allele.

Immune system

Phenytoin has been known to cause drug-induced lupus. Phenytoin is also associated with induction of reversible IgA deficiency.

Psychological

Phenytoin may increase risk of suicidal thoughts or behavior. People on phenytoin should be monitored for any changes in mood, the development or worsening depression, and/or any thoughts or behavior of suicide.

Bones

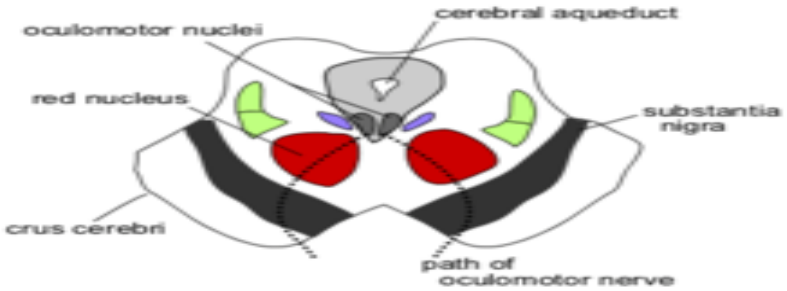
Chronic phenytoin use has been associated with decreased bone density and increased bone fractures. Phenytoin induces metabolizing enzymes in the liver. This leads to increased metabolism of vitamin D, thus decreased vitamin D levels. Vitamin D deficiency, as well as low calcium and phosphate in the blood cause decreased bone mineral density.

DRUGS FOR NEURODEGENERATIVE DISEASES: ANTIPARKINSON DRUGS

An **antiparkinson medication** is a type of drug which is intended to treat and relieve the symptoms of Parkinson's disease. Most of these agents act by either increasing dopamine activity or reducing acetylcholine activity in the central nervous system.

Parkinson's disease

Parkinson's disease is a motor system disorder of the nervous system. It is outlined as a progressive disorder that affects movement and results in the loss of dopamine-producing brain cells, causing tremor in the hands, arms, legs, jaw, and face and/or rigidity or stiffness of the limbs and trunk. The primary symptoms are muscular rigidity, slowness of movement, a resting tremor, and postural instability. Parkinson’s disease is caused by degeneration of the nigrostriatal system, which is the dopamine-secreting neurons of the substantia nigra that send axons to the basal ganglia. The basal ganglia controls the automatic, habitual responses performed by the human body.



This picture shows the Substantia nigra, the part of the brain that is affected in *Parkinson's disease*.

It is difficult to diagnose Parkinson's disease, as there is no specific test for it. Doctors usually perform other tests in order to rule out other conditions. Often seen in the dopaminergic neurons in the brains of patients who have Parkinson's disease, are Lewy bodies, which are abnormal circular structures found within the cytoplasm. Lewy bodies have a dense protein core, surrounded by a halo of radiating fibers.

Mutations on chromosome 4 can cause Parkinson's disease. This gene produces a protein known as a-synuclein. This protein which is normally found in the presynaptic terminals and is thought to be involved in synaptic transmission in dopaminergic neurons. The mutation produces what it known as a toxic gain of function because it produces a protein that results in effects that are toxic to the cell. Parkinson's disease can also be caused by a mutation on chromosome 6. This gene has been named parkin. This mutation causes a loss of function, which makes it a recessive disorder.

Common medication

The goal of the most common Antiparkinson drugs is to either replace the dopamine levels in the brain, or mimic the actions of dopamine. The main categories of Antiparkinson drugs are anticholinergic drugs and dopaminergic drugs. Anticholinergic drugs block the action of acetylcholine, compensating for the low levels of dopamine. As stated before, dopaminergic drugs aim to replace dopamine or inhibit the degradation of dopamine in the brain.

L-DOPA

Once a preliminary diagnosis is made, carbidopa-levodopa can be given as an antiparkinson medication. If this medication shows improvement, doctors will likely confirm their diagnosis. This standard treatment for Parkinson's disease is referred to as L-DOPA, the precursor of dopamine. L-DOPA causes the person's remaining dopaminergic neurons to

produce and secrete more dopamine, counteracting the effects of Parkinson's disease. However, eventually the nigrostriatal dopaminergic neurons in the brain drop to a low enough count where the symptoms of Parkinson's disease become worse. This is due to the short half-life of L-DOPA in the body; typically 1.5–2 hours. L-DOPA also activates DA neurons in the mesolimbic/mesocortical system and produces side effects such as hallucinations and delusions.

Deprenyl

A medicine that can be given with L-DOPA, or separately, is deprenyl. Deprenyl inhibits the activity of the enzyme MAO-B, which then will slow the progression of Parkinson's disease. Deprenyl, however, does not completely stop the degeneration of dopaminergic neurons. Deprenyl delays the time before other antiparkinson drugs, like L-DOPA, need to be used.

Tyrosine hydroxylase

Tyrosine hydroxylase catalyzes the formation of L-DOPA, the rate-limiting step in the biosynthesis of dopamine. In other words, it is a precursor to neurotransmitters and increases plasma neurotransmitter levels of dopamine and norepinephrine. This medication should not be used when taking L-DOPA, as L-DOPA interferes with the absorption of Tyrosine.

Apomorphine

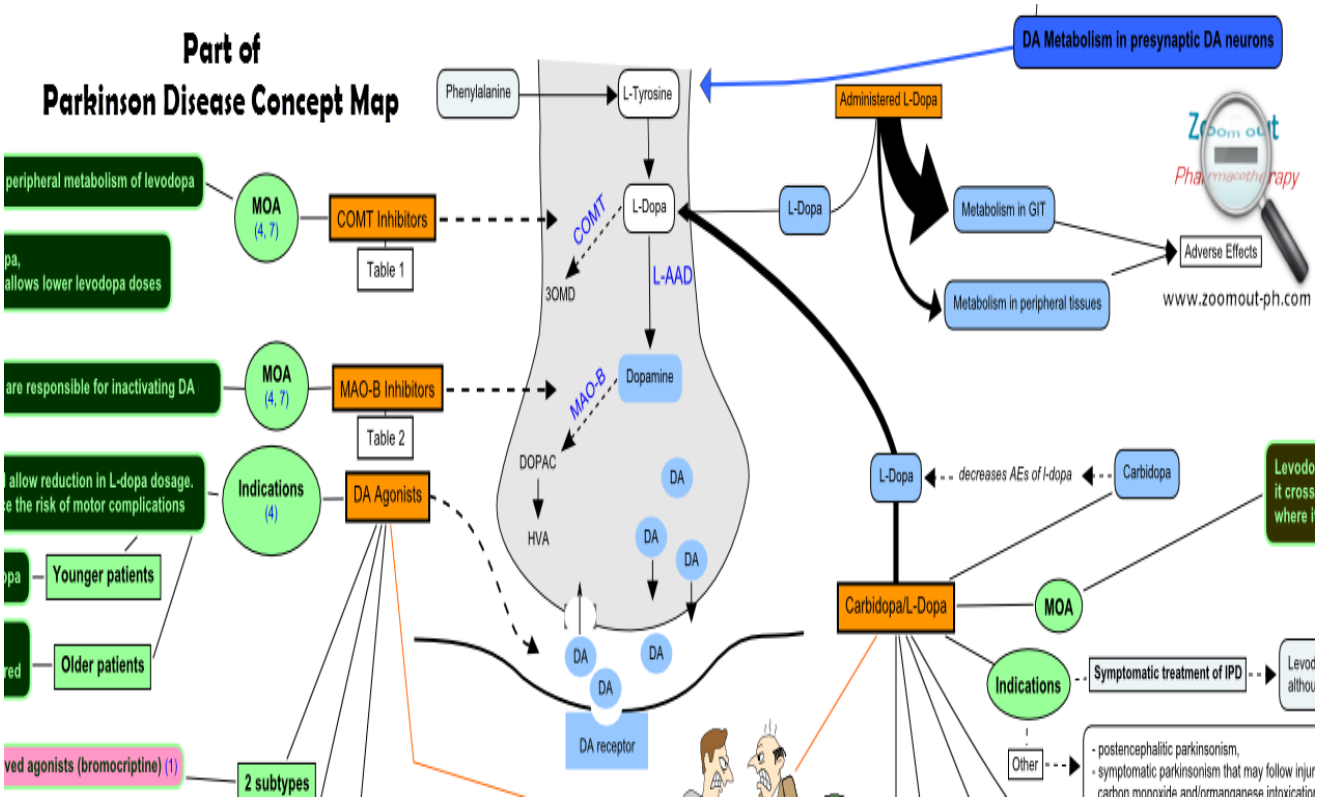
Apomorphine has also been used to treat Parkinson's disease. It is referred to as a dopamine receptor agonist. However, it does cause severe side effects when used on its own.

Anticholinergic drugs

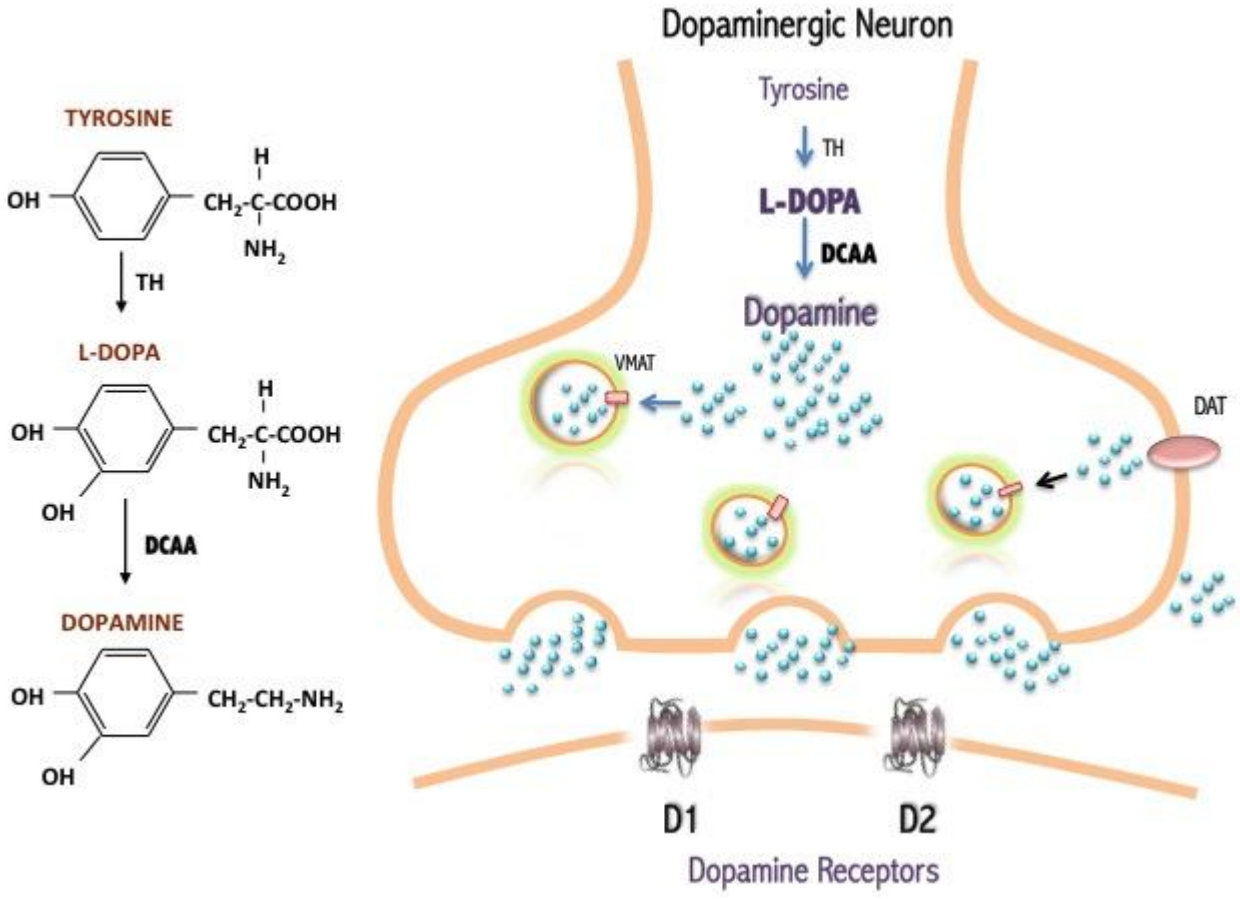
Anticholinergic drugs include benzhexol and orphenadrine. These drugs reduce the effect of acetylcholine in the brain by antagonizing cholinergic receptors. This helps restore the acetylcholine/dopamine balance within the brain. Again with these treatments, about 70% of patients taking anticholinergics develop serious side effects, including hallucinations, dyskinetic movements, vision effects, difficulty swallowing, dry mouth and urine retention.

mGluR4

N-phenyl-7-(hydroxylimino)cyclopropa[b]chromen-1a-carboxamide (PHCCC) is now being studied as a selective allosteric potentiator of mGluR4. Metabotropic glutamate receptor 4 (mGluR4) is a potential drug target for Parkinson's disease. PHCCC selectively potentiated agonist-induced mGluR4 activity in cells expressing this receptor and did not itself act as an agonist. PHCCC also potentiated the effect of L-(+)-2-amino-4-phosphonobutyric acid in inhibiting transmission at the striatopallidal synapse. This is significant due to the striatopallidal synapse being proposed as a target for Parkinson's disease treatment. This can hopefully restore balance in the basal ganglia motor circuit.



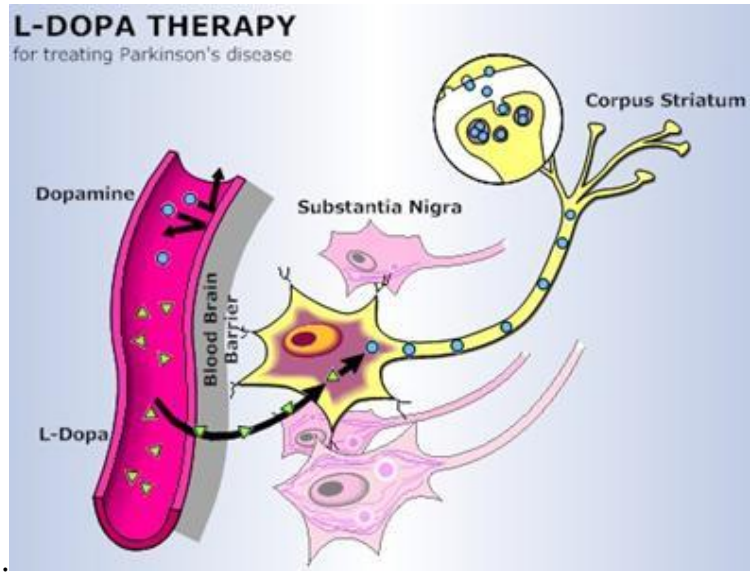
Parkinson's disease is a progressive condition that is characterized by bradykinesia.



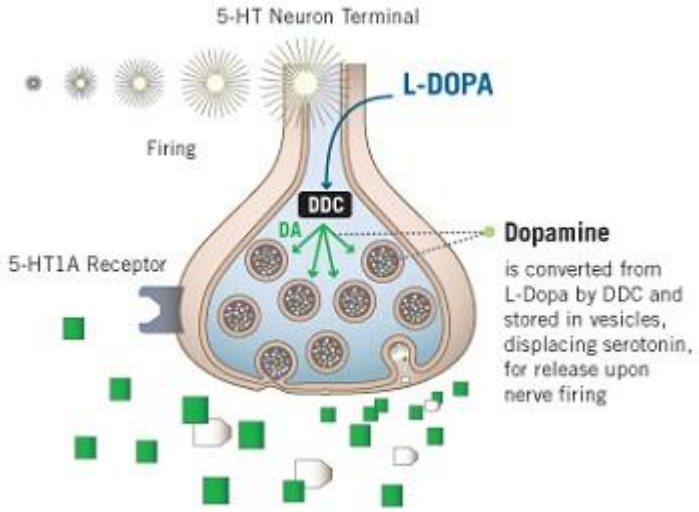
Dopamine D1 D2 Receptors

L-dopa-carbidopa Combined Therapy For The Treatment Of Parkinson's Disease, Levodopa Carbidopa Side Effects, Carbidopa Levodopa High Protein Diet.

Parkinson’s disease. It is formed in the brain by conversion of its precursor L-DOPA.

,. 

How Does Work in L Dopa Parkinson's



OPIOID ANALGESICS AND THEIR ANTAGONISTS

Opioids are substances that act on opioid receptors to produce morphine-like effects. Opioids are most often used medically to relieve pain. Opioids include *opiates*, an older term that refers to such drugs derived from *opium*, including morphine itself. Other opioids are semi-synthetic and synthetic drugs such as hydrocodone, oxycodone and fentanyl; antagonist drugs such as naloxone and endogenous peptides such as the endorphins.

The terms *opiate* and *narcotic* are sometimes encountered as synonyms for opioid. *Opiate* is properly limited to the natural alkaloids found in the resin of the opium poppy although some include semi-synthetic derivatives. *Narcotic*, derived from words meaning *numbness* or *sleep*, as an American legal term, refers to cocaine and opioids, and their source materials; it is also loosely applied to any illegal or controlled psychoactive drug. In other jurisdictions all controlled drugs are legally classified as *narcotics*. The term can have pejorative connotations and its use is generally discouraged where that is the case

Medical uses

Pain

Opioids are indicated for the relief of mild to severe pain, but are usually reserved for moderate to severe pain. The weak opioid codeine, in low doses and combined with one or more other drugs, is commonly available without a prescription.

Acute pain

Opioids are effective for the treatment of acute pain (such as pain following surgery). For immediate relief of moderate to severe acute pain opioids are frequently the treatment of choice due to their rapid onset, efficacy and reduced risk of dependence. They have also been found to be important in palliative care to help with the severe, chronic, disabling pain that may occur in some terminal conditions such as cancer, and degenerative conditions such as rheumatoid arthritis. In many cases opioids are a successful long-term care strategy for those with chronic cancer pain.

Chronic non-cancer pain

Guidelines have suggested that the risk of opioids is likely greater than their benefits when used for most non-cancer chronic conditions including headaches, back pain, and fibromyalgia. Thus they should be used cautiously in chronic non-cancer pain. If used the benefits and harms should be reassessed at least every three months

Pharmacological action of morphine

Medical uses

Pain

Morphine is used primarily to treat both acute and chronic severe pain. It is also used for pain due to myocardial infarction and for labor pains. Its duration of analgesia is about three to seven hours.

However, concerns exist that morphine may increase mortality in the setting of non ST elevation myocardial infarction. Morphine has also traditionally been used in the treatment of acute pulmonary edema. A 2016 Cochrane review concluded that morphine is effective in relieving cancer pain. Side-effects of nausea and constipation are rarely severe enough to warrant stopping treatment.

Shortness of breath

Immediate-release morphine is beneficial in reducing the symptom of shortness of breath due to both cancer and noncancer causes. In the setting of breathlessness at rest or on minimal

exertion from conditions such as advanced cancer or end-stage cardiorespiratory diseases, regular, low-dose sustained-release morphine significantly reduces breathlessness safely, with its benefits maintained over time.

Opioid use disorder

Morphine is also available as a slow-release formulation for opiate substitution therapy (OST) in Austria, Bulgaria, and Slovenia, for addicts who cannot tolerate either methadone or buprenorphine.

Contraindications

Relative contraindications to morphine include:

- respiratory depression when appropriate equipment is not available
- Although it has previously been thought that morphine was contraindicated in acute pancreatitis, a review of the literature shows no evidence for this.

Adverse effects
Adverse effects of opioids

Common and short term

- Itch
- Nausea
- Vomiting
- Constipation
- Drowsiness
- dry mouth

Other

- Opioid dependence
- Dizziness
- Decreased sex drive
- impaired sexual function
- Decreased testosterone levels
- Depression
- Immunodeficiency
- opioid-induced abnormal pain sensitivity
- Irregular menstruation
- Increased risk of falls
- Slowed breathing

A localized reaction to intravenous morphine caused by histamine release in the veins

Constipation

Like loperamide and other opioids, morphine acts on the myenteric plexus in the intestinal tract, reducing gut motility, causing constipation. The gastrointestinal effects of morphine are

mediated primarily by μ-opioid receptors in the bowel. By inhibiting gastric emptying and reducing propulsive peristalsis of the intestine, morphine decreases the rate of intestinal transit. Reduction in gut secretion and increased intestinal fluid absorption also contribute to the constipating effect. Opioids also may act on the gut indirectly through tonic gut spasms after inhibition of nitric oxide generation. This effect was shown in animals when a nitric oxide precursor, L-arginine, reversed morphine-induced changes in gut motility.

Hormone imbalance

Opioid § Hormone imbalance

Clinical studies consistently conclude that morphine, like other opioids, often causes hypogonadism and hormone imbalances in chronic users of both sexes. This side effect is dose-dependent and occurs in both therapeutic and recreational users. Morphine can interfere with menstruation in women by suppressing levels of luteinizing hormone. Many studies suggest the majority (perhaps as much as 90%) of chronic opioid users have opioid-induced hypogonadism. This effect may cause the increased likelihood of osteoporosis and bone fracture observed in chronic morphine users. Studies suggest the effect is temporary. As of 2013, the effect of low-dose or acute use of morphine on the endocrine system is unclear.

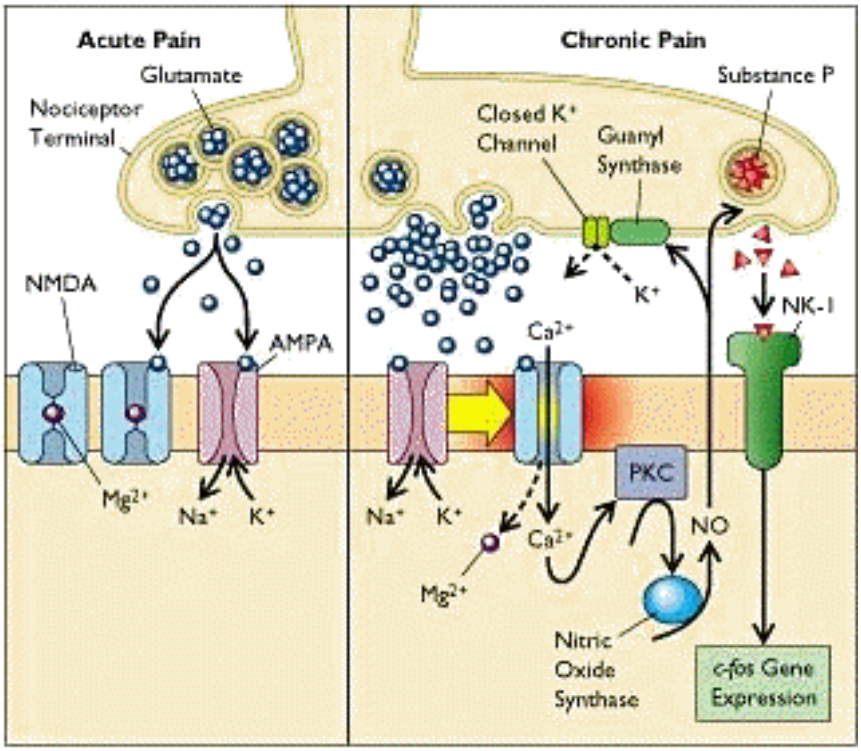
Effects on human performance

Most reviews conclude that opioids produce minimal impairment of human performance on tests of sensory, motor, or attentional abilities. However, recent studies have been able to show some impairments caused by morphine, which is not surprising, given that morphine is a central nervous system depressant. Morphine has resulted in impaired functioning on critical flicker frequency (a measure of overall CNS arousal) and impaired performance on the Maddox wing test (a measure of deviation of the visual axes of the eyes). Few studies have investigated the effects of morphine on motor abilities; a high dose of morphine can impair finger tapping and the ability to maintain a low constant level of isometric force (i.e. fine motor control is impaired), though no studies have shown a correlation between morphine and gross motor abilities.

In terms of cognitive abilities, one study has shown that morphine may have a negative impact on anterograde and retrograde memory, but these effects are minimal and transient. Overall, it seems that acute doses of opioids in non-tolerant subjects produce minor effects in some sensory and motor abilities, and perhaps also in attention and cognition. It is likely that the effects of morphine will be more pronounced in opioid-naive subjects than chronic opioid users.

In chronic opioid users, such as those on Chronic Opioid Analgesic Therapy (COAT) for managing severe, chronic pain, behavioural testing has shown normal functioning on perception, cognition, coordination and behaviour in most cases. One recent study analysed COAT patients to determine whether they were able to safely operate a motor vehicle. The findings from this study suggest that stable opioid use does not significantly impair abilities inherent in driving (this includes physical, cognitive and perceptual skills). COAT patients showed rapid completion of tasks that require speed of responding for successful performance (e.g., Rey Complex Figure Test) but made more errors than controls. COAT patients showed no deficits in visual-spatial perception and organization (as shown in the WAIS-R Block Design Test) but did show impaired immediate and short-term visual memory

(as shown on the Rey Complex Figure Test – Recall). These patients showed no impairments in higher order cognitive abilities (i.e., planning). COAT patients appeared to have difficulty following instructions and showed a propensity toward impulsive behaviour, yet this did not reach statistical significance. It is important to note that this study reveals that COAT patients have no domain-specific deficits, which supports the notion that chronic opioid use has minor effects on psychomotor, cognitive, or neuropsychological functioning.



An **opioid antagonist**, or **opioid receptor antagonist**, is a receptor antagonist that acts on one or more of the opioid receptors.

> Naloxone and naltrexone are commonly used opioid antagonist drugs which are competitive antagonists that bind to the opioid receptors with higher affinity than agonists but do not activate the receptors. This effectively blocks the receptor, preventing the body from responding to opioids and endorphins.

Some opioid antagonists are not pure antagonists but in fact do produce some weak opioid partial agonist effects, and can produce analgesic effects when administered in high doses to opioid-naive individuals. Examples of such compounds include nalorphine and levallorphan. However, the analgesic effects from these specific drugs are limited and tend to be accompanied by dysphoria, most likely due to additional agonist action at the κ-opioid receptor. As they induce opioid withdrawal effects in people who are taking, or have recently used, opioid full agonists, these drugs are considered to be antagonists for practical purposes.

The weak partial agonist effect can be useful for some purposes, and has previously been used for purposes such as long-term maintenance of former opioid addicts using nalorphine, however it can also have disadvantages such as worsening respiratory depression in patients who have overdosed on non-opioid sedatives such as alcohol or barbiturates. Naloxone on the other hand has no partial agonist effects, and is in fact a partial inverse

agonist at μ-opioid receptors, and so is the preferred antidote drug for treating opioid overdose.

Naltrexone is also a partial inverse agonist, and this property is exploited in treatment of opioid addiction, as a sustained course of low-dose naltrexone can reverse the altered homeostasis which results from long-term abuse of opioid agonist drugs. This is the only treatment available which can reverse the long-term after effects of opioid addiction known as post acute withdrawal syndrome, which otherwise tends to produce symptoms such as depression and anxiety that may lead to eventual relapse. A course of low-dose naltrexone is thus often used as the final step in the treatment of opioid addiction after the patient has been weaned off the substitute agonist such as methadone or buprenorphine, in order to restore homeostasis and minimize the risk of post acute withdrawal syndrome once the maintenance agonist has been withdrawn.

PSYCHOPHARMACOLOGICAL AGENTS:

1.ANTIANXIETY AGENTS

An **anxiolytic** (also **antipanic** or **antianxiety agent**) is a medication or other intervention that inhibits anxiety. This effect is in contrast to anxiogenic agents, which increase anxiety. Together these categories of psychoactive compounds or interventions may be referred to as anxiotropic compounds or agents. Some recreational drugs such as ethanol (alcohol) induce anxiolysis initially; however, studies show that many of these drugs are anxiogenic. Anxiolytic medications have been used for the treatment of anxiety disorder and its related psychological and physical symptoms. Anxiolytics have been shown to be useful in the treatment of anxiety disorder. Light therapy and other interventions have also been found to have an anxiolytic effect.

Beta-receptor blockers such as propranolol and oxprenolol, although not anxiolytics, can be used to combat the somatic symptoms of anxiety such as tachycardia and palpitations.

Anxiolytics are also known as **minor tranquilizers**. The term is less common in modern texts and was originally derived from a dichotomy with major tranquilizers, also known as neuroleptics or antipsychotics.

There are concerns that some GABAergics, such as benzodiazepines and barbiturates, may have an anxiogenic effect if used over long periods of time.

Medications

Barbiturates

Barbiturates exert an anxiolytic effect linked to the sedation they cause. The risk of abuse and addiction is high. Many experts consider these drugs obsolete for treating anxiety but valuable for the short-term treatment of severe insomnia, though only after benzodiazepines or non-benzodiazepines have failed.

Benzodiazepines

Benzodiazepines are prescribed for short-term or episodic relief of severe and disabling anxiety. Benzodiazepines may also be indicated to cover the latent periods associated with the medications prescribed to treat an underlying anxiety disorder. They are used to treat a wide variety of conditions and symptoms and are usually a first choice when short-term CNS sedation is needed. Longer-term uses include treatment for severe anxiety. If benzodiazepines are discontinued rapidly after being taken daily for two or more weeks there is some risk of benzodiazepine withdrawal and rebound syndrome, which varies by the specific drug. Tolerance and dependence may also occur, but may be clinically acceptable. Cognitive and behavioral adverse effects are possible. Benzodiazepines include:

- Alprazolam (Xanax)
- Bromazepam (Lectopam, Lexotan)
- Chlordiazepoxide (Librium)
- Clonazepam (Klonopin, Rivotril)
- Clorazepate (Tranxene)
- Diazepam (Valium)
- Flurazepam (Dalmane)
- Lorazepam (Ativan)
- Oxazepam (Serax, Serapax)
- Temazepam (Restoril)
- Triazolam (Halcion)

Benzodiazepines exert their anxiolytic properties at moderate dosage. At higher dosage hypnotic properties occur.

- Tofisopam (Emandaxin and Grandaxin) is a drug that is a benzodiazepine derivative. Like other benzodiazepines, it possesses anxiolytic properties, but, unlike other benzodiazepines, it does not have anticonvulsant, sedative, skeletal muscle relaxant, motor skill-impairing, or amnestic properties.

Carbamates

Marketed as a safer alternative to barbiturate anxiolytics, meprobamate (Miltown, Equanil) was commonly used to relieve anxiety in the late 1950s and 1960s. Like barbiturates, therapeutic doses produce sedation and significant overdoses may be fatal. In the US, meprobamate has generally been replaced with benzodiazepines while the drug is now withdrawn in many European countries and Canada. The muscle relaxant carisoprodol has anxiolytic effects by metabolizing to meprobamate. Various other carbamates have been found to share these effects, such as tybamate and lorbamate.

Opioids

Opioids are drugs that are usually only prescribed for their painkilling properties, but some research is beginning to find that some varieties are effective at treating depression, obsessive compulsive disorder, and other ailments often associated with or caused by anxiety. They have a very high potential for abuse and have one of the highest addiction rates for all drugs. Many people become addicted to these drugs because they are so effective at blocking emotional pain, including anxiety. Similarly to alcohol, people with anxiety disorders are

more likely to become addicted to opioids due to their anxiolytic effect. These drugs range from the commonly prescribed hydrocodone, to the often illegal Diamorphine, and all the way to much more potent varieties like fentanyl often used in trauma or end of life pain management. Most people purchasing these drugs illegally are seeking them out to get a euphoric like high, but many others seek them out because they are so effective at reducing both physical pain and emotional pain.[10]

Because of their high potential for abuse and high overdose rates, prescribing opioids for mental health issues is very uncommon and frowned upon within the medical community. Safer opioids which are less likely to be abused, have less deadly drug interactions, and are less likely to cause overdose are the ones that are being looked into the most for their anxiolytic-type properties. Given that many anxiety sufferers are more prone to alcohol and opioid addiction, the potential danger in prescribing opioids is apparent. Benzodiazepines are very similar to alcohol in how they impact the user and the brain, and even though anxiety sufferers are more prone to alcohol addiction these drugs are still prescribed. The same logic is being used in the push to get opioids used for anxiety treatment.

Opioids and benzodiazepines are very dangerous to use together, and using them together is one of the most common reasons for accidental mixed drug overdose in the United States, so great caution should be taken if opioid prescriptions for anxiety become more accepted.

It appears that buprenorphine is gaining some acceptability within in the medical community for being used to treat anxiety, OCD, and depression. Buprenorphine is similar to methadone in that it is used in opioid replacement therapy as well as pain management. It is much safer than methadone and lots of other opioids and has a very long half-life leading to less compulsive use among those who attempt to abuse it or become mentally addicted to it. There has been research into more commonly abused opioids being prescribed for anxiety disorder, but given that these drugs produce more euphoria and require more constant dosing when compared to buprenorphine, there is a much higher danger for abuse and overdose

Therapeutic actions of benzodiazepines. Regardless of their potency, speed of elimination or duration of effects, the actions in the body are virtually the same for all benzodiazepines. This is true whether they are marketed as anxiolytics, hypnotics or anti-convulsants. All benzodiazepines exert five major effects which are used therapeutically: anxiolytic, hypnotic, muscle relaxant, anticonvulsant and amnesic (impairment of memory) .

Table: THERAPEUTIC ACTIONS OF BENZODIAZEPINES (IN SHORT-TERM USE)

Action	Clinical Use
Anxiolytic - relief of anxiety	- Anxiety and panic disorders, phobias
Hypnotic - promotion of sleep	- Insomnia
Myorelaxant - muscle relaxation	- Muscle spasms, spastic disorders
Anticonvulsant - stop fits, convulsions	- Fits due to drug poisoning, some forms of epilepsy
Amnesia - impair short-term memory	- Premedication for operations, sedation for minor surgical procedures

Other clinical uses, utilising combined effects:

- Alcohol detoxification
- Acute psychosis with hyperexcitability and aggressiveness

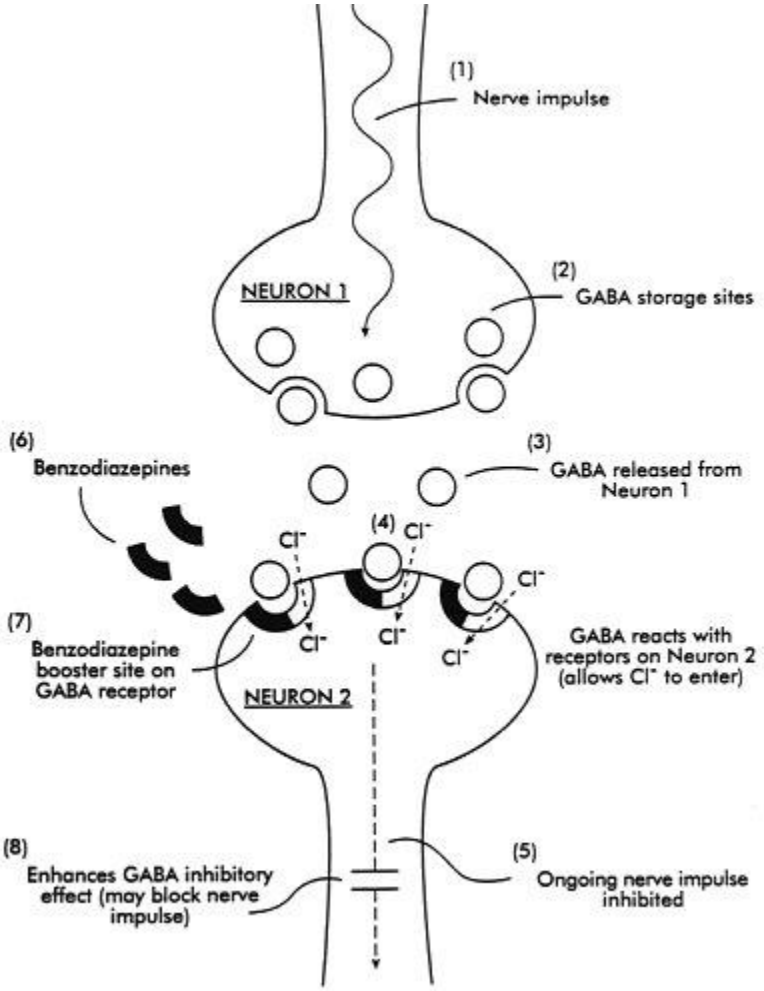
These actions, exerted by different benzodiazepines in slightly varying degrees, confer on the drugs some useful medicinal properties. Few drugs can compete with them in efficacy, rapid onset of action and low acute toxicity. In short-term use, benzodiazepines can be valuable, sometimes even life-saving, across a wide range of clinical conditions as shown inTable. Nearly all the disadvantages of benzodiazepines result from long-term use (regular use for more than a few weeks). The UK Committee on Safety of Medicines in 1988 recommended that benzodiazepines should in general be reserved for short-term use (2-4 weeks only).

Mechanisms of action

Anyone struggling to get off their benzodiazepines will be aware that the drugs have profound effects on the mind and body apart from the therapeutic actions. Directly or indirectly, benzodiazepines in fact influence almost every aspect of brain function. For those interested to know how and why, a short explanation follows of the mechanisms through which benzodiazepines are able to exert such widespread effects.

All benzodiazepines act by enhancing the actions of a natural brain chemical, GABA (gamma-aminobutyric acid). GABA is a neurotransmitter, an agent which transmits messages from one brain cell (neuron) to another. The message that GABA transmits is an inhibitory one: it tells the neurons that it contacts to slow down or stop firing. Since about 40% of the millions of neurons all over the brain respond to GABA, this means that GABA has a general quietening influence on the brain: it is in some ways the body's natural hypnotic and tranquilliser. This natural action of GABA is augmented by benzodiazepines which thus exert an extra (often excessive) inhibitory influence on neurons (Fig. 1).

Fig. 1. Diagram of mechanism of action of the natural neurotransmitter GABA (gamma-aminobutyric acid) and benzodiazepines on nerve cells (neurons) in the brain



(1,2) Nerve impulse causes release of GABA from storage sites on neuron 1
(3) GABA released into space between neurons
(4) GABA reacts with receptors on neuron 2; the reaction allows chloride ions (Cl^-) to enter the neuron
(5) This effect inhibits further progress of the nerve impulse
(6,7) Benzodiazepines react with booster site on GABA receptors
(8) This action enhances the inhibitory effects of GABA; the ongoing nerve impulse may be completely blocked

The way in which GABA sends its inhibitory message is by a clever electronic device. Its reaction with special sites (GABA-receptors) on the outside of the receiving neuron opens a channel, allowing negatively charged particles (chloride ions) to pass to the inside of the neuron. These negative ions "supercharge" the neuron making it less responsive to other neurotransmitters which would normally excite it. Benzodiazepines also react at their own special sites (benzodiazepine receptors), situated actually on the GABA-receptor. Combination of a benzodiazepine at this site acts as a booster to the actions of GABA, allowing more chloride ions to enter the neuron, making it even more resistant to excitation. Various subtypes of benzodiazepine receptors have slightly different actions. One subtype (alpha 1) is responsible for sedative effects, another (alpha 2) for anti-anxiety effects, and both alpha 1 and alpha 2, as well as alpha 5, for anticonvulsant effects. All benzodiazepines combine, to a greater or lesser extent, with all these subtypes and all enhance GABA activity in the brain.

As a consequence of the enhancement of GABA's inhibitory activity caused by benzodiazepines, the brain's output of excitatory neurotransmitters, including norepinephrine (noradrenaline), serotonin, acetyl choline and dopamine, is reduced. Such excitatory neurotransmitters are necessary for normal alertness, memory, muscle tone and co-ordination, emotional responses, endocrine gland secretions, heart rate and blood pressure control and a host of other functions, all of which may be impaired by benzodiazepines. Other benzodiazepine receptors, not linked to GABA, are present in the kidney, colon, blood cells and adrenal cortex and these may also be affected by some benzodiazepines. These direct and indirect actions are responsible for the well-known adverse effects of dosage with benzodiazepines.

ADVERSE EFFECTS OF BENZODIAZEPINES

Oversedation.

Oversedation is a dose-related extension of the sedative/hypnotic effects of benzodiazepines. Symptoms include drowsiness, poor concentration, incoordination, muscle weakness, dizziness and mental confusion. When benzodiazepines are taken at night as sleeping pills, sedation may persist the next day as "hangover" effects, particularly with slowly eliminated preparations (Table 1). However, tolerance to the sedative effects usually develops over a week or two and anxious patients taking benzodiazepines during the day rarely complain of sleepiness although fine judgement and some memory functions may still be impaired.

Oversedation persists longer and is more marked in the elderly and may contribute to falls and fractures. Acute confusional states have occurred in the elderly even after small doses of benzodiazepines. Oversedation from benzodiazepines contributes to accidents at home and at work and studies from many countries have shown a significant association between the use of benzodiazepines and the risk of serious traffic accidents. People taking benzodiazepines should be warned of the risks of driving and of operating machinery.

ANTIPSYCHOTIC DRUGS

Antipsychotics also known as **neuroleptics** or **major tranquilizers**, are a class of psychiatric medication primarily used to manage psychosis (including delusions, hallucinations, paranoia or disordered thought), principally in schizophrenia and bipolar disorder. They are increasingly being used in the management of non-psychotic disorders. Antipsychotics are usually effective in relieving symptoms of psychosis in the short term. However, their long term use is associated with significant side effects such as involuntary movement disorders and metabolic syndrome.

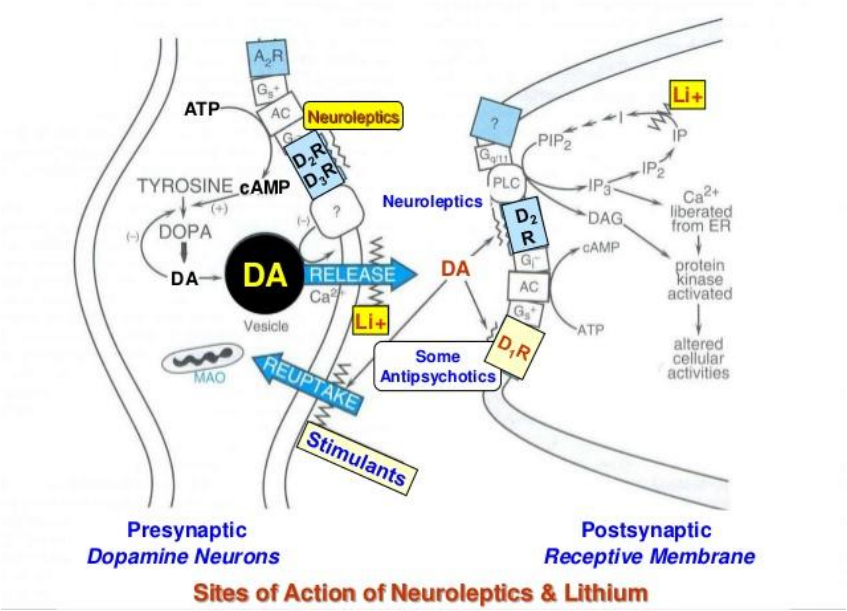
Medical uses

Antipsychotics are most frequently used for the following conditions:

- Schizophrenia
- Schizoaffective disorder most commonly in conjunction with either an antidepressant (in the case of the depressive subtype) or a mood stabiliser (in the case of the bipolar subtype).

- Bipolar disorder (acute mania and mixed episodes) may be treated with either typical or atypical antipsychotics, although atypical antipsychotics are usually preferred because they tend to have more favourable adverse effect profiles and, according to a recent meta-analysis, they tend to have a lower liability for causing conversion from mania to depression.
- Psychotic depression. In this indication it is a common practice for the psychiatrist to prescribe a combination of an atypical antipsychotic and an antidepressant as this practice is best supported by the evidence.
- Treatment-resistant (and not necessarily psychotic) major depression as an adjunct to standard antidepressant therapy.

They are not recommended for dementia or insomnia unless other treatments have not worked. They are not recommended in children unless other treatments are not effective or unless the child has psychosis.



Sites of Action of Neuroleptics & Lithium

MECHANISM OF ACTION OF ANTIPSYCHOTIC DRUGS

- The major action of all antipsychotics in the nervous system is to block receptors for the neurotransmitter dopamine.
- The typical antipsychotic drugs are potent antagonists (blockers) of dopamine receptors D2, D3, and D4.
- This makes them effective in treating target symptoms but also produces many extrapyramidal side effects.

ANTIDEPRESSANTS DRUGS

Antidepressants are drugs used for the treatment of major depressive disorder and other conditions, including dysthymia, anxiety disorders, obsessive compulsive disorder, eating disorders, chronic pain, neuropathic pain and, in some cases, dysmenorrhoea, snoring, migraine, attention-deficit hyperactivity disorder (ADHD), addiction, dependence, and sleep disorders. They can be used alone or in combination with other medications but only when prescribed.

The most important classes of antidepressants are the selective serotonin reuptake inhibitors (SSRIs), serotonin–norepinephrine reuptake inhibitors (SNRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), reversible monoamine oxidase A inhibitors (rMAO-A inhibitors), tetracyclic antidepressants (TeCAs), and noradrenergic and specific serotonergic antidepressant (NaSSAs). St John's wort is also used in the treatment of depression.

Types

Selective serotonin reuptake inhibitors

Selective serotonin reuptake inhibitors (SSRIs) are believed to increase the extracellular level of the neurotransmitter serotonin by limiting its reabsorption into the presynaptic cell, increasing the level of serotonin in the synaptic cleft available to bind to the postsynaptic receptor. They have varying degrees of selectivity for the other monoamine transporters, with pure SSRIs having only weak affinity for the norepinephrine and dopamine transporters.

SSRIs are the most widely prescribed antidepressants in many countries. The efficacy of SSRIs in mild or moderate cases of depression has been disputed.

Serotonin-norepinephrine reuptake inhibitors

Serotonin-norepinephrine reuptake inhibitors (SNRIs) are potent inhibitors of the reuptake of serotonin and norepinephrine. These neurotransmitters are known to play an important role in mood. SNRIs can be contrasted with the more widely used selective serotonin reuptake inhibitors (SSRIs), which act mostly upon serotonin alone.

The human serotonin transporter (SERT) and norepinephrine transporter (NET) are membrane proteins that are responsible for the reuptake of serotonin and norepinephrine. Balanced dual inhibition of monoamine reuptake can possibly offer advantages over other antidepressants drugs by treating a wider range of symptoms. SNRIs are sometimes also used to treat anxiety disorders, obsessive-compulsive disorder (OCD), attention deficit hyperactivity disorder (ADHD), chronic neuropathic pain, and fibromyalgia syndrome (FMS), and for the relief of menopausal symptoms.

Serotonin modulators and stimulators

Serotonin modulator and stimulators (SMSs), sometimes referred to more simply as **serotonin modulators**, are a type of drug with a multimodal action specific to the serotonin neurotransmitter system. To be precise, SMSs simultaneously modulate one or more

serotonin receptors and inhibit the reuptake of serotonin. The term was created to describe the mechanism of action of the serotonergic antidepressant vortioxetine (**Brintellix/Trintellix**), which acts as a serotonin reuptake inhibitor (SRI), partial agonist of the 5-HT_{1A} receptor, and antagonist of the 5-HT_3 and 5-HT_7 receptors. However, it can also technically be applied to vilazodone (**Viibryd**), which is an antidepressant as well and acts as an SRI and 5-HT_{1A} receptor partial agonist.

An alternative term is **serotonin partial agonist/reuptake inhibitor** (**SPARI**), which can be applied only to vilazodone.[148]

Serotonin antagonists and reuptake inhibitors

Serotonin antagonist and reuptake inhibitors (SARIs) while mainly used as antidepressants, are also anxiolytics and hypnotics. They act by antagonizing serotonin receptors such as 5-HT_{2A} and inhibiting the reuptake of serotonin, norepinephrine, and/or dopamine. Additionally, most also act as α_1-adrenergic receptor antagonists. The majority of the currently marketed SARIs belong to the phenylpiperazine class of compounds.

Norepinephrine reuptake inhibitors

Norepinephrine reuptake inhibitors (NRIs or NERIs) are a type of drug that acts as a reuptake inhibitor for the neurotransmitter norepinephrine (noradrenaline) by blocking the action of the norepinephrine transporter (NET). This in turn leads to increased extracellular concentrations of norepinephrine.

NRIs are commonly used in the treatment of conditions like ADHD and narcolepsy due to their psychostimulant effects and in obesity due to their appetite suppressant effects. They are also frequently used as antidepressants for the treatment of major depressive disorder, anxiety and panic disorder. Additionally, many drugs of abuse such as cocaine and methylphenidate possess NRI activity, though it is important to mention that NRIs without combined dopamine reuptake inhibitor (DRI) properties are not significantly rewarding and hence are considered to have a negligible abuse potential. However, norepinephrine has been implicated as acting synergistically with dopamine when actions on the two neurotransmitters are combined (e.g., in the case of NDRIs) to produce rewarding effects in psychostimulant drugs of abuse.

Tricyclic antidepressants

The majority of the tricyclic antidepressants (TCAs) act primarily as serotonin-norepinephrine reuptake inhibitors (SNRIs) by blocking the serotonin transporter (SERT) and the norepinephrine transporter (NET), respectively, which results in an elevation of the synaptic concentrations of these neurotransmitters, and therefore an enhancement of neurotransmission. Notably, with the sole exception of amineptine, the TCAs have negligible affinity for the dopamine transporter (DAT), and therefore have no efficacy as dopamine reuptake inhibitors (DRIs). Both serotonin and norepinephrine have been highly implicated in depression and anxiety, and it has been shown that facilitation of their activity has beneficial effects on these mental disorders.

Although TCAs are sometimes prescribed for depressive disorders, they have been largely replaced in clinical use in most parts of the world by newer antidepressants such as

selective serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs) and norepinephrine reuptake inhibitors (NRIs). Adverse effects have been found to be of a similar level between TCAs and SSRIs.

Tetracyclic antidepressants

Tetracyclic antidepressants (TeCAs) are a class of antidepressants that were first introduced in the 1970s. They are named after their chemical structure, which contains four rings of atoms, and are closely related to the tricyclic antidepressants (TCAs), which contain three rings of atoms.

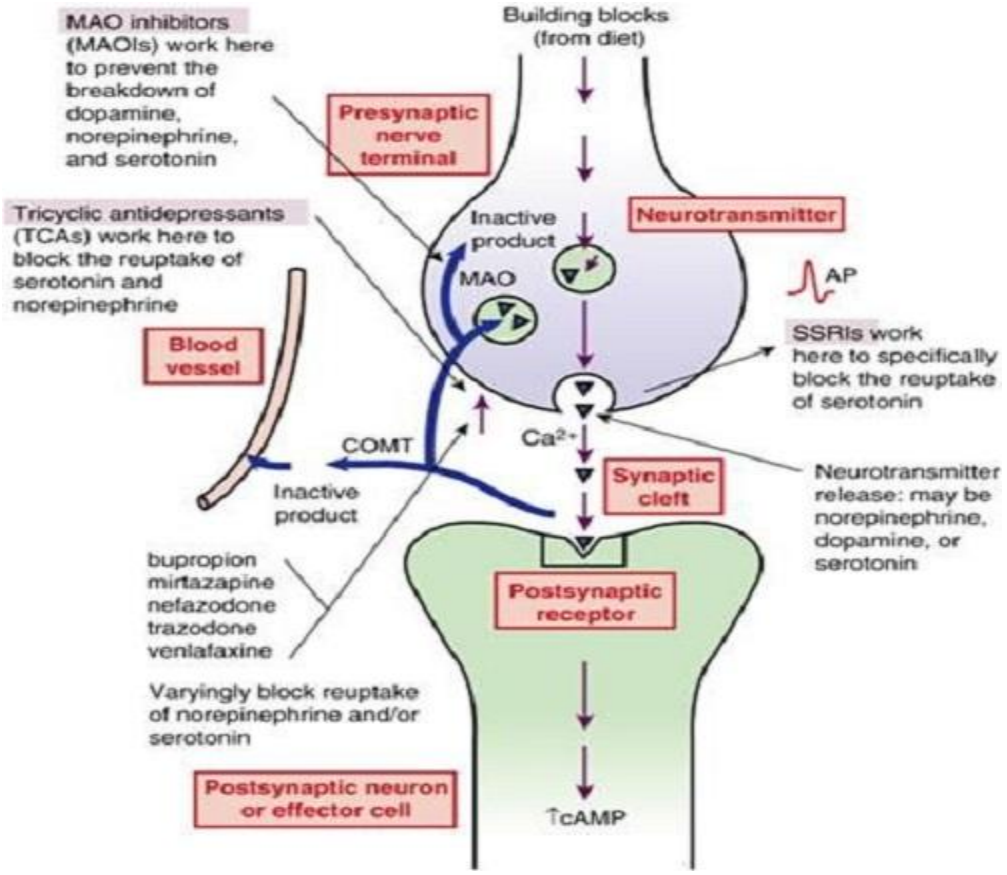
Monoamine oxidase inhibitors

Monoamine oxidase inhibitors (MAOIs) are chemicals which inhibit the activity of the monoamine oxidase enzyme family. They have a long history of use as medications prescribed for the treatment of depression. They are particularly effective in treating atypical depression. They are also used in the treatment of Parkinson's disease and several other disorders.

Because of potentially lethal dietary and drug interactions, monoamine oxidase inhibitors have historically been reserved as a last line of treatment, used only when other classes of antidepressant drugs (for example selective serotonin reuptake inhibitors and tricyclic antidepressants) have failed.[157]

MAOIs have been found to be effective in the treatment of panic disorder with agoraphobia,[] social phobia, atypical depression or mixed anxiety and depression, bulimia, and post-traumatic stress disorder, as well as borderline personality disorder. MAOIs appear to be particularly effective in the management of bipolar depression according to a recent retrospective-analysis. There are reports of MAOI efficacy in obsessive-compulsive disorder (OCD), trichotillomania, dysmorphophobia, and avoidant personality disorder, but these reports are from uncontrolled case reports.

MAOIs can also be used in the treatment of Parkinson's disease by targeting MAO-B in particular (therefore affecting dopaminergic neurons), as well as providing an alternative for migraine prophylaxis. Inhibition of both MAO-A and MAO-B is used in the treatment of clinical depression and anxiety disorders.



Imipramine, sold as **Tofranil** and also known as **melipramine**, is a tricyclic antidepressant (TCA) of the dibenzazepine group. Imipramine is mainly used in the treatment of major depression and enuresis (inability to control urination).

Imipramine was discovered in 1951. It has also been evaluated for use in panic disorder

Therapeutic uses

Imipramine is used in the treatment of depression, such as depression associated with agitation or anxiety. It is similar in efficacy to the antidepressant drug moclobemide. It has also been used to treat nocturnal enuresis because of its ability to shorten the time of delta wave stage sleep, where wetting occurs. In veterinary medicine, imipramine is used with xylazine to induce pharmacologic ejaculation in stallions

Mechanism of action

Imipramine, a tertiary amine, affects numerous neurotransmitter systems known to be involved in the etiology of depression, anxiety, ADHD, enuresis and numerous other mental and physical conditions. Imipramine is similar in structure to some muscle relaxants, and has a significant analgesic effect and, thus, is very useful in some pain conditions.

The mechanisms of imipramine's medicinal action include, but are not limited to, effects on:

- **Serotonin** (5-HT): very strong reuptake inhibition.
- **Norepinephrine** (NE): strong reuptake inhibition. Desipramine has more affinity to NET than imipramine.

- **Dopamine** (DA): Imipramine blocks D_2 receptors. Imipramine, and its metabolite desipramine, have no appreciable affinity for the dopamine transporter (8,500 and >10,000 K_inM respectively).
- **Acetylcholine** (ACh): imipramine is an anticholinergic. Thus, it is prescribed with caution to the elderly and with extreme caution to those with psychosis, as the general brain activity enhancement in combination with the "dementing" effects of anticholinergics increases the potential of imipramine to cause hallucinations, confusion and delirium in this population. Imipramine is an antagonist at M_2 muscarinic acetylcholine receptors (see external links).
- **Epinephrine**: imipramine antagonizes adreno-receptors (II), thus sometimes causing increased heart rate (contributed to by other effects as well), orthostatic hypotension, and a general decrease in the responsiveness of the central nervous system (hence, a contribution to its potent anti-anxiety properties).
- **σ Receptor and enkephalinase**: Activity on σ-receptors is present, but it is very low (Ki of 520 nM on σ-receptors, see references) and it is about half the power of amitryptiline (300 nM).
- **Histamine**: imipramine is an antagonist at histamine H_1 receptors.
- **BDNF**: BDNF is implicated in neurogenesis in the hippocampus, and studies suggest that depressed patients have decreased levels of BDNF and reduced hippocampal neurogenesis. It is not clear how neurogenesis restores mood, as ablation of hippocampal neurogenesis in murine models do not show anxiety related or depression related behaviours. Chronic imipramine administration results in increased histone acetylation (which is associated with transcriptional activation and decondensed chromatin) at the hippocampal BDNF promotor, and also reduced expression of hippocampal HDAC5.
- **μ Receptor**: imipramine has been shown to increase the expression of μ-opioid receptors in rat forebrain.[

Side effects

- Central nervous system: *dizziness*, *drowsiness*, confusion, seizures, headache, anxiety, tremors, stimulation, weakness, insomnia, nightmares, extrapyramidal symptoms in geriatric patients, increased psychiatric symptoms, paresthesia
- Cardiovascular: *orthostatic hypotension*, *ECG changes*, *tachycardia*, hypertension, palpitations, dysrhythmias
- Eyes, ears, nose and throat: blurred vision, tinnitus, mydriasis
- Gastrointestinal: *dry mouth*, nausea, vomiting, paralytic ileus, increased appetite, cramps, epigastric distress, jaundice, hepatitis, stomatitis, constipation, taste change
- Genitourinary: *urinary retention*
- Hematological: agranulocytosis, thrombocytopenia, eosinophilia, leukopenia
- Skin: rash, urticaria, diaphoresis, pruritus, photosensitivity