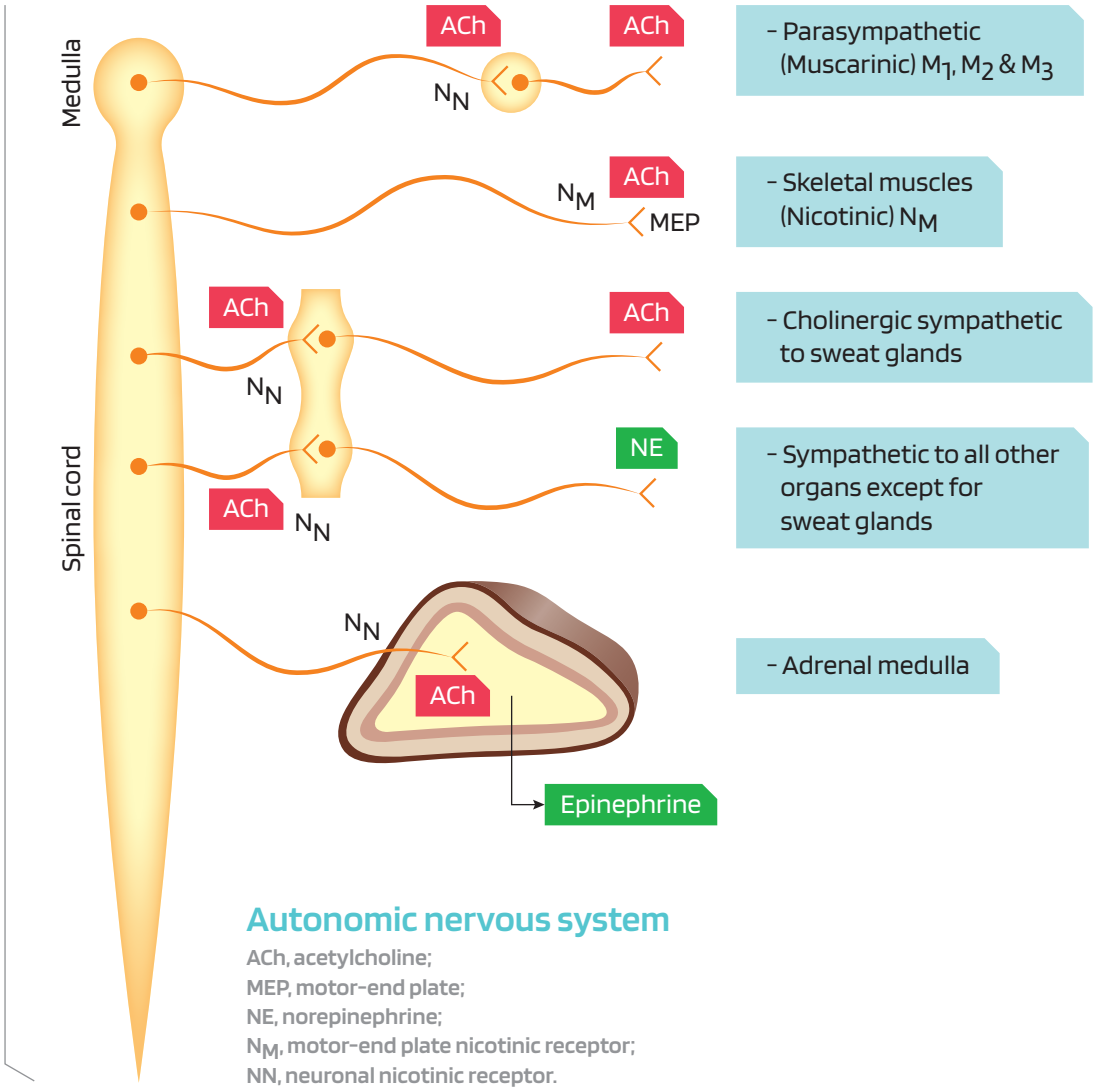
Pharmacology

The autonomic nervous system (ANS)

The autonomic nervous system (ANS) provides the unconscious control of heart rate, blood pressure, gastrointestinal and genitourinary system. It has two divisions, including the **thoracolumbar sympathetic** and the **craniosacral parasympathetic systems.** The ANS needs relay stations , which are called the autonomic ganglia. The sympathetic ganglia are located next to their vertebra, and the parasympathetic ganglia are mostly located inside the organs.

The two acetylcholine receptors are the **nicotinic** and **muscarinic** receptors. Nicotinic receptors, which are found in motor endplate structures, are not the same as preganglionic nicotinic receptors and are not part of the autonomic nervous system. The 3 main muscarinic receptors are **M1**, **M2**, and **M3**.

All postganglionic parasympathetic fibers are cholinergic. Most postganglionic sympathetic fibers are noradrenergic fibers. The only **exceptions are the sweat glands and piloerector muscles** which are cholinergic. The adrenal medulla is similar to a large sympathetic ganglion that secretes epinephrine into the blood. All preganglionic fibers (sympathetic and parasympathetic) are cholinergic.



Autonomic nervous system

ACh, acetylcholine;
MEP, motor-end plate;
NE, norepinephrine;
N_M, motor-end plate nicotinic receptor;
NN, neuronal nicotinic receptor.

Blood pressure control

↑ Blood pressure

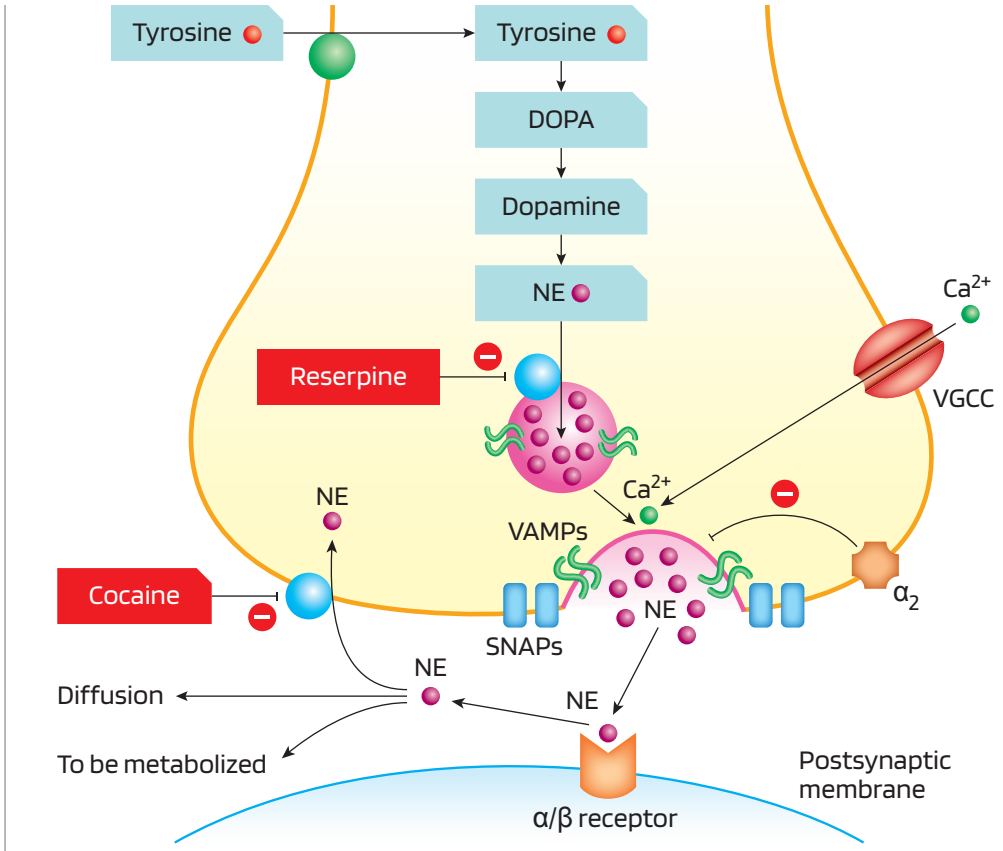
The baroreceptors in the carotid sinus and aortic arch detect an increase in blood pressure. These receptors send signals to the brain stem cardiovascular center that activates the parasympathetic (CN X) and inhibits sympathetic systems. The result is ↓HR & ↓contractility (decreased cardiac output) and vasodilation (decreased total peripheral resistance).

↓ Blood pressure

Low blood pressure causes a decrease in the **baroreceptor afferent** signal to the medulla. The medulla (vagus nerve) parasympathetic outflow slows down, and the sympathetic system fires more signals. Vasoconstriction, increased heart rate, and increased contractility are the result of these changes. The outcome is increased cardiac output and blood pressure. A decreased blood pressure in the kidney stimulates the **renin-angiotensin-aldosterone system**, which causes vasoconstriction and sodium reabsorption. Angiotensin II is the most potent vasoconstrictor in the body.

Adrenergic system

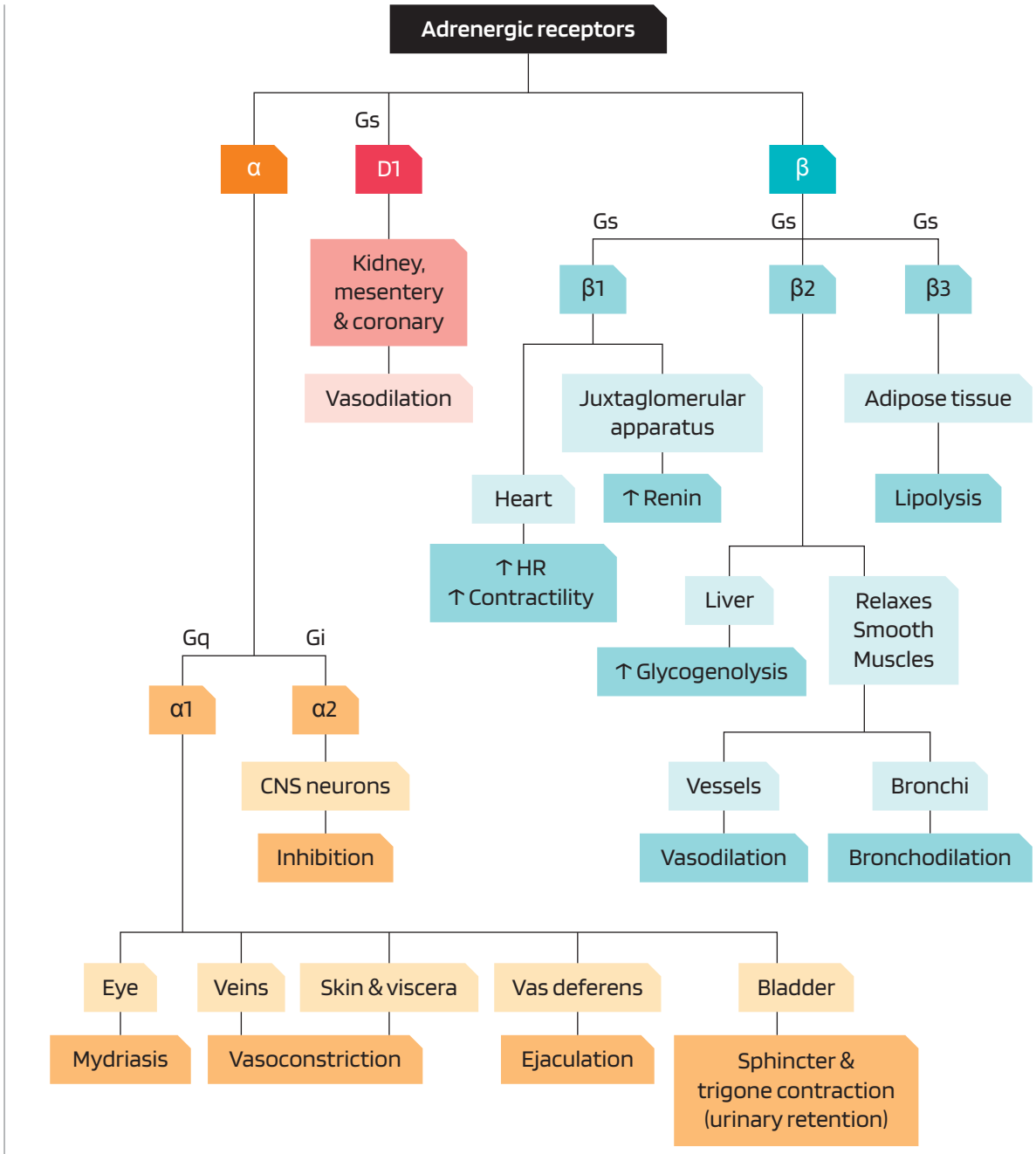
Adrenergic transmission



Adrenergic transmission

DOPA, dihydroxy phenylalanine; NE, norepinephrine; VGCC, voltage gated calcium channel.

Tyrosine enters the nerve ending (active transport), and undergoes hydroxylation, decarboxylation, and hydroxylation makes norepinephrine. The norepinephrine is stored in the presynaptic granules so that monoamine oxidase (MAO) will not be able to metabolize that. When an action potential reaches the nerve ending, voltage-gated calcium channels open and calcium enters. Calcium causes degranulation, and norepinephrine is released into the synaptic cleft. Norepinephrine activates the α-1 and β-1 receptors, and by activating the α-2 presynaptic receptor exerts negative feedback on itself.
The fate of norepinephrine includes inactivation by COMT, diffusion into the postsynaptic membrane, and presynaptic reuptake.



Adrenergic receptors

Adrenergic receptors activation

α-1 receptors

α-1 receptors use the IP3/DAG and Gq system to cause vascular smooth muscle contraction, which increases total peripheral resistance and reflex bradycardia (M2 receptors in the heart).
α-1 increases glycogenolysis, and decreases renin secretion. However, the sympathetic system›s overall effect is to increase renin secretion since the β-1 effect is more than α-1.

The α-1 receptors are all about contraction of smooth muscles.

Contraction of the radial muscles of the eye	Mydriasis
Contraction of the arterioles of the skin and viscera	Vasoconstriction, ↑ TPR, ↑ DBP
Contraction of the veins	↑ Preload
Contraction of the bladder neck	Urinary retention
Contraction of vas deferens	Ejaculation

α-1 effects are all about contraction of smooth muscles

α-2 receptors

These receptors use Gi and inhibit adenylate cyclase. The presynaptic α-2 agonists inhibit the release and synthesis of norepinephrine. Other effects include platelet aggregation and inhibition of insulin secretion.
In the CNS, α-2 activation decreases the sympathetic outflow. Clonidine is an α-2 agonist with a powerful antihypertensive effect.

β-1 receptors

β-1 receptors use Gs and activate adenylate cyclase. Activation of these receptors increases the heart rate, conduction velocity of atria, ventricles, AVN, HIS bundle, and Purkinje fibers. Additionally, the contractility of both atria and ventricles and their O2 consumption are increased. In kidneys, renin secretion is increased.

β-2 receptors

β-2 receptors use Gs and activate adenylate cyclase. β-2 is all about relaxation and dilation. Activation of these receptors causes vasodilation in the skeletal muscles and a decrease in total peripheral resistance. This results in a decrease in total peripheral resistance, which is detected by the baroreceptors causing reflex tachycardia (β-1 receptors in the heart).
Relaxation of the myometrium, bronchodilation, increase in gluconeogenesis & glycogenolysis, decrease motility of the GI system, relaxation of the bladder wall, and insulin secretion are other effects of β-2 receptors. Activation of β-2 receptors increases muscle contractility and causes tremor. β-blockers are used in the treatment of essential tremor.

D1 receptors

D1 receptors use Gs and activate adenylate cyclase. They cause vasodilation of mesentery, coronary and kidney vessels which increases renal blood flow, GFR, and sodium secretion.

Adrenergic medications

α-1 agonists

Alpha receptor stimulation causes vasoconstriction, which increases blood pressure and causes **reflex** bradycardia. Because both systolic and diastolic pressures are increased, pulse pressure stays the same.

Phenylephrine

Phenylephrine is a decongestant and mydriatic without cycloplegia.

Midodrine

Midodrine is used in low blood pressure, especially in renal patients who undergo dialysis.

Methoxamine

Methoxamine is used in paroxysmal atrial tachycardia because it causes reflex bradycardia.

α-2 agonists

Clonidine and **methyldopa** act on CNS and decrease the sympathetic outflow.
Methyldopa is used hypertensive pregnant women, and clonidine is a very effective antihypertensive agent.

α-2 antagonists

Mirtazapine increases the sympathetic outflow centrally and is used in depression.

Blocking α-2 increases sympathetic activity, and stimulating α-2 decreases sympathetic activity.

β-agonists

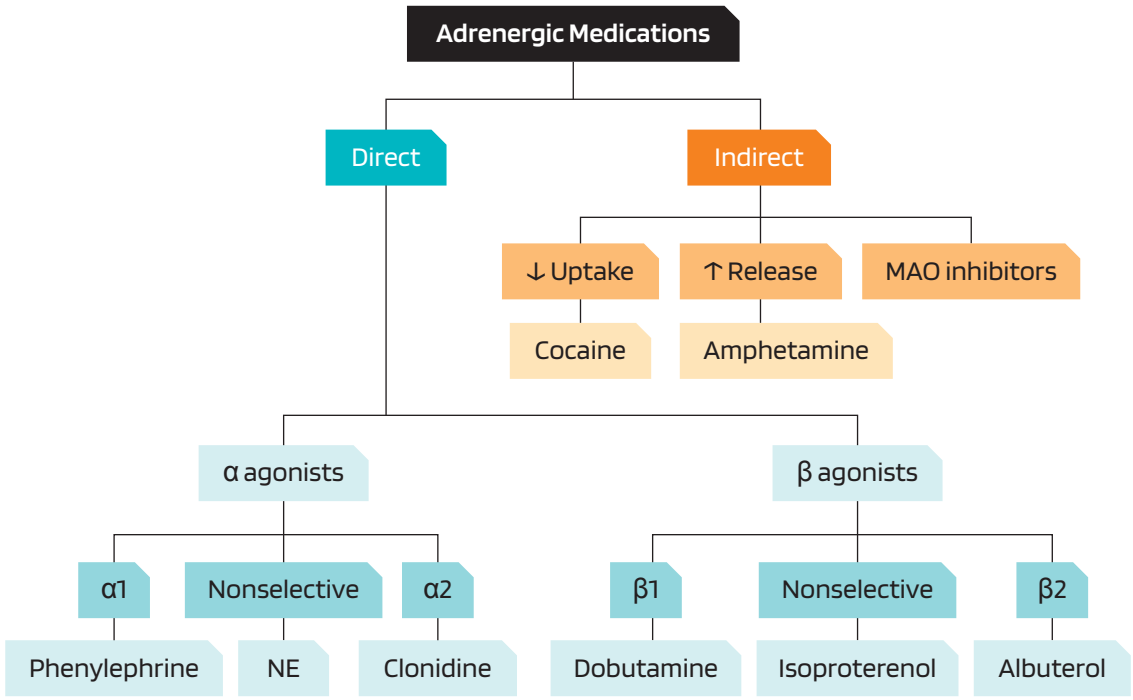
Nonselective β-agonists, including **isoproterenol**, because of their β-2 activity, overall decrease the mean blood pressure.

β-1 agonists

β-1 agonists increase HR, SV, cardiac output, and pulse pressure. **Dobutamine** has more β-1 activity and is used to increase contractility in congestive heart failure.

β-2 agonists

β-2 agonists cause vasodilation, which decreases total peripheral resistance and blood pressure.
Albuterol, a beta-2 agonist, is used in asthma. **Ritodrine** relaxes the smooth muscles of the uterus and is used for tocolysis.



Adrenergic medications

MAO, monoamine oxidase; NE, norepinephrine.

Norepinephrine versus epinephrine

Norepinephrine is an α-1, α-2, and β-1 agonist. It increases systolic (β-1), and diastolic blood pressure (α-1). The β-1 effect on heart rate is minimal since it is countered by reflex bradycardia.
Epinephrine has α-1, β-1, and β-2 agonist effects. The inotropic and chronotropic effects are due to the β-1 effect. The vasoconstrictive effect in the viscera is due to the α-1 effect. A decrease in total peripheral resistance is the result of the β-2 effect. The result is a drop in diastolic pressure.

Clinical use of epinephrine and norepinephrine

Epinephrine and norepinephrine are used in CPR, shock, and hypotension. Epinephrine is also used in asthma, anaphylactic shock, and in combination with local anesthetics.

Indirect adrenergic medications

↑ release

Amphetamine, ephedrine, and **methylphenidate** increase the release of norepinephrine.

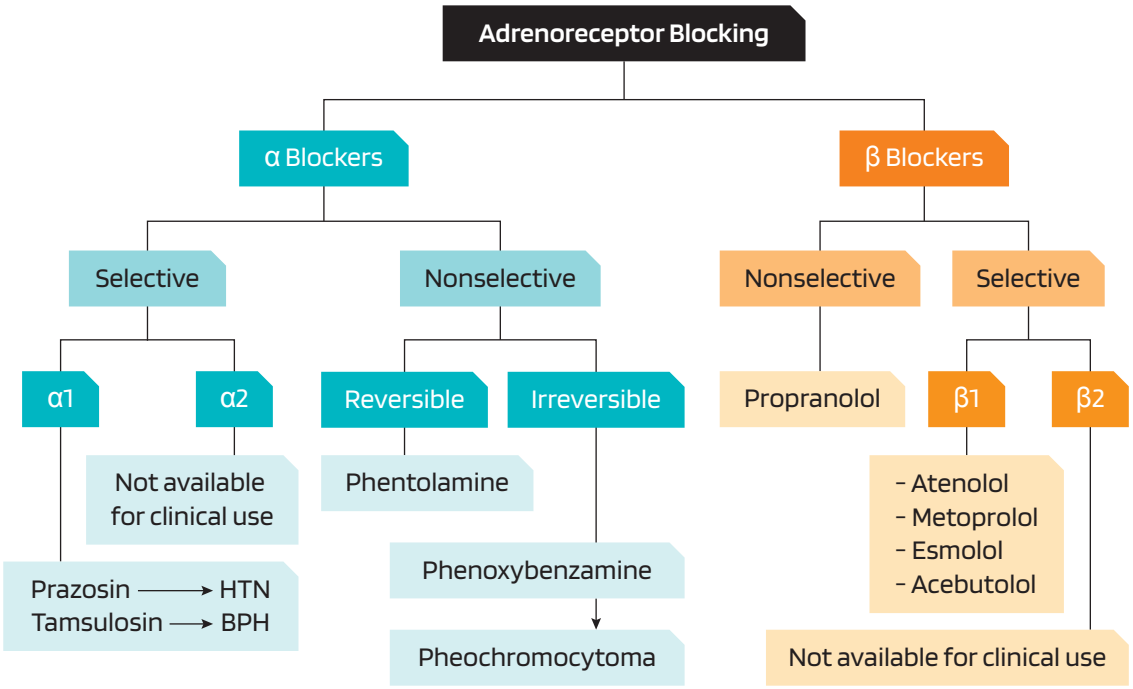
Reuptake inhibitors

Cocaine and **tricyclic antidepressants** inhibit norepinephrine reuptake.

MAO inhibitors

Selegiline is an MAO-B inhibitor that is used in Parkinson's disease. MAO-B is found in the CNS and metabolizes dopamine. MAO-A is found in many tissues and metabolizes tyramine, norepinephrine, and serotonin. **Tyramine** is a monoamine substance found in red wine and certain types of cheese. It is metabolized by MAO-A; therefore, patients taking MAO inhibitors should not ingest tyramine containing substances.

Adrenoreceptor blockers



Adrenoreceptor blocking agents

α-antagonists

α-antagonists decrease blood pressure and cause reflex tachycardia. They are used in pheochromocytoma, hypertension, and benign prostatic hyperplasia.

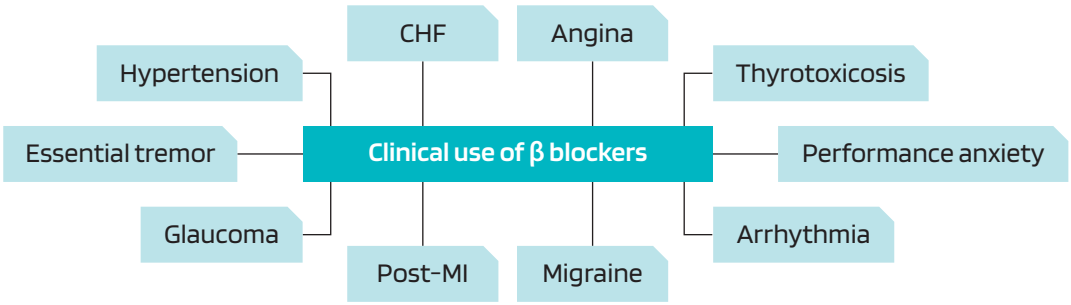
Nonselective α-antagonists include **phenoxybenzamine** (non-competitive), and **phentolamine** (competitive). Phenoxybenzamine is used in the treatment of pheochromocytoma.

Selective α-1 blockers include **prazosin** and **tamsulosin.**

Alpha-2 blocker(mirtazapine) is used for **depression.**

β-blockers

β-blockers decrease heart rate, stroke volume, cardiac output, renin, and aqueous humor production. They can mask signs of hypoglycemia, including tremors. Propranolol acts centrally and is sedative. β-blocker overdose and medication-induced hypoglycemia are treated with **glucagon** injection.



Clinical use of β-blockers

Chronic use of β-blockers causes the upregulation of their receptors; therefore, tapering their dose is necessary to prevent the **rebound effect.**

β-1 blockers include metoprolol, atenolol, and acebutolol and are mainly used in ischemic heart disease and hypertension.

β-2 blockers cause bronchospasm, vasospasm, decrease gluconeogenesis, decrease glycogenolysis, increase LDL, and increase triglycerides. β-2 receptors are present in the uterus, lungs, vasculature, and they are involved in metabolic processes.

Guanethidine

Guanethidine is an antihypertensive agent not available in the US. It causes pharmacologic sympathectomy.

Cholinergic medications

Cholinergic receptors

Nicotinic receptors

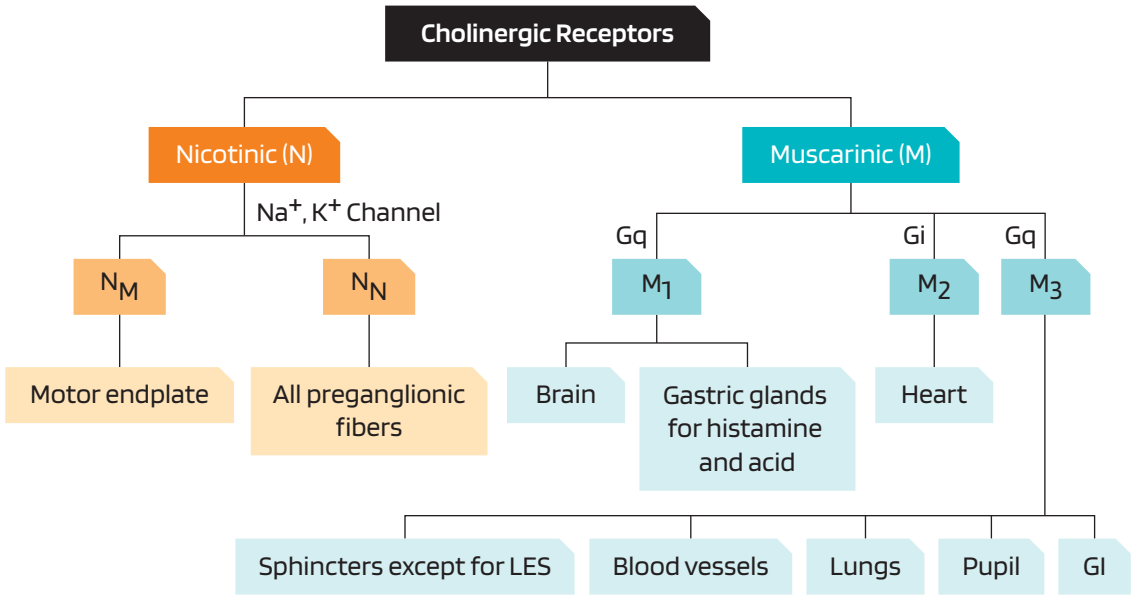
Motor end plate nicotinic (NM) receptors are Na^+ or K^+ channels with 2 alpha subunits and one of each of beta, gamma, and delta subunits.

In the synaptic cleft, 2 acetylcholine molecules bind the alpha subunits and open the channel. Na^+ enters, and K^+ goes out, which leads to depolarization of the muscle membrane. Overactivation of this receptor causes **fibrillation** and **fasciculation** of muscle fibers.

The neuronal nicotinic receptor (N_N) is present in all autonomic ganglia, including the adrenal medulla.

Muscarinic receptors

The effect of parasympathetic innervation on vascular smooth muscle cells is through nitric oxide. Sympathetic innervation of the blood vessels is through the postganglionic fibers which travel with them. GI tract is dominated by parasympathetic. The three main muscarinic receptors include M_1 (Gq), M_2 (Gi), and M_3 (Gq).



Cholinergic receptors

GI, gastrointestinal tract; LES, lower esophageal sphincter.

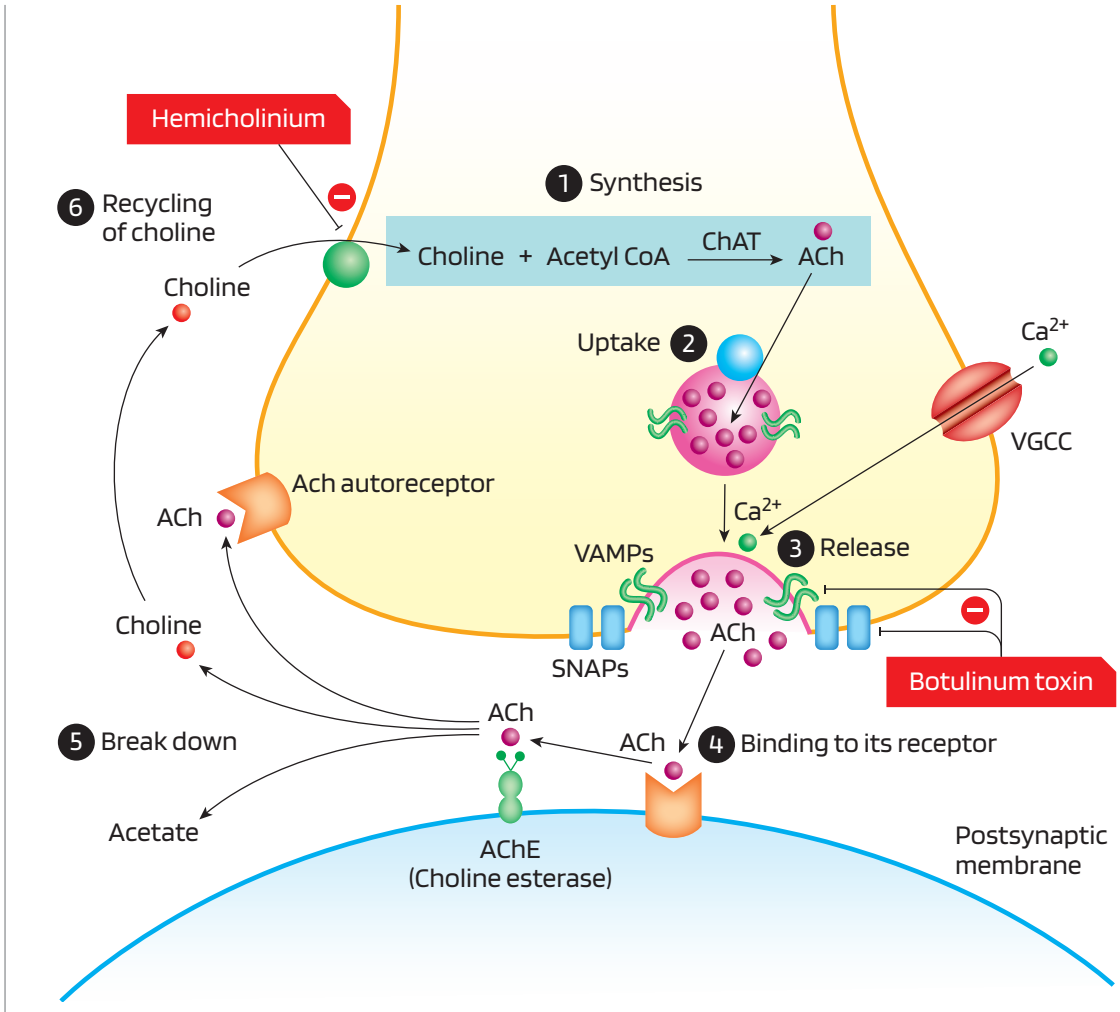
Cholinergic transmission

Choline acetyltransferase (CAT) catalyzes the synthesis of acetylcholine from choline plus acetyl-CoA. An action potential reached the presynaptic membrane, which opens the voltage-gated calcium channels. Ca^{2+} enters and causes degranulation and release of ACh into the synaptic cleft. In the synaptic cleft, ACh binds its receptor, and it is metabolized by acetylcholinesterase into choline and acetate. Choline uses a Na^{+}-dependent secondary active transport and is reabsorbed back into the presynaptic membrane. **Hemicholinium** blocks this carrier protein.

Botulinum toxin prevents the release of acetylcholine and causes flaccid paralysis. The toxin is used in the treatment of achalasia, blepharospasm, cosmetics, dystonia, strabismus, and hyperhidrosis.

Sweat glands are sympathetic but cholinergic.

Acetylcholine has a negative feedback effect on its presynaptic receptor. Acetylcholinesterase degrades acetylcholine into choline and acetyl-CoA in the synaptic cleft. Anticholinesterases are used in the treatment of **myasthenia gravis** (presence of Ab against the postsynaptic acetylcholine receptor.



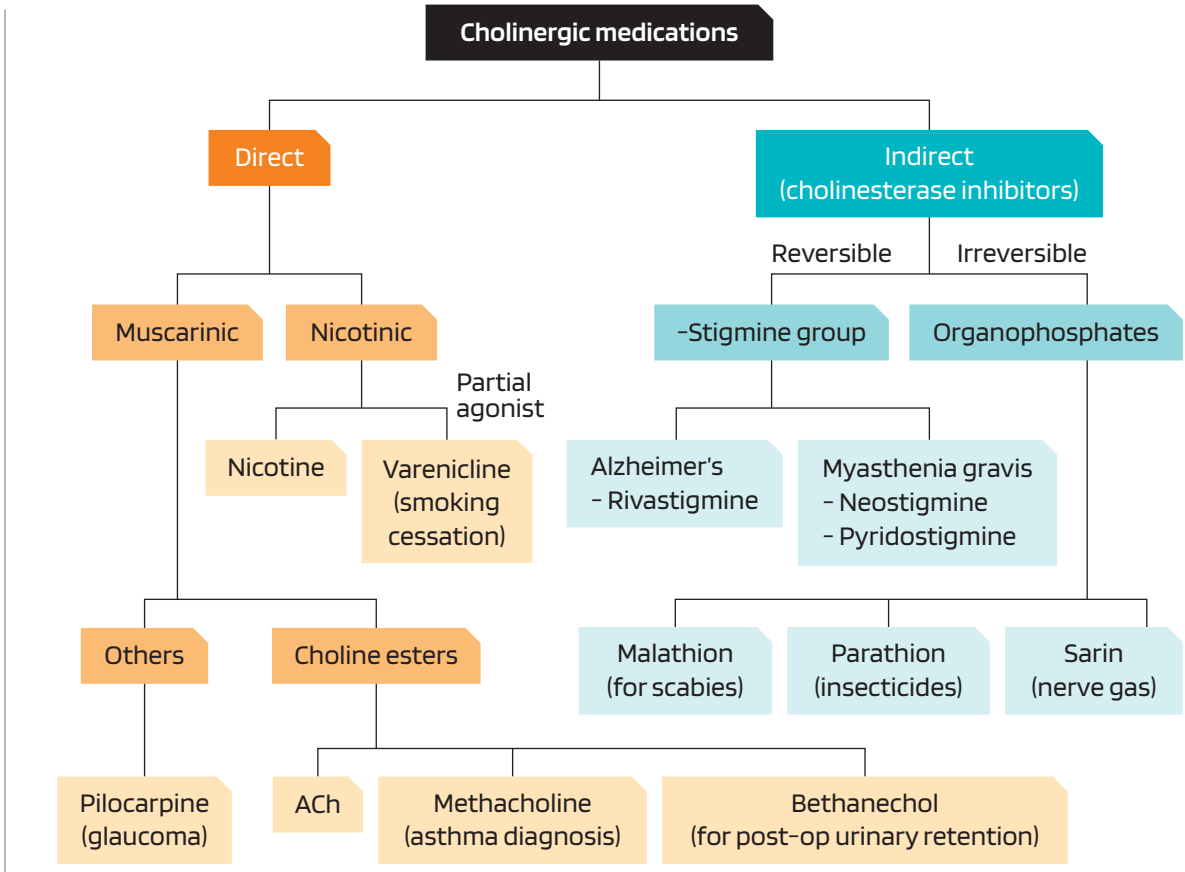
Cholinergic transmission

ACh, acetylcholine; AChE, choline esterase; ChAT, choline acetyltransferase; SNAP, synaptosomes associated protein ;VAMP , vesicle associated membrane protein; VGCC, voltage gated calcium channel.

Cholinergic medications

Direct cholinergic medications

ACh has a short half-life; however, **bethanechol** has a longer half-life and is used for paralytic ileus or urinary retention seen in post-op patients.
Methacholine is used for asthma diagnosis because it can cause bronchoconstriction. **Pilocarpine** is used for glaucoma and xerostomia (Sjögren syndrome).



Cholinergic medications

ACh, acetylcholine.

Indirect cholinergic medications- reversible anticholinesterases

Edrophonium is an ultra short-acting anticholinesterase that was used in the past for the diagnosis of myasthenia gravis (instant temporary relief from symptoms)
Physostigmine is used for atropine overdose and glaucoma.
Neostigmine & pyridostigmine are quaternary amines (cannot enter the CNS), which are used for paralytic ileus, urinary retention and myasthenia gravis. They are also used against non-depolarizing neuromuscular blocking (NDNMB) agents.
Rivastigmine, donepezil, galantamine, tacrine are used in Alzheimer's.

Irreversible anticholinesterases (organophosphates)

These medications include insecticides (**malathion, parathion, echothiophate**) and **nerve gases.**
Toxicity of these compounds causes lacrimation, rhinorrhea, salivation, micturition and diarrhea. There are also fasciculation, bradycardia, and miosis.

Management includes atropine (anticholinergic) and pralidoxime (regeneration of acetylcholinesterase). Pralidoxime should be used as soon as possible; otherwise, it will not work. Oximes take the phosphate ion away from the acetylcholinesterase molecule and release it from the toxin.
Cyt P450 converts parathion into paraoxon (the active metabolite).
Chronic organophosphate poisoning causes demyelination and neuropathy.

Anticholinesterase effects

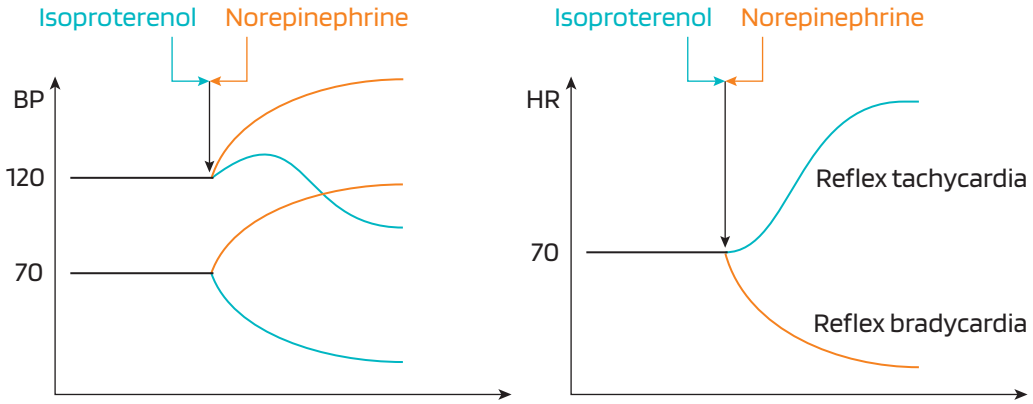
- **Eyes:** miosis and accommodation
- **Sphincters:** relaxation except for lower esophageal sphincter
- **Lungs:** bronchospasm and increased secretion
- **GI tracts (except glands):** increase motility and defecation
- **Bladder(micturition):** activation of detrusor muscles and inhibition of the sphincter and trigone
- **Blood vessels:** relaxation through nitric oxide
- **Other glands:** increase salivation, lacrimation, and sweating

Varenicline

This is a partial agonist of the NN receptor and is useful in **smoking cessation.**

Norepinephrine versus isoproterenol

The effects of isoproterenol and norepinephrine on HR and BP are completely opposite of each other. Isoproterenol increases HR and decreases BP. Norepinephrine increases blood pressure and decreases heart rate.
Isoproterenol is a pure β agonist that decreases systemic vascular resistance & blood pressure. The **drop in blood pressure** causes **reflex tachycardia.**
Norepinephrine, however, has α-1 activity, which increases systemic vascular resistance and blood pressure. The **rise in blood pressure** causes **reflex bradycardia.**



Norepinephrine and isoproterenol effects on heart rate and blood pressure

Effect of epinephrine

Epinephrine increases blood pressure because of its beta-1 and alpha-1 effects. However, there is some beta-2 effect that is dominated by beta-1 and alpha-1 effects. If you give an alpha-blocker with epinephrine, then the beta-2 effect is more pronounced, and blood pressure decreases.

Phenylephrine effect

Phenylephrine increases blood pressure by α-1 stimulation and causes **reflex bradycardia.** An alpha-blocker can prevent the effect of phenylephrine.

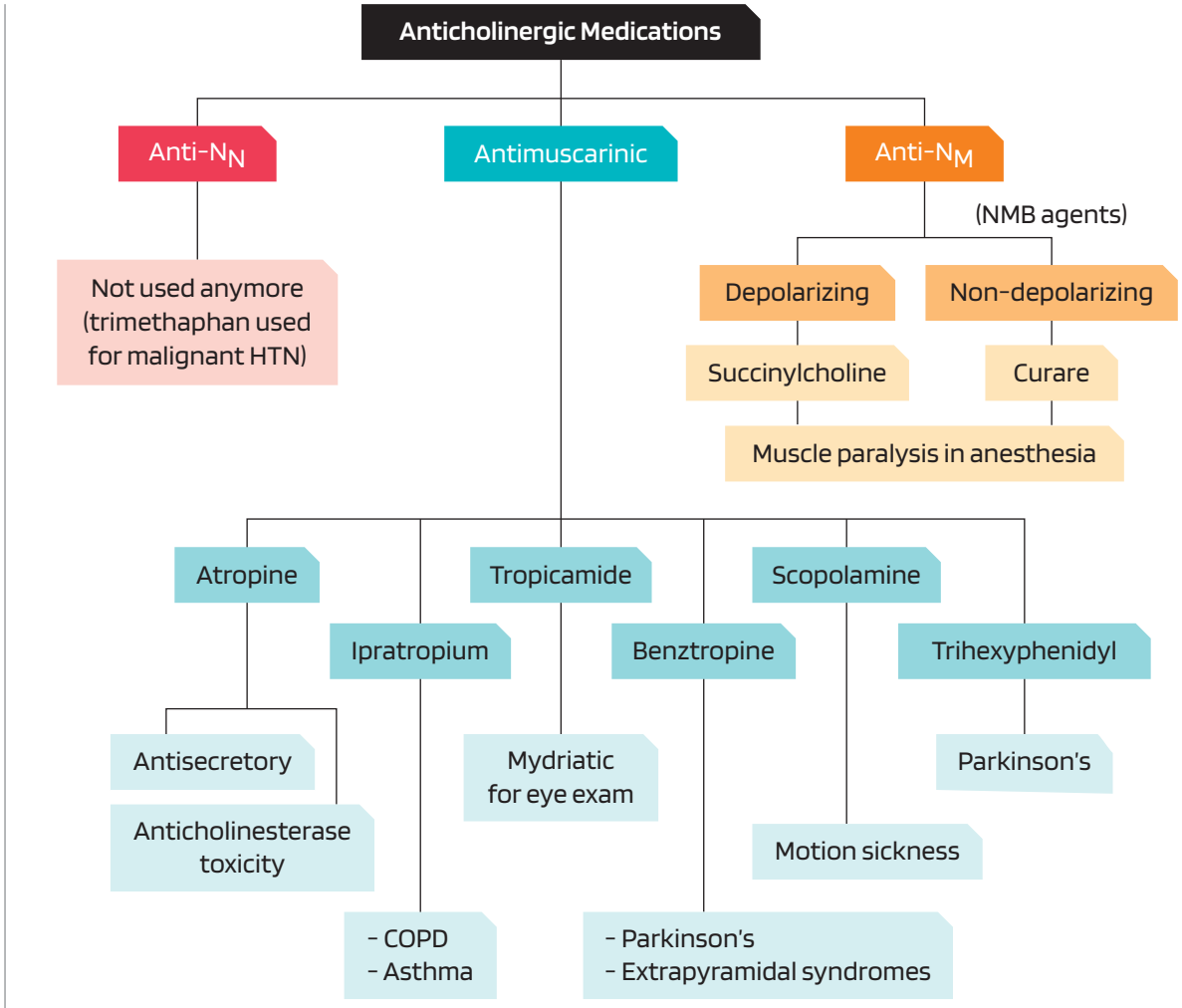
Norepinephrine and phenoxybenzamine

Norepinephrine increases both systolic and diastolic pressure. The heart rate drops because of reflex bradycardia. If phenoxybenzamine is given with norepinephrine, the alpha-1 is blocked, and the blood pressure drops. However, reflex tachycardia increases heart rate.

Anticholinergic medications

Antinicotinic medications (neuromuscular blocking agents)

These muscle relaxants include non-depolarizing (competitive) and depolarizing (non-competitive) agents.



Anticholinergic medications

Non-depolarizing (competitive) neuromuscular blocking agents

These medications are curare derivatives and include **d- tubocurarine, atracurium**, and **pancuronium.** They compete with acetylcholine receptors and paralyze the patient. Anticholinesterases, including neostigmine, reverse their effects. Progressive paralysis starts from the face then goes down to the limbs, and then respiratory muscles. Since nicotinic receptors are only available at the motor endplate, these non-depolarizing NMB agents do not affect CNS, cardiac, and smooth muscles.
Atracurium shows a rapid recovery and is safe in liver and kidney diseases. However, its spontaneous inactivation into laudanosine can cause **seizures.**
Mivacurium has a very short duration of action since plasma cholinesterase destroys that.

Depolarizing neuromuscular blocking agent

Succinylcholine is the only non-competitive NMB agent. Its mechanism of action involves two **phases:**
phase I include depolarization, fasciculation, and flaccid paralysis
phase II is desensitization (repolarized but blocked)
Anti-cholinesterases increase the duration of phase I, but they are the antidote for phase II. Succinylcholine is rapidly hydrolyzed by **pseudocholinesterase** (**butyrylcholinesterase**, which is available in plasma). In people with atypical pseudocholinesterase, succinylcholine is not rapidly metabolized, which leads to the toxicity of succinylcholine. Muscle paralysis is prolonged in these patients.
Toxicity of succinylcholine includes malignant hyperthermia, hyperkalemia, and hypercalcemia.

Malignant hyperthermia

Malignant hyperthermia is an autosomal dominant disease that following general anesthesia presents with muscle rigidity, stiffness, extreme body temperature, and rhabdomyolysis. Cardiac arrhythmia (hyperkalemia) and increased CPK are other clinical features. Wrapping the patient in a cooling blanket can help reduce fever and risk of serious complications.
Dantrolene prevents the release of calcium from the sarcoplasmic reticulum of skeletal muscle and is used against malignant hyperthermia. Lidocaine or a beta-blocker can help with arrhythmia.

Ganglionic blocking agent

These medications **block both sympathetic and parasympathetic systems** at the ganglionic level, and because of numerous adverse effects, their uses have been abandoned. The adverse effects include marked venous pooling and postural hypotension. Other effects are anhidrosis, increase heart rate (normally the parasympathetic effect is more than the sympathetic one), mydriasis, cycloplegia, constipation, and xerostomia.

Antimuscarinic agents

Atropine is an antisecretory agent (used in anesthesia), is used in the treatment of organophosphate poisoning and other anticholinesterase overdoses, and is used in symptomatic bradycardia.
Tropicamide is a mydriatic used for eye examinations.
Ipratropium is a bronchodilator used in COPD & asthma.
Scopolamine is effective against motion sickness.
Benztropine & trihexyphenidyl are effective against extrapyramidal syndromes (especially akathisia) and parkinsonism.

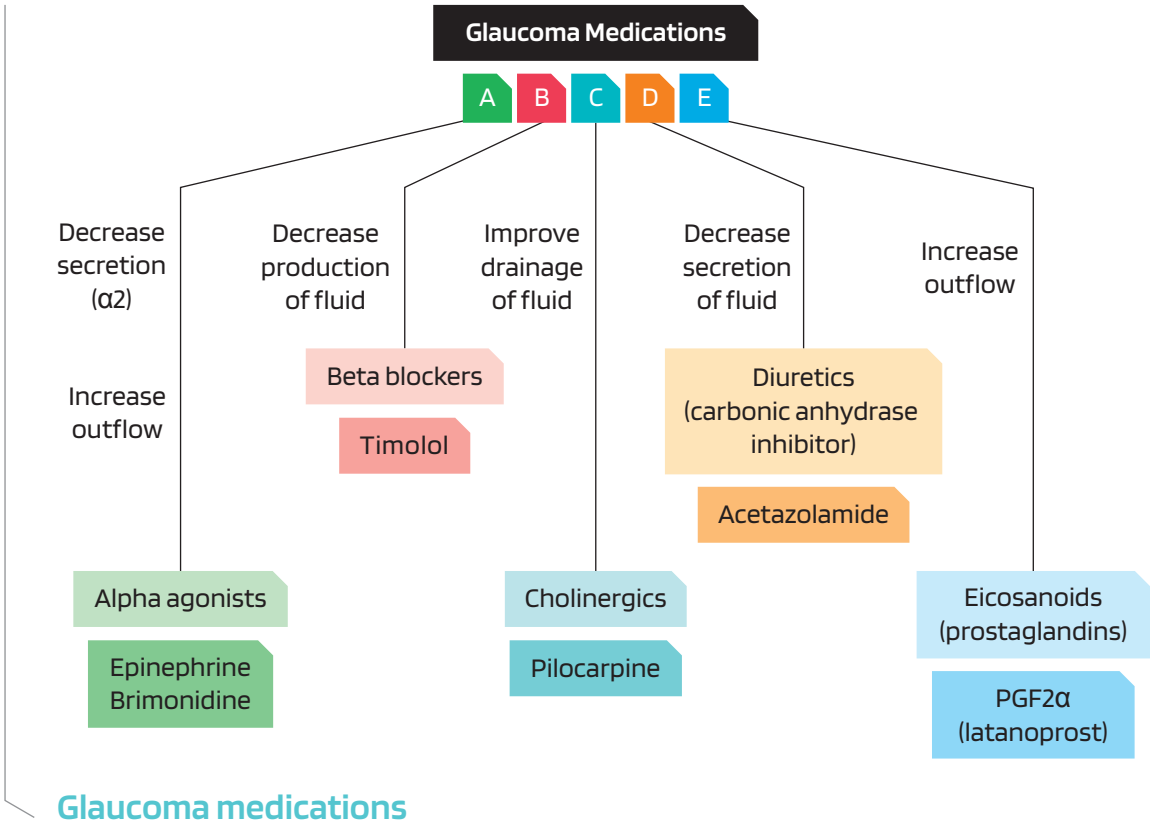
Anticholinergic (antimuscarinic) toxicity (hot, red, dry, blind and mad)

Patients with anticholinergic toxicity are hot, red, and dry because of decreased sweating. They are also confused (mad) and have blurry visions because of cycloplegia and mydriasis (blind). Urinary retention, tachycardia, and sedation are other features of anticholinergics.
Manage with physostigmine and symptomatic treatment.

Other medication with anticholinergic effects

Antihistamines, tricyclic antidepressants, antipsychotics, meperidine, clonidine, and amantadine are among many medications with anticholinergic effects.

Neuropharmacology of glaucoma medications



Glaucoma medications

Autonomic innervation of the eye

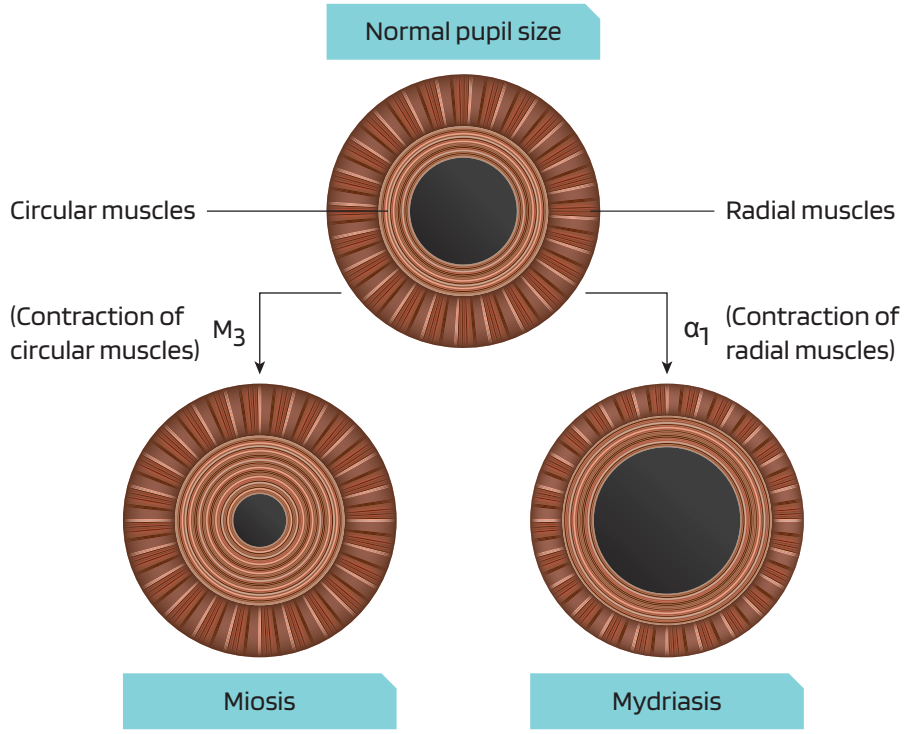
The pupils have the radial muscles, which have α-1 (a contraction of radial muscles cause mydriasis), and the sphincter muscle, which has M3 receptors (a contraction of these muscles causes miosis and accommodation).

Antimuscarinic agents cause mydriasis and cycloplegia. Contraction of ciliary muscles causes relaxation of fibers attached to the lens and cause more convexity.

Cholinergic medications contract ciliary muscles and increase the flow in the canal of Schlemm.

Antimuscarinic and α-1 agonists are contraindicated in closed-angle glaucoma since they cause mydriasis and exacerbate an already high intraocular pressure. Use pilocarpine in glaucoma emergencies.

Epinephrine and brimonidine are alpha agonists that increase the outflow and decrease the secretion of aqueous humor.



Autonomic innervation of the eye

Pharmacology of CNS medications

The ion channels in the nervous system are either regulated by action potential (voltage-gated) or by neurotransmitters (neurotransmitter gated).

The axonal membrane has sodium channels, and the presynaptic membrane has calcium channels. These voltage-gated channels are regulated by action potential and are blocked by some anesthetics and anticonvulsants.

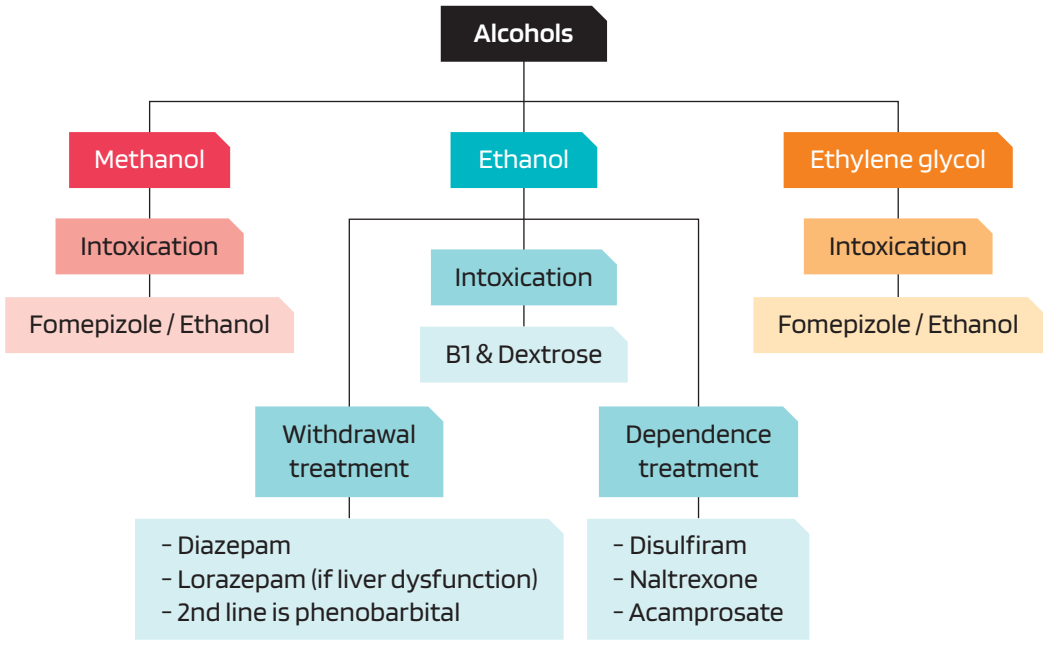
Other ion channels in the nervous system bind to neurotransmitters such as GABA, glycine, acetylcholine, and glutamate. Some anesthetics, anticonvulsants, sedative-hypnotics, and anticholinergic medications act on these channels.

Alcohol

Ethanol

Ethanol is a CNS depressant that acts on GABA receptors. Ethanol is converted to acetaldehyde by alcohol dehydrogenase. Acetaldehyde is converted to acetic acid by a mitochondrial enzyme called acetaldehyde dehydrogenase. Because acetaldehyde is a toxin that causes nausea, vomiting, headache, and hypotension, blocking acetaldehyde dehydrogenase accumulates acetaldehyde in the body and toxicity of alcohol is increased. **Disulfiram** blocks acetaldehyde dehydrogenase and is used to discourage ethanol ingestion. Metronidazole and some cephalosporins (cefamandole) block this enzyme and mimic disulfiram reaction.

Ethanol metabolism needs NAD^+; therefore, increased ingestion of ethanol causes a drop in NAD^+ reserve. Glycolysis requires NAD^+; thus, ethanol intake stops glycolysis and causes hypoglycemia. It also increases NADH and acetyl-CoA, both of which increase fatty acid synthesis and decrease beta-oxidation of fatty acid. The result is the accumulation of fat in the liver (fatty liver).



Ethanol, methanol and ethylene glycol intoxications

Also, high NADH stops the citric acid cycle by converting oxaloacetate to malate, which results in the accumulation of acetyl-CoA molecules made from fatty acids. Acetyl-CoA molecules turn to Ketone bodies (alcoholic ketoacidosis).
Ethanol is a mitochondrial toxin and causes lactic acidosis. Lactate competes with uric acid reabsorption in the kidneys, which increases gout attacks.

Increased reaction time, ataxia, impaired memory, and finally, coma and death are signs of alcohol toxicity.

Methanol

Alcohol dehydrogenase turns methanol into formaldehyde, which is converted into formic acid by aldehyde dehydrogenase. **Formic acid** can cause severe anion gap metabolic **acidosis** and **blindness.**

Ethylene glycol

Ethylene glycol toxicity causes oxaluria, nephropathy, and severe metabolic acidosis. **Fomepizole** is used for the treatment of both methanol and ethylene glycol toxicity.

Opioids

Morphine, hydromorphone, codeine, oxycodone, hydrocodone, heroin, methadone, meperidine, diphenoxylate, fentanyl and dextromethorphan are all opioids.
There are three receptors for opioids, including mu (μ), kappa (κ), and delta (δ). μ is for morphine, δ is for encephalin, and κ is for dynorphin.
Opioids open K^+ channels and close Ca^{2+} channels; therefore, they decrease synaptic transmission and inhibit the release of acetylcholine, norepinephrine, 5-hydroxytryptamine, glutamate, and substance P.

Clinical use of opioids

Pain: for chronic pain, use oral slow-release and for acute pain use injection
Cough: dextromethorphan
Diarrhea: loperamide and diphenoxylate
Acute pulmonary edema: morphine injection (vasodilatory effect)
Methadone: for opioid addiction because it has a very long half-life
Anesthesia: fentanyl and morphine are used in high IV doses

Toxicity

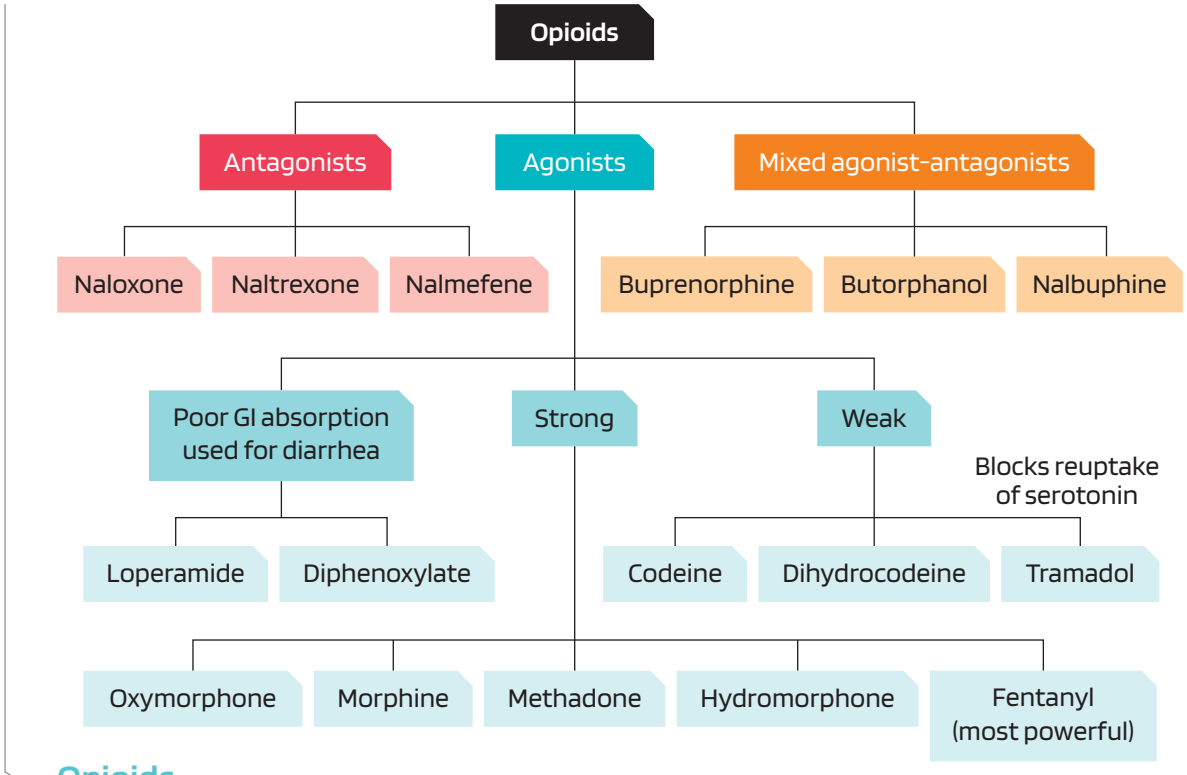
Adverse effects include respiratory depression, addiction, meiosis, constipation, and CNS depression (additive effect with other medications).
Tolerance is a common issue; however, it is not seen with miosis and constipation.
Toxicity is treated with **naloxone** or **naltrexone** (opioid receptor antagonist)
Contraction of biliary smooth muscles and sphincter of Oddi is an adverse effect of opioids, which can increase amylase and lipase level due to the reflux of biliary and pancreatic secretions.

Butorphanol

This is a **partial agonist of μ** receptors and **agonist of κ.** This is a good analgesic medication with less risk of respiratory depression. It is approved for the treatment of opioid dependence. The analgesia has a ceiling effect (it has a limit). It acts on different receptors and has both agonist and antagonist effects.

Tramadol

Tramadol is a weak opioid agonist used for **chronic pain, especially in rheumatology.** History of seizure is a contraindication for tramadol use since it **decreases seizure threshold.** It also inhibits serotonin and norepinephrine reuptake, which increases the risk of **serotonin syndrome.**



Naloxone

This opioid receptor antagonist has a short duration of action; therefore, repeated doses might be necessary to reverse the effect of opioids.

Naltrexone

It has antagonist activity against opioid receptors and has a half-life of 48 hours. Naltrexone is used in **alcohol dependency.**

Respiratory depression is less seen with partial agonists; however, their effect is not predictably reversed by naloxone.

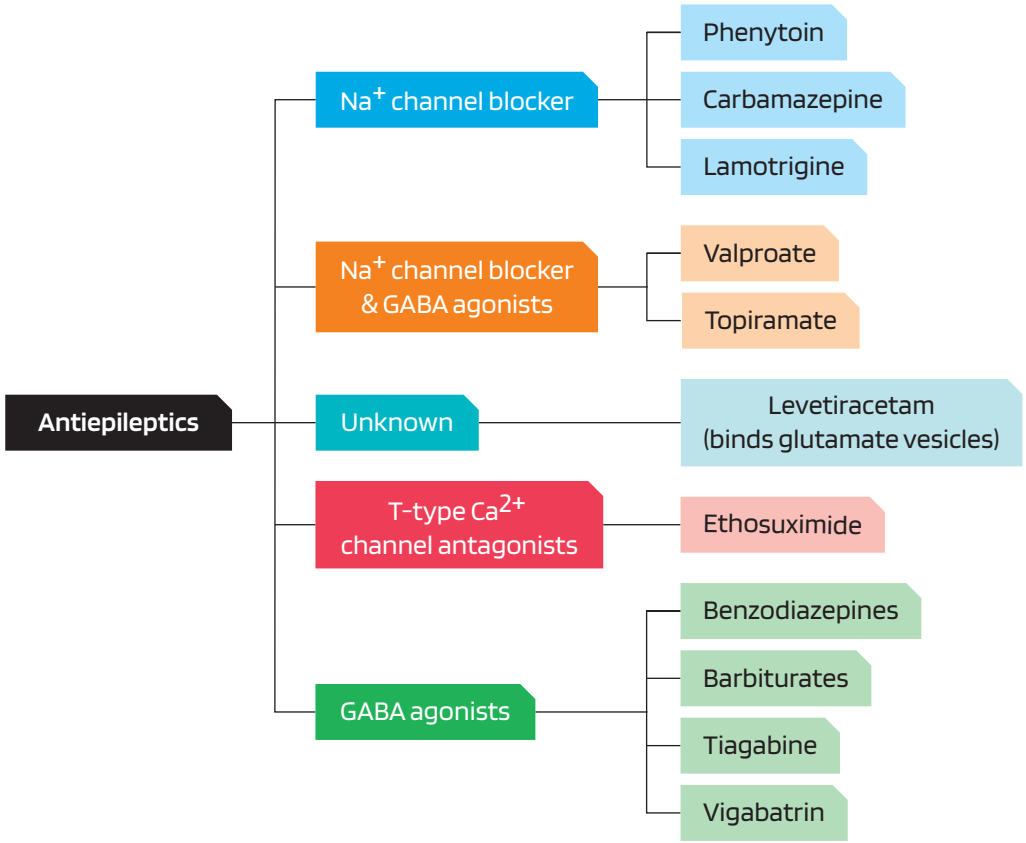
Meperidine

Meperidine has **antimuscarinic** activity and causes tachycardia. It decreases shivering in induced hypothermia used in post cardiopulmonary resuscitation patients.

Antiepileptic medications

Contrary to its name, **gabapentin** is not a GABA agonist and inhibits voltage-gated calcium channels. GABA receptor is a chloride channel. Barbiturates increase the duration of the opening chloride channel, and benzodiazepines increase the frequency of opening chloride channels. **Tiagabine** and **vigabatrin** both are GABA agonists.

Levetiracetam may modulate GABA and glutamate release and has an effect on calcium channels. It is used widely because of the low probability of adverse effects.



Antiepileptics

Medication	Adverse effects
Benzodiazepines	STD (sedation, tolerance, dependence)
Valproate	- Hepatotoxicity is rare but can be deadly - Spina bifida in fetus - GI distress - Weight gain - Teratogenicity
Lamotrigine	- Stevens-Johnson syndrome
Phenytoin	- Gingival hyperplasia - Hirsutism - Megaloblastic anemia - Fetal hydantoin syndrome - Lupus - Ataxia, nystagmus and tremor - Diplopia - Sedation - Cytochrome P450 induction
Ethosuximide	- Fatigue - GI distress - Urticaria - Stevens-Johnson syndrome
Carbamazepine	- Agranulocytosis and aplastic anemia - Liver toxicity - SIADH - Stevens-Johnson syndrome - Induction of cytochrome P450 - Diplopia, ataxia - Teratogenesis
Gabapentin	- Sedation and ataxia
Topiramate	- Sedation - Weight loss - Kidney stones

Adverse effects of antiepileptics

Simple partial (focal) seizure	- Phenytoin - Lamotrigine - Gabapentin - Valproate - Levetiracetam - Phenobarbital - Tiagabine
Complex partial (focal) seizure	- Valproate - Phenytoin - Levetiracetam - Lamotrigine - Topiramate - Gabapentin - Phenobarbital
Absence seizure	- Ethosuximide - 2nd line is valproate
Tonic-clonic seizure	- Valporate - Phenytoin - Carbamazepine - Levetiracetam - Lamotrigine
Myoclonic seizure	- Valproate - Levetiracetam
Status epilepticus	- IV diazepam / lorazepam - IV fosphenytoin for longer effect - Repeat doses - General anesthesia as last resource

Treatment of epilepsy

Treatment of status epilepticus

Lorazepam is the drug of choice for status epilepticus; however, its half-life is relatively short, and **fosphenytoin or phenytoin** is given at the same time. Gabapentin, carbamazepine, and phenobarbital can replace phenytoin if there is any contraindication to phenytoin (pregnancy and allergy are the main contraindications).

Phenobarbital is the first line of treatment in children and pregnant women except for absence seizure in children.

Lorazepam can be used in eclampsia as the second line of treatment (1st line is magnesium sulfate).

Sedative hypnotic drugs

Barbiturates

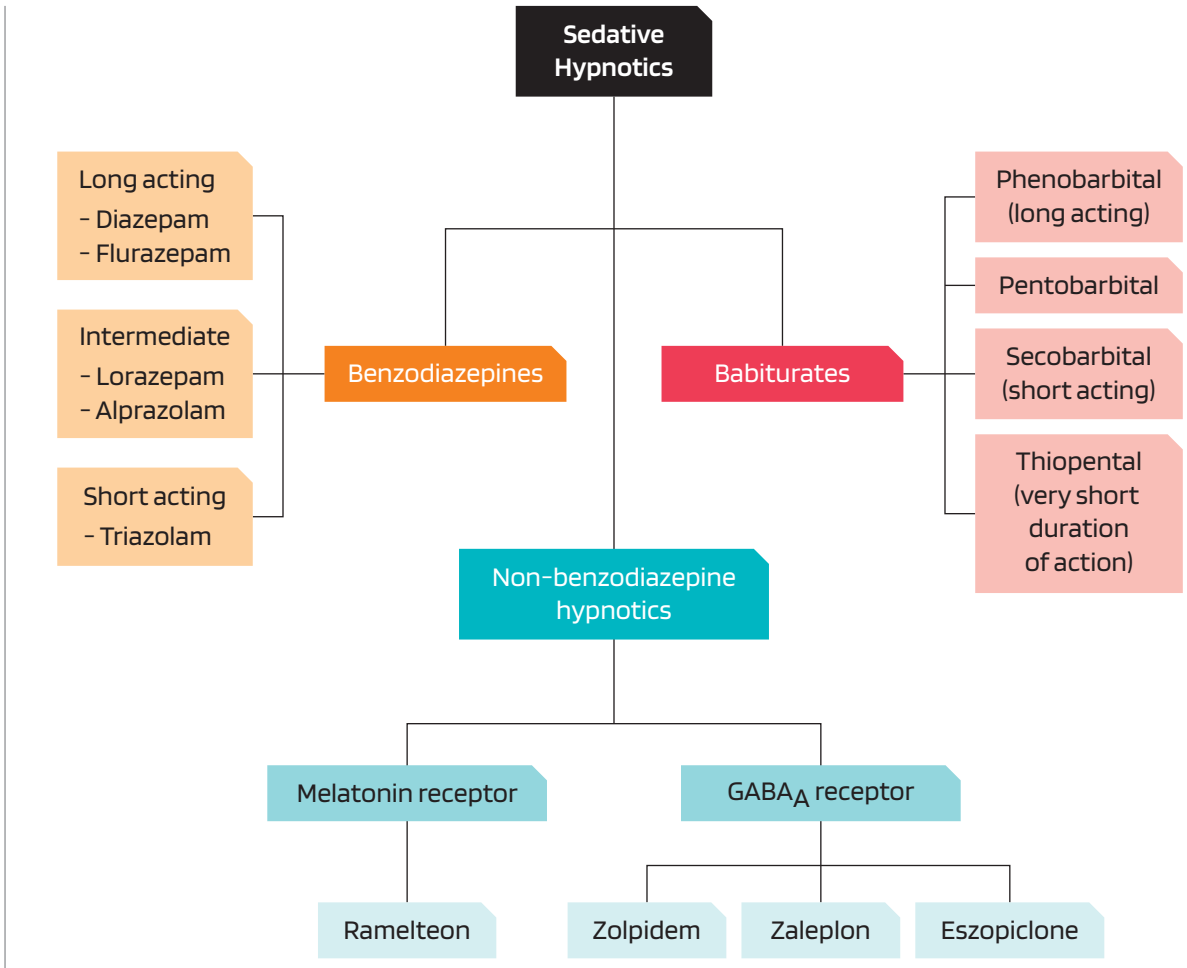
Phenobarbital, pentobarbital, thiopental, and **secobarbital** are the main members of this group of medication. They **depress the activity of midbrain reticular formation.** Their mechanism of action is through increasing the duration of chloride channel opening. They act on the GABA-A chloride channel.

Clinical use

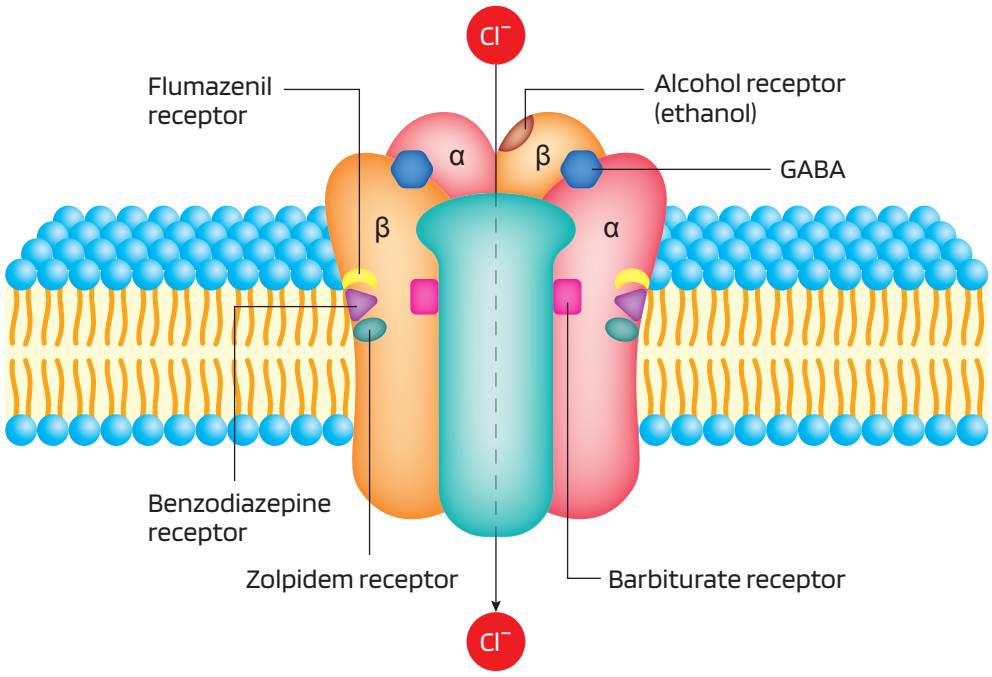
Barbiturates are used in anxiety, insomnia, seizure, and induction of anesthesia. Thiopental is used for induction of anesthesia. Barbiturates are **contraindicated in porphyria** since they activate the ALA synthase enzyme.

Toxicity

Toxicity includes STD (sedation, tolerance, and dependence), induction of cytochrome P450, cardiovascular and respiratory depression, and additives CNS depression effect with alcohol.
Overdose is treated with supportive therapy to assist respiration and increase blood pressure.



Sedative-hypnotic drugs



GABAA receptor

Benzodiazepine

They increase the frequency of chloride channel opening and decrease REM sleep. Important benzodiazepines include **diazepam, lorazepam, triazolam, temazepam, oxazepam, midazolam, chlordiazepoxide, and alprazolam.**

Alcohol, benzodiazepines, and barbiturates have the same receptor (GABA-A), which is a ligand-gated chloride channel.

Triazolam, oxazepam, and midazolam are short-acting and have the highest addictive potential.

Insomnia	Used less nowadays because of zolpidem and similar medications
Anxiety management	Used for acute anxiety Quick management of panic attacks
Muscle relaxant	Diazepam
Alcohol withdrawal	Chlordiazepoxide and diazepam are mainly used because of long duration of action. Lorazepam used in liver dysfunction.
Status epilepticus and other types of seizure	Diazepam for status epilepticus clonazepam and phenobarbital are used for epilepsy
Adjunct for sedation and amnesia during anesthesia	Thiopental and midazolam
Bipolar disorders	Clonazepam

Clinical use of sedative-hypnotics

Clinical use

Status epilepticus (lorazepam or diazepam), anxiety (rapid control of anxiety), spasticity, delirium tremens, night terrors, sleepwalking, insomnia (triazolam, flurazepam), muscle relaxation (midazolam, diazepam), and they induce amnesia in general anesthesia.

Toxicity

Toxicity includes STD (sedation, tolerance, dependence), additive effect with alcohol to cause CNS depression, and respiratory depression, which is less likely compared with barbiturates.
Overdose is treated with **flumazenil.**

Non-benzodiazepine hypnotics

Zolpidem, zaleplon, and **eszopiclone** are used for insomnia. They act on the benzodiazepine receptor subtype (BZ1). Dependence is less compared with benzodiazepines, and there is less amnesia and psychomotor depression the following day. This is because they are rapidly metabolized by liver enzymes.

Toxicity

Ataxia, headache, and confusion are the major adverse effects. Toxicity is treated with **flumazenil.**

Anesthetics

These medications are lipid-soluble and usually pass the blood-brain barrier easily. Otherwise, they have to be actively transported through the blood-brain barrier. If an agent shows low solubility in blood, anesthesia is achieved quickly. **N2O has low lipid solubility (low potency) and has low blood solubility (fast induction).**
If the anesthetic is more soluble in tissue (fat), it takes longer to achieve anesthesia since blood flow to fat is not high. Halothane is highly soluble in blood, and it takes longer to see its effect. Halothane is not available in the United States.
Minimal alveolar concentration (**MAC**), which depends on the age of the patients, is the dose that can cause general anesthesia in 50% of the population.
The respiratory rate and tidal volume determine the gas tension. The higher the solubility of the gas, the lower is the onset of action, and it takes longer for the gas to saturate the blood.
The higher the arteriovenous concentration gradient, the slower is the onset of action. Three types of anesthetics are inhaled, intravenous, and local.

IV anesthetics

Barbiturates

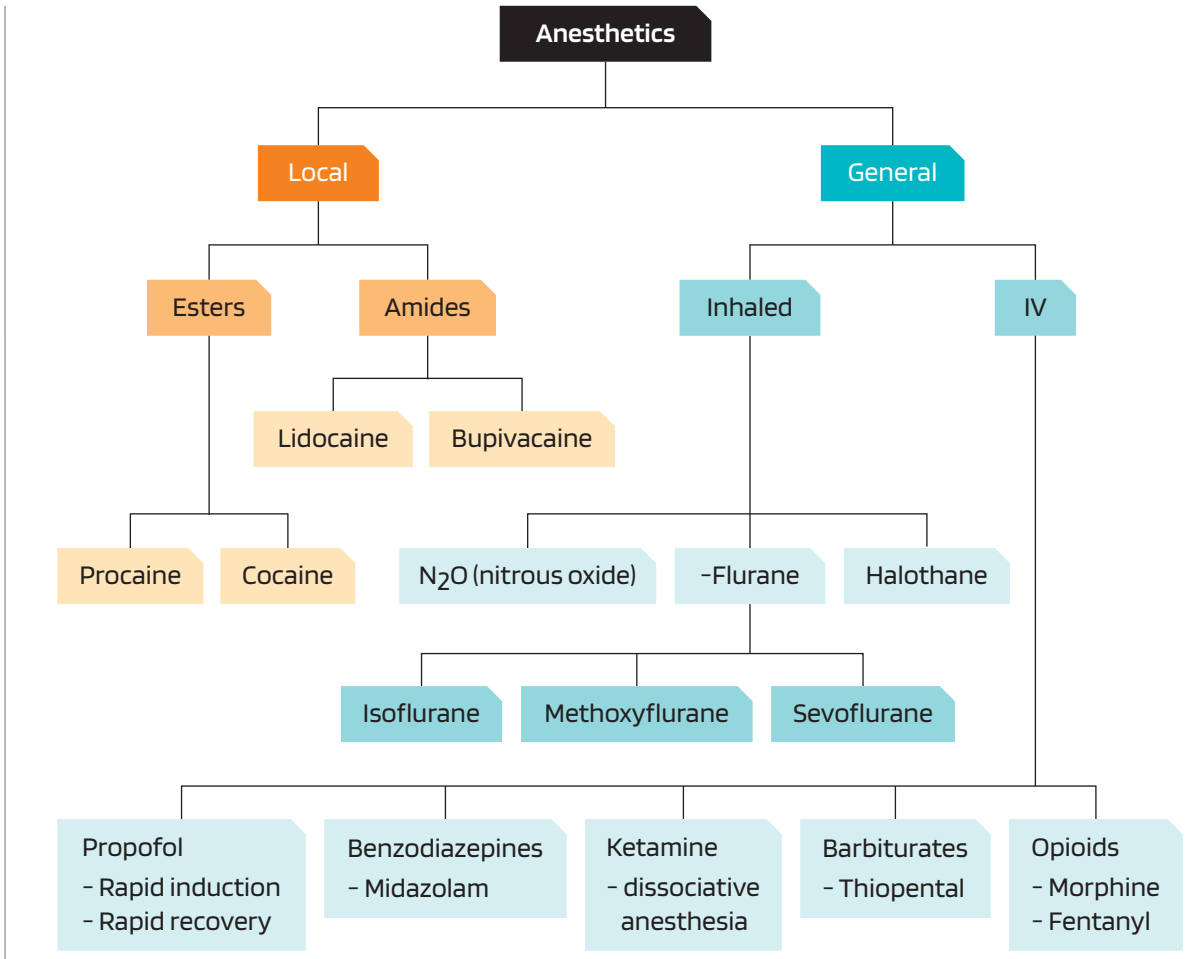
Thiopental is highly lipid-soluble and is used for induction of anesthesia, and short surgical procedures. It decreases cerebral blood flow and has rapid distribution into skeletal muscles and adipose tissues.

Benzodiazepines

Midazolam is commonly used for endoscopy and with other general anesthetics. It causes amnesia, respiratory depression, and hypotension.

Ketamine

Ketamine increases cerebral blood flow and is a cardiostimulant. It blocks NMDA receptors and induces dissociative anesthesia. Dissociative anesthesia is characterized by catalepsy, catatonia, and amnesia without complete loss of consciousness. Ketamine is used in children frequently. The addition of benzodiazepines can help with decreasing hallucinations and bad dreams.



Anesthetics

Opiate

Fentanyl and **morphine** are used with other general anesthetics.

Propofol

Propofol is used for the rapid induction of anesthesia and short procedures. It potentiates the GABA effect. Propofol causes rapid induction and rapid recovery anesthesia; it has antiemetic action and is used in many outpatient surgeries. Propofol may cause marked hypotension.

General anesthetics

Inhaled anesthetics include

- **isoflurane, sevoflurane, methoxyflurane**
- **nitrous oxide**
- **halothane** (not available in the US anymore)

The exact mechanism of action is unknown; however, they cause respiratory depression, nausea, vomiting, increase cerebral blood flow, and cause myocardial depression.

Methoxyflurane causes nephrotoxicity, enflurane increases the probability of seizure, halothane causes hepatotoxicity and all of them can cause **malignant hyperthermia.** Nitrous oxide can cause the expansion of trapped gas, which causes damage in body cavities and the eyes.

Local anesthetic

Esters

Procaine, **cocaine** & **tetracaine** are esters.

Amides

Lidocaine, bupivacaine & **mepivacaine** are amides.

Both amides and esters, block Na^+ channels and particularly the rapidly firing ones. Their tissue penetration is limited in infected tissues & abscesses (acidic environment), and higher doses are required.

Smaller fibers and myelinated fibers are blocked first. First, feeling the pain is lost. Then sensing temperature is gone. Touch and pressure are the last.

Local anesthetics **preparations contain epinephrine**, which causes local vasoconstriction. In this way, they in the area longer with less systemic absorption, and there is less bleeding. Only cocaine has vasoconstrictive activity and is not given with epinephrine.

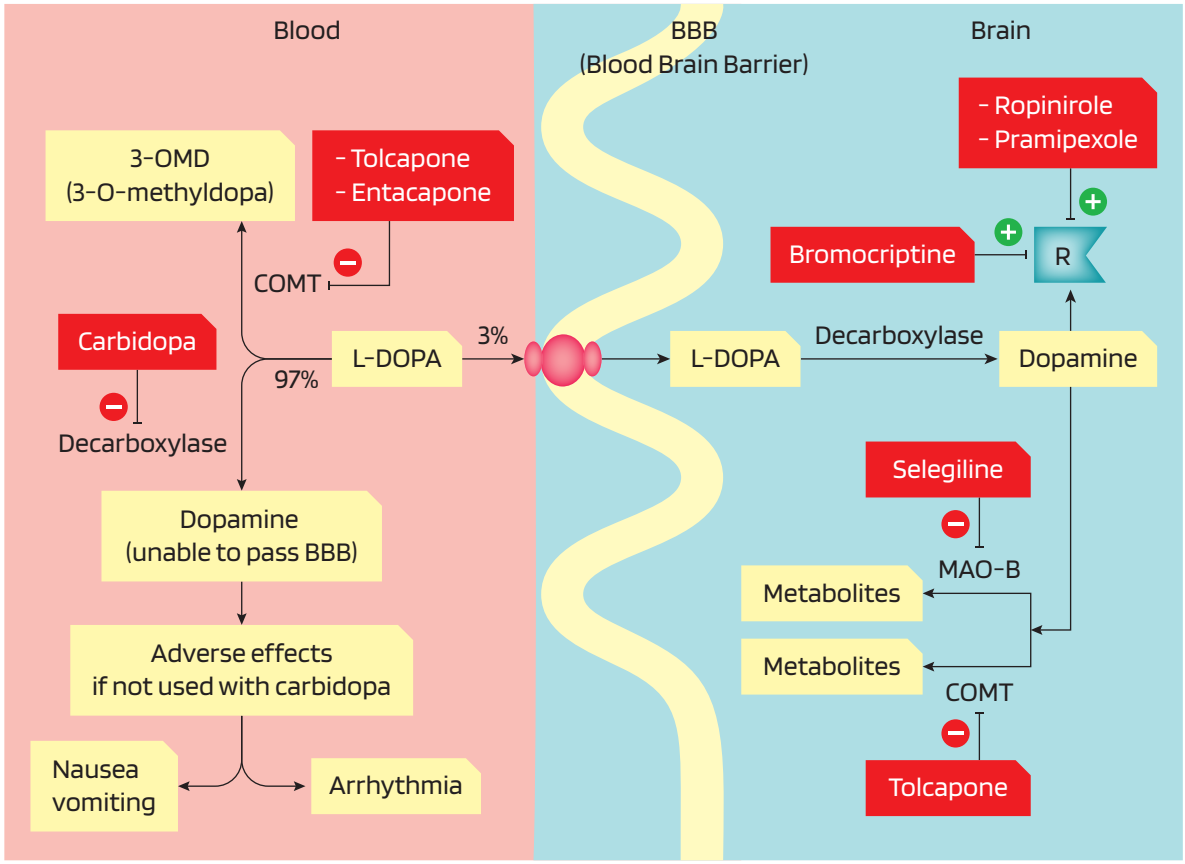
Clinical use

Spinal anesthesia and minor surgical procedures are the main indications of local anesthetics.

Side effects include cardiovascular toxicity, changes in blood pressure, arrhythmia, and CNS excitation.

If there is a history of allergy to esters, use amides.

Treatment of Parkinson's disease



Medications used in Parkinson's disease

In **mild forms**, and in **under 60**, use benztropine or trihexyphenidyl to decrease tremor and rigidity. In **over 60**, amantadine is the drug of choice because benztropine and trihexyphenidyl have anticholinergic effects.
Levodopa/carbidopa is used in moderate diseases; **bromocriptine** and **pramipexole** or **ropinirole** are used in resistance or severe cases.
Selegiline (MAO-B inhibitor), and **tolcapone** (COMT Inhibitor) are also used in Parkinson's disease.
Carbidopa is a peripheral decarboxylase inhibitor that is used to increase the bioavailability of L-dopa.

Medications used in other movement disorders

Medication used in tremor

We can use **propranolol** and other beta-blockers to treat essential and physiological tremor. In patients with pulmonary diseases, use selective beta-blockers, including metoprolol. Antiepileptics like topiramate and primidone have been used for essential tremor.

Treatment of Alzheimer's disease

Anticholinesterases, including galantamine, rivastigmine & donepezil, help in the early stages of Alzheimer's disease. Toxicity includes dizziness, insomnia, and nausea.
Memantine blocks NMDA and prevents excitotoxicity mediated by calcium. Its adverse effect is confusion and hallucination.

Treatment of Huntington's disease

In Huntington's disease, dopamine is increased; therefore, **haloperidol** is used to antagonize dopamine receptors. Reserpine and tetrabenazine by depleting dopamine can help in some patients.

Treatment of Tourette's syndrome

Haloperidol and other dopamine receptor blockers (D2) such as pimozide are used to treat Tourette's syndrome.

Medications used in the treatment of migraine

Sumatriptan

Sumatriptan is a **5HT 1B/1D** receptor agonist that causes vasoconstriction and inhibits trigeminal nerve activation. It is used in acute migraine and cluster headache attacks.

Coronary vasospasm is a serious adverse effect of sumatriptan.

Ergot alkaloids

Ergot alkaloids, including ergotamine, are partial serotonin agonists and partial α-agonist. They can cause **severe vasoconstriction** & limb gangrene. They cause uterine contraction and can be used in obstetric bleeding.