
DESTINATION
PHARMAGENS

The Autonomic Nervous System

- The autonomic nervous system (ANS) regulates visceral functions, i.e. functions of the internal organs such as the heart, stomach and intestines.
- The ANS is part of the peripheral nervous system and also has control over some muscles within the body.
- Within the brain, the autonomic nervous system is regulated by the hypothalamus.
- The functions of the ANS are involuntary and reflexive
- Autonomic functions include control of respiration, cardiac regulation (the cardiac control center), vasomotor activity (the vasomotor center), and certain reflex actions such as coughing, sneezing, swallowing and vomiting
- The parasympathetic and sympathetic nervous systems, along with the enteric nervous system make up the ANS.

What is the sympathetic nervous system?

- Part of the autonomic nervous system, originates in the spinal cord; specifically in the thoracic and lumbar regions.
- It controls the body's "fight or flight" responses, or how the body reacts to perceived danger

What is the parasympathetic nervous system?

- It originates in the spinal cord and the medulla and controls homeostasis, or the maintenance of the body's systems.
- The parasympathetic nervous system controls the "rest and digest" functions of the body

Comparison of functions:

Organ	PARASYMPATHETIC	SYMPATHETIC
General Body Response	Counterbalance; restores body to state of calm.	Body speeds up, tenses up, becomes more alert. Functions not critical to survival shut down.
Cardiovascular System (heart rate)	***Decreases heart rate***	***Increases contraction, heart rate***
Pulmonary System (lungs)	Bronchial tubes constrict	Bronchial tubes dilate
Musculoskeletal	Muscles relax	Muscles contract

System		
Pupils	Constrict	Dilate
Gastrointestinal System	Increases stomach movement and secretions	Decreases stomach movement and secretions
Salivary Glands	Saliva production increases	Saliva production decreases
Adrenal Gland	***No involvement***	***Releases adrenaline***
Glycogen to Glucose Conversion	No involvement	Increases; converts glycogen to glucose for muscle energy
Urinary Response	Increase in urinary output	Decrease in urinary output

Cholinergic drugs

Muscarinic actions

Target cell > action > consequences

1. **Heart:**
   The cardiac receptors are of M2 subtype.
- ACh **hyperpolarizes** the **SA nodal cells** and decreases the **rate of diastolic depolarization.**
- At the **A-V node and His-Purkinje fibres refractory period (RP)** is increased and **conduction is slowed: P-R interval increases**
- The **force of atrial contraction** *is markedly reduced* and **RP** of **atrial fibres** is abbreviated.

2. **Blood vessels**
- All **blood vessels** are **dilated**, though only few (skin of face, neck, salivary glands) receive cholinergic innervation.
- **Fall in BP and flushing,** especially in the blush area occurs.
- Muscarinic (M3) receptors are present on vascular endothelial cells: **vasodilatation** is primarily mediated through the release of an ***endothelium dependent relaxing factor*** **(EDRF)** which is **nitric oxide (NO).**

3. **Smooth muscle**
- **Smooth muscle** in most organs is **contracted** (mainly through **M3 receptors**).
- **Tone and peristalsis in the gastrointestinal tract is increased and sphincters relax >abdominal cramps and evacuation of bowel.**
- **Peristalsis** in **ureter** is increased. The **detrusor muscle contracts** while the **bladder trigone and sphincter relaxes** > **voiding of bladder.**
- Bronchial muscles constrict, asthmatics are highly sensitive > dyspnoea

4. **Glands**
- Secretion from all **parasympathetically innervated glands** is increased *via* **M3 and some M2** receptors: **sweating, salivation, lacrimation, tracheobronchial and gastric secretion > ACTIONS TO BE MENTIONED**
- The effect on pancreatic and intestinal glands is not marked.

5. **Eye**
- **Contraction** of **circular muscle of iris** > **miosis**
- **Contraction** of **ciliary muscle** > **spasm of accommodation, increased outflow facility, reduction in intraocular tension**

Nicotinic action

1. Autonomic ganglia

Both sympathetic and parasympathetic ganglia are stimulated.

2. Skeletal muscles

Iontophoretic application of ACh to muscle endplate causes contraction of the fibre.

Intraarterial injection of high dose can cause twitching and fasciculations, but i.v. injection is generally without any effect (due to rapid hydrolysis of ACh).

USES of Anti CholineEsterases

1. **As miotic**
   - To reverse the effect of mydriatics after **refraction testing**
   - To prevent formation of **adhesions** between **iris and lens or iris and cornea**, and even to break those which have formed due to **iritis, corneal ulcer**, etc.—a miotic is alternated with a mydriatic.
   - However, they are effective in **aphakic glaucoma**.
   - **IN GLAUCOMA**
     - **Pilocarpine** is the preferred miotic
     - **Physostigmine** (0.1%) is used only to supplement pilocarpine.
2. **Postoperative paralytic ileus/urinary retention**

This can be relieved by **0.5–1 mg s.c. neostigmine**, provided *no organic obstruction* is present.

3. **Postoperative decurarization**

Neostigmine 0.5–2.0 mg i.v., preceded by **atropine** to block muscarinic effects, rapidly reverses muscle paralysis induced by competitive neuromuscular blockers.

4. **Cobra bite**

Cobra venom has a curare like **neurotoxin**. Though specific **antivenom serum** is the primary treatment, **neostigmine + atropine** prevent respiratory paralysis.

5. **Belladonna poisoning**

Physostigmine 0.5–2 mg i.v. repeated as required is the specific antidote for poisoning with belladonna or other anticholinergics. It penetrates **blood-brain barrier** and **antagonizes both central and peripheral actions**. However, physostigmine often itself **induces hypotension and arrhythmias**; is employed only as a last resort. Neostigmine does not block the central effect, but is less risky.

6. Myasthenia gravis : It is autoimmune disorder

development of antibodies directed to **nicotinic$_M$ receptors (NR)** at the **muscle endplate** > **reduction in number of free NM cholinoceptors** to 1/3 of normal or less and **structural damage to the neuromuscular junction** > **weakness and easy fatigability on repeated activity, with recovery after rest**.

Neostigmine and its congeners improve muscle contraction by allowing ACh released from prejunctional endings to accumulate and act on receptors over a larger area, and by directly depolarizing the endplate.

Generally, i.v. methylprednisolone pulse therapy is given while anti-ChEs are withheld for 2–3 days followed by their gradual reintroduction.

Individual drug account of anticholinesterases:

- Physostigmine: (tertiary amine derivative obtained from natural source)

Well absorbed from GIT and corneal sites (hence used in form of eye drops in glaucoma, which are **freshly prepared before use**)

- Neostigmine: (quartneruy amine derivative obtained from synthetic source)

Poorly absorbed from GIT and poor corneal penetration.

- Pyridostigmine:

Less potent than neostigmine. Poorly absorbed from GIT and poor corneal penetration.

- Ambegonium: longer acting analogue
- Edrophonium:

Similar to neostigmine

Brief duration of action (10-30 min)

Used as diagnostic agent in Mysthania gravis.

- Tachrine:

Iipophilic derivative , hence crosess BBB

Has longer duration of action

- Cerebroselective agents:

Used for alzimers disease

Rivastigmine, galantamine, donepezile, Tachrine.

- Anticholine esterase poisoning:

Cholinesterase activators as specific antidote- **Pralidoxime (2-PAM), diacetyl monoxime (DAM)**

ANTICHOLINERGIC PHARMACOLOGICAL ACTIONS

1. **CNS**

Atropine has an **overall CNS stimulant action**. However, these effects are not appreciable at low doses which produce only peripheral effects because of restricted entry into the brain.

Hyoscine produces **central effects (depressant)** even at low doses.

• Atropine stimulates many medullary centres —vagal, respiratory, vasomotor.

• It **depresses vestibular excitation** **located in** **medulla** and has **anti-motion sickness** property.

The site of this action is not clear—probably there is a **cholinergic link in the vestibular pathway**, or it is exerted at the cortical level.

• By **blocking the relative cholinergic over-activity** in **basal ganglia**, it **suppresses tremor and rigidity of Parkinsonism.**

• High doses cause cortical excitation, restlessness, disorientation, hallucinations and delirium followed by respiratory depression and coma.

2. **CVS**

Heart

The most prominent effect of atropine is on **heart SA node** through which **vagal tone decreases HR** to cause **tachycardia**. It is due to **blockade of M2 receptors**. Atropine **abbreviates refractory period** of **A-V node** and facilitates **A-V conduction**, especially if it has been depressed by high vagal tone.

P-R interval is shortened. Higher the existing vagal tone— more marked is the tachycardia (maximum in young adults, less in children and elderly).

On i.m./s.c. injection transient initial bradycardia often occurs. Earlier believed to be due to stimulation of vagal centre, it is now thought to be caused by blockade of muscarinic autoreceptors (M1) on vagal nerve endings augmenting ACh release.

This is suggested by the finding that selective M1 antagonist pirenzepine is equipotent to atropine in causing bradycardia as are atropine substitutes which do not cross blood-brain barrier.

BP _Since cholinergic impulses are not involved in maintenance of vascular tone, atropine does not have any consistent or marked effect on BP. Atropine blocks vasodepressor action of cholinergic agonists. Tachycardia and vasomotor centre stimulation tend to raise BP, while histamine release and direct vasodilator action (at high doses) tend to lower BP.

3. **Eye**

The autonomic controls of **iris muscles** and the action of mydriatics as well as miotics

Topical instillation of atropine acts on **iris muscles** causes **mydriasis**, **abolition of light reflex and cycloplegia lasting 7–10 days**. This results in **photophobia and blurring of near vision**. The **ciliary muscles** recover somewhat earlier than **sphincter pupillae**. The **intraocular tension** tends to rise, especially in narrow angle glaucoma; conventional systemic doses produce minor ocular effects.

4. **Smooth muscles**

All **visceral smooth muscles** that receive parasympathetic motor innervation are **relaxed** by atropine **(M3 blockade). Tone and amplitude of contractions** of **stomach and intestine** are **reduced**; the **passage of chyme is slowed—constipation may occur**, **spasm** may be relieved.

However, peristalsis is only incompletely suppressed because it is primarily regulated by local reflexes and other neurotransmitters (5-HT, enkephalin, etc.) as well as hormones are involved.

Enhanced motility due to injected cholinergic drugs is more completely antagonised than that due to vagal stimulation. **Atropine** causes **bronchodilation** and **reduces airway resistance, especially in COPD and asthma patients.**

Inflammatory mediators like **histamine, PGs and kinins** increase **vagal activity** in addition to their direct action on **bronchial muscle and glands leading to constriction of bronchial airways**. Atropine attenuates their action by antagonizing the reflex vagal component.

Atropine has **relaxant action** on **ureter and urinary bladder; urinary retention** can occur in older males with **prostatic hypertrophy.** However, the **Atropine** can be beneficial for **increasing bladder capacity** and controlling **detrusor hyperreflexia** in **neurogenic bladder/enuresis.**

Relaxation of **biliary tract** is less marked and effect on **uterus** is minimal.

5. **Glands**

Atropine markedly **decreases sweat, salivary, tracheobronchial and lacrimal secretion (M3 blockade)**. **Skin and eyes become dry, talking and swallowing may be difficult**. **Atropine decreases secretion of acid, pepsin and mucus in the stomach**, but the **primary action is on volume of secretion so that pH of gastric contents may not be elevated unless diluted by food**. Since **bicarbonate secretion is also reduced**, **rise in pH of fasting gastric juice is only modest**. Relatively higher doses are needed and atropine is less efficacious than **H2 blockers** in reducing acid secretion. **Intestinal and pancreatic secretions** are not significantly reduced. Bile production is not under cholinergic control, so not affected.

6. **Body temperature**

Rise in body temperature occurs at higher doses. Children are highly susceptible to **atropine fever**. It is due to both **inhibition of sweating as well as stimulation of temperature regulating centre in the hypothalamus.**

7. **Local anaesthetic:** Atropine has a **mild anaesthetic action** on the **cornea**.

The sensitivity of different organs and tissues to atropine varies and can be graded as—

Saliva, sweat, bronchial secretion > eye, bronchial muscle, heart > smooth muscle of intestine, bladder > gastric glands and smooth muscle.

USES OF ANTICHOLINERGIC DRUGS

1. As antisecretory

- To check excessive sweating or salivation, e.g. in ***parkinsonism***.
- ***Pulmonary embolism (blockage in lung artery)***: These drugs benefit by **reducing reflex secretions**.
- ***Peptic ulcer (ulcers in duodenum)*:** Atropinic drugs **decrease gastric secretion** (fasting and neurogenic phase, but little effect on gastric phase) and afford symptomatic relief in peptic ulcer, though effective doses always produce side effects.
- ***Preanaesthetic medication***
    - When **irritant general anaesthetics** (ether) are used, **prior administration** of anticholinergics (atropine, hyoscine, glycopyrrolate) is imperative to limit the increased salivary and tracheobronchial secretions.
    - However, with increasing use of nonirritating anaesthetics (**halothane**) the requirement has decreased, though atropine may still be employed because halothane sensitizes the heart to **NA mediated ventricular arrhythmias** which are especially prone to occur during vagal slowing.

2. **As antispasmodic**

- **Intestinal and renal colic, abdominal cramps**: symptomatic relief is afforded if there is no mechanical obstruction.
- Nervous and drug induced diarrhoea, functional diarrhoea
- **Pylorospasm, gastric hypermotility, gastritis, nervous dyspepsia.**
- To relieve **urinary frequency and urgency, enuresis in children**. Oxybutynin, tolterodine and flavoxate have demonstrated good efficacy, but dry mouth and other anticholinergic effects are dose limiting.

3. **Bronchial asthma, asthmatic bronchitis, COPD**

- **Orally administered** atropinic (anticholinergics) drugs are **bronchodilators**
- **Inhaled ipratropium bromide** has been found to be especially effective in **asthmatic bronchitis and COPD**, **though less so in bronchial asthma. Given by aerosol, it has been shown not to decrease respiratory secretions or to impair mucociliary clearance, and there are few systemic side effects**. **Thus, it has a place in the management of COPD.**
- **Its time course of action makes it more suitable for regular prophylactic use rather than for control of acute attacks.**
- The additive bronchodilator action with adrenergic drugs is utilized to afford relief in acute exacerbation of asthma / COPD by administering a combination of nebulized ipratropium and β2 agonist through a mask.

4. **As mydriatic and cycloplegic**

- ***Diagnostic purpose:***
    - **For testing error of refraction**, both mydriasis and cycloplegia are needed **(Tropicamide having briefer action has now largely replaced homatropine for this purpose)**
    - These drugs do not cause sufficient cycloplegia in children: more potent agents like atropine or hyoscine have to be used. Atropine ointment (1%) applied 24 hours and 2 hours before is often preferred for children below 5 years.
    - To facilitate **fundoscopy** only mydriasis is needed; a short acting antimuscarinic may be used, but **phenylephrine** is preferred
- ***Therapeutic***
    - **Atropine**, because of its long lasting **mydriatic-cycloplegic and local anodyne action (pain relief action)** on **cornea**, is very valuable in the treatment of **iritis, iridocyclitis, choroiditis, keratitis and corneal ulcer.**

5. As cardiac vagolytic

- **Atropine** is useful in counteracting **bradycardia and partial heart block** in selected patients where increased vagal tone is responsible, e.g. in some cases of myocardial infarction, digitalis toxicity.

- However, cardiac arrhythmias or ischaemia may be precipitated in some cases.

6. For central action

- ***Parkinsonism:*** Central anticholinergics are less effective than levodopa; They are used in mild cases, in drug induced extrapyramidal syndromes and as adjuvant to levodopa.
- ***Motion sickness:*** Hyoscine is the most effective drug for motion sickness.
- **Hyoscine and other anticholinergics are not effective in other types of vomiting.**
- **Hyoscine** has been used to produce **sedation and amnesia during labour (twilight sleep)** and to control maniacal states.

ATROPIN SUBSTITUTES - Quarternay compounds

- Hyoscine butyl bromide: used in **esophageal and git spastic condition**
- Atropine methonitrate: used in **adbominal colics and hyperacidity condition**
- Ipratropium bromide: (given by inhalation)**DOC for COPD** because DOESN'T AFFECT MUCOCILLIARY CLEARANCE
- Tiotropium bromide: Congener of ipratropium **DOC for COPD**
- Propantheline: used in **PU (USE DECLINED DUE TO AVAILABILITY OF H2 BLOCKERS AND PPI's)**
- Oxyphenonium: used in **PU and GIT HYPERMOTILITY**
- Clidnium: ANTISECRETORY-ANTISPSMODIC DRUG; USED IN combination with benzodiazepam for **nervous dyspepsia, GASTRIC IBS, PU.**
- Pipenzolate methyl bromide: **FLATUALANT DYSPEPSIA, ABDOMINAL CRAMPS, INFANTAILE COLICS.**
- Isopropamide: **GIT PROBLEMS ASSOCIATED WITH MENTAL DISORDER/ EMOTIONAL DISTURBANCES**
- Glycopyrrolate: **POTENT AND RAPIDLY ACTING, USED AS PREANAESTHETICS**CLICK HERE

ATROPIN SUBSTITUTES - Tertiary amine:

Dicyclomine: **nocturnal ensuresis, spina bifida neurogenic bladder.**

Valenthamate: **overactive bladder**

Pirenzepine : **nocturnal ensuresis**

Adrenergic System and Drugs

Adrenergic (more precisely 'Noradrenergic') transmission is restricted to the sympathetic division of the ANS. There are three closely related endogenous catecholamines (CAs).

Noradrenaline **(NA)** It acts as transmitter at **postganglionic sympathetic sites** (except sweat glands, hair follicles and some vasodilator fibres) and in certain areas of brain.

Adrenaline **(Adr)** It is secreted by **adrenal medulla** and may have a transmitter role in the brain.

Dopamine **(DA)** It is a major transmitter in **basal ganglia, limbic system, CTZ, anterior pituitary,** etc. and in a limited manner in the periphery.

Synthesis of CAs

Catecholamines are synthesized from the amino acid phenylalanine. **Tyrosine hydroxylase** is the rate limiting enzyme and its inhibition by **α - methyl-p-tyrosine** results in depletion of CAs; this can be used in **pheochromocytoma** before surgery and in inoperable cases.

Storage of CAs

NA is stored in synaptic vesicles or 'granules' within the adrenergic nerve terminal. The vesicular membrane actively takes up DA from the cytoplasm and the final step of synthesis of NA takes place inside the vesicle which contains dopamine β- hydroxylase.

NA is then stored as a complex with **ATP (in a ratio of 4 : 1)** which is adsorbed on a protein ***chromogranin.***

In the adrenal medulla the NA thus formed within the **chromaffin granules** diffuses out into the cytoplasm, is methylated and Adr so formed is again taken up by a separate set of granules.

The cytoplasmic pool of CAs is kept low by the enzyme monoamine oxidase (MAO) present on the outer surface of mitochondria.

Release of CAs

The nerve impulse coupled release of CA takes place by *exocytosis* and all the vesicular contents (NA or Adr, ATP, β-hydroxylase, chromogranin) are poured out.

Uptake of CAs

There is a very efficient mechanism by which NA released from the nerve terminal is recaptured. This occurs in 2 steps— ***Axonal uptake & Vesicular uptake***

Axonal uptake

An active amine pump **norepinephrine transporter (NET)** is present at the **neuronal membrane** which transports NA by a **Na+ coupled mechanism.** It takes up NA at a higher rate than Adr and had been labelled ***uptake-1***. The indirectly acting sympathomimetic amines like **tyramine**, but not isoprenaline, also utilize this pump for entering the neurone. This uptake is the most important mechanism for terminating the postjunctional action of NA. This pump is inhibited by **cocaine, desipramine** and few other drugs.

Vesicular uptake

The membrane of **intracellular vesicles** has another amine pump the **'vesicular monoamine transporter' (VMAT-2)**, which transports CA from the cytoplasm to within the storage vesicle. The VMAT-2 transports monoamines by **exchanging with H+ ions.** The vesicular NA is constantly leaking out into the axoplasm and is recaptured by this mechanism. This carrier also takes up DA formed in the axoplasm for further synthesis to NA. Thus, it is very important in maintaining the NA content of the neurone. This uptake is inhibited by **reserpine**, resulting in depletion of CAs.

5. Metabolism of CAs

Part of the NA leaking out from granules into cytoplasm as well as that taken up by axonal transport is first attacked by MAO, while that which diffuses into circulation is first acted upon by catechol-o-methyl transferase (COMT) in liver and other tissues.

Adrenergic receptors

Adrenergic receptors are membrane bound G-protein coupled receptors which function primarily by increasing or decreasing the intracellular production of second messengers cAMP or IP3/DAG.

THERAPEUTIC USES OF ADRENERGIC AGONISTS

1. Vascular Uses

(i) ***Hypotensive states***

- (shock, spinal anaesthesia, hypotensive drugs) One of the **pressor agents** can be used along with **volume replacement** for **neurogenic and haemorrhagic shock**; also as an expedient measure to maintain cerebral circulation for other varieties of shock.

- **Adr 0.5 mg injected promptly i.m. is the drug of choice in anaphylactic shock.** It not only raises BP, but counteracts bronchospasm/ laryngeal edema that may accompany. **Because of the rapidity and profile of action Adr is the only life saving measure.**
- **Oral ephedrine** has been used to treat **postural hypotension due to autonomic neuropathy (diabetes, parkinsonism, idiopathic) or advanced age.**

(ii) ***Along with local anaesthetics***

- **Adr** 1 in 200,000 to 1 in 100,000 for **infiltration, nerve block and spinal anaesthesia. Duration of anaesthesia is prolonged and systemic toxicity of local anaesthetic is reduced. Local bleeding is minimised.**

(iii) ***Control of local bleeding***

- (From skin and mucous membranes) **epistaxis**: compresses of **Adr** 1 in 10,000, **phenylephrine/ephedrine** 1% soaked in cotton can control **arteriolar and capillary bleeding.**
- **NA** 8 mg in 100–200 ml saline put in stomach through a tube can control bleeding from **gastric erosions and stress ulcers.**

(iv) ***Nasal decongestant***

- In **colds, rhinitis, sinusitis, blocked nose or eustachian tube**—one of the α-agonists is used as nasal drops. Shrinkage of mucosa provides relief, but after-congestion, atrophy of mucosa on prolonged use are still a problem.
- The imidazolines should be used in lower concentrations in infants and young children, because they are more sensitive to central effects of these drugs.

(v) *Peripheral vascular diseases* like Buerger's disease, Raynaud's phenomena, diabetic vascular insufficiency, gangrene, frost bite, ischaemic ulcers, night leg cramps, cerebral vascular inadequacy : vasodilators including isoxsuprine have been used, but are far from satisfactory in most cases, because often the capacity of the affected vessels to dilate is severely limited, and ischaemia itself is a potent vasodilator.

2. Cardiac uses

(i) ***Cardiac arrest*** **(drowning, electrocution, Stokes-Adams syndrome and other causes)** - **Adr** may be used to stimulate the heart; i.v. administration is justified in this setting with external cardiac massage.

(ii) ***Partial or complete A-V block*** - **Isoprenaline** may be used as temporary measure to maintain sufficient ventricular rate.

(iii) ***Congestive heart failure (CHF)***-**Adrenergic inotropic drugs** are not useful in the routine treatment of CHF. However, controlled short term i.v. infusion of DA/dobutamine can tide over acute cardiac decompensation during myocardial infarction, cardiac surgery and in resistant CHF.

3. Bronchial asthma

Adrenergic drugs, especially β2 stimulants are the primary drugs for relief of reversible airway obstruction

4. Allergic disorders

Adr is a physiological antagonist of histamine which is an important mediator of many acute hypersensitivity reactions. It affords quick relief in **urticaria, angioedema**; is life saving in **laryngeal edema and anaphylaxis**.

It is ineffective in delayed, retarded and other types of allergies, because histamine is not involved.

5. Mydriatic

Phenylephrine is used to facilitate fundus examination; cycloplegia is not required.

It tends to reduce intraocular tension in wide angle glaucoma.

The ester prodrug of Adr **dipivefrine** is a second choice/adjuvant drug for open angle glaucoma

6. Central uses

(i) ***Hyperkinetic children*** - (minimal brain dysfunction, attention deficit hyperkinetic disorder)-**Amphetamines** have an apparently paradoxical effect to calm down hyperkinetic children.

(ii) ***Narcolepsy***- Narcolepsy is sleep occurring in fits and is adequately controlled by **amphetamines**. Development of tolerance, abuse and behavioural abnormalities are the calculated risks of such therapy. **Imipramine** like drugs are generally tried first.

(iii) ***Epilepsy*** - **Amphetamines** are occasionally used as adjuvants and to **counteract sedation caused by antiepileptics.**

(iv) ***Parkinsonism***- **Amphetamines** improve mood and reduce rigidity (slightly) but do not benefit tremor. They are occasionally used as adjuvants in parkinsonism.

(v) ***Obesity*** - The **anorectic drugs** can help the obese to tolerate a reducing diet for short periods, but do not improve the long-term outlook. Their use (for 2–3 months) may be considered in severe obesity, but not for cosmetic reasons in mild to moderate obesity.

In the absence of dietary restriction none of them has any significant weight reducing effect, and lifestyle modification is required to maintain weight loss.

7. Nocturnal enuresis in children and urinary incontinence

Amphetamine affords benefit both by its central action as well as by increasing tone of vesical sphincter.

8. Uterine relaxant

Isoxsuprine has been used in **threatened abortion and dysmenorrhoea**, but efficacy is doubtful. Selective β2 stimulants, specially **ritodrine**, infused i.v. have been successfully used to **postpone labour** but maternal morbidity and mortality may be increased due to their cardiac and metabolic actions and incidents of pulmonary edema

9. Insulin hypoglycaemia

Adr may be used an expedient measure, but glucose should be given as soon as possible.

Antiadrenergic drugs- α BLOCKERS

1. **Blockade of α1 (also α2) receptors > Blockade of vasoconstriction > reduces total peripheral resistance and causes pooling of blood in capacitance vessels > venous return and cardiac output are reduced > fall in BP.**
2. Postural reflex is interfered with > marked hypotension occurs on standing > **dizziness and syncope**.
3. Hypovolemia accentuates the hypotension. **The α blockers abolish the pressor action of Adr, which then produces only fall in BP due to β2 mediated vasodilatation**— *vasomotor reversal of Dale*. Pressor and other actions of selective α agonists (NA, phenylephrine) are suppressed.
4. Reflex tachycardia occurs due to fall in mean arterial pressure and increased release of NA due to blockade of presynaptic α2 receptors.
5. (**blockade of α2 receptors**) **nasal blood vessels and in radial muscles of iris > Nasal stuffiness and miosis**
6. **Intestinal motility** is increased due to partial inhibition of relaxant sympathetic influences— **diarrhoea** may occur.
7. Hypotension produced by α blockers can reduce renal blood flow > **g.f.r. is reduced and more complete reabsorption of Na+ and water occurs in the tubules > Na+ retention and increase in blood volume**. This is accentuated by reflex increase in renin release mediated through β1 receptors.
8. **Tone of smooth muscle in bladder trigone, sphincter and prostate** is reduced by blockade of α1 receptors (mostly of the α1A subtype) > **urine flow in patients with benign hypertrophy of prostate (BHP) is improved.**

Individual drugs account:

Phenoxybenzamine

It is lipid soluble drug, cyclises spontaneously in the body generating ethylenimnium intermediate which forms covalent bond with α receptor, leading to gradual and irreversible antagonism.

Drugs features: POSTURAL FALL IN BP (venodilation >arteriolar dilation). Shifts blood from pulmonary circuit to systemic circulation.

Natural and hydrogenated ergot alkaloids:

Amino acid alkaloids **(ergotamine and ergotoxin)** are partial agonist & antagonist of α receptors, serotonergic receptors, dopaminergic receptors. **Ergotamine**- potent vasoconstrictor, **Ergotoxin**-less potent vasoconstrictor. **Used in migraine.**

Amine alkaloid **(ergometrine)** has no α blocking activity.

Dihyroergotoxine used as cognition enhancer.

Phentolamine- rapidly acing α blocker and with short duration of action. Used in diagnosis of pheocytochroma and for control of hypertension occurring due to clonidine withdrawl.

Prazosin- It is highly selective α1 blocker, blocks sympathetic vasoconstriction, and produces fall in BP. (arteriolar dilation > venodilation). inhibits PDE (thus inhibits Camp degradation)

Terazosin, Doxazosin - Chemically and pharmacologically similar to **prazosin**. HIGHER Bioavailabilty 90%) and longer $t_{1/2}$. Used in BHP **(PROSTATIC APOPTOSIS PROMOTING PROPERTY)**

Alfuzosin- Short acting congener of prazosin. Rarely used in BHP, not approved for antihypertensive purpose.

Tamsulosin- Relatively uroselective drug (α_{1d}) used in BHP. **(DO NOT HAVE PROSTATIC APOPTOSIS PROMOTING PROPERTY).** Not approved for antihypertensive purpose.

USES OF α BLOCKERS

1. **Pheochromocytoma**

- **Phenoxybenzamine** can be used as definitive therapy for inoperable and malignant tumours.
- When surgical removal of the tumour is contemplated, it is desirable to give phenoxybenzamine orally for 1–2 weeks preoperatively and infuse it i.v. during surgery because:
    - Due to excess circulating CAs blood volume is low (they shift fluid from vascular to extravascular compartment). Treatment with α blocker normalizes blood volume and distribution of body water.
    - Handling of the tumour during surgery may cause outpouring of CAs in blood > marked rise in BP. This is prevented by phenoxybenzamine given pre and intraoperatively. Alternatively, phentolamine drip can be instituted during the operation.
    - Removal of the tumour is often attended by marked fall in BP as blood vessels dilate and the blood volume is low. This does not happen if volume has been restored before hand with the aid of an α blocker.

2. **Hypertension**

Phentolamine / Phenoxybenzamine are of great value in controlling episodes of rise in BP during **clonidine withdrawal and cheese reaction in patients on MAO inhibitors**. These are not used in essential hypertension.

3. **Benign hypertrophy of prostate (BHP)**

- The urinary obstruction caused by BHP has a static component due to increased size of prostate and a dynamic component due to increased tone of bladder neck/prostate smooth muscle.
- α1 adrenergic blockers (prazosin like): decrease tone of prostatic/bladder neck muscles.
- Since activation of α1 adrenoceptors in bladder trigone, prostate and prostatic urethra increases smooth muscle tone, their blockade relaxes these structures, reducing dynamic obstruction, increasing urinary flow rate and causing more complete emptying of bladder in many patients of BHP.

- Voiding symptoms (hesitancy, narrowing of stream, dribbling and increased residual urine) are relieved better than irritative symptoms like urgency, frequency and nocturia.
- Even with continued therapy, benefit may decline after several years due to disease progression. They may be used concurrently with finasteride.
- **Terazosin, doxazosin and tamsulosin are the peferred α1 blockers because of once daily dosing.**
- There is some evidence that **terazosin and doxazosin** promote apoptosis in prostate. **Tamsulosin** appears to cause fewer vascular side effects because of relative α1A /α1D selectivity.

4. **Secondary shock**

   Shock due to blood or fluid loss is accompanied by reflex vasoconstriction.

   If volume replacement fails to reverse this (extremities remain pale and cold, pulse pressure does not improve), therapy with an α1 blocker **(phenoxybenzamine i.v.)** can help by:

   (i) Counteracting vasoconstriction.

   (ii) Shifting blood from pulmonary to systemic circuit.

   (iii) Returning fluid from extravascular to the vascular compartment so that cardiac output improves.

5. **Peripheral vascular diseases**

   α blockers do increase skin and to some extent muscle blood flow in normal individuals, but these drugs are largely disappointing in peripheral vascular diseases when obstruction is organic (Buerger's disease). However, when vasoconstriction is a prominent feature (Raynaud's phenomenon, acrocyanosis), good symptomatic relief is afforded by prazosin or phenoxybenzamine.

6. **Congestive heart failure (CHF)** The vasodilator action of prazosin can afford symptomatic relief in CHF in the short-term, but long-term prognosis is not improved.

Antiadrenergic drugs β-blockers

1. **CVS (heart and blood vessel)**

Heart

- **Decrease in heart rate**, **force of contraction (at relatively higher doses) and cardiac output (c.o.).**
- It prolongs systole by retarding conduction so that synergy of contraction of ventricular fibres is disturbed.
- The effects on a normal resting subject are mild, but become prominent under sympathetic overactivity (exercise, emotion). Ventricular dimensions are decreased in normal subjects, but dilatation can occur in those with reduced reserve—CHF may be precipitated or aggravated.
- **Cardiac work and oxygen consumption are reduced**
- **Propranolol abbreviates refractory period of myocardial fibres and decreases automaticity— rate of diastolic depolarization in ectopic foci is reduced**
- The A-V conduction is delayed.

Blood vessels

- Propranolol blocks **vasodilatation** and fall in BP evoked by isoprenaline and enhances the rise in BP caused by Adr—there is re-reversal of vasomotor reversal that is seen after α blockade. On prolonged administration BP gradually falls in hypertensive subjects but not in normotensive.
- Total peripheral resistance (t.p.r.) is increased initially (due to blockade of β mediated vasodilatation) and c.o. is reduced—little change in BP.
- With continued treatment, resistance vessels gradually adapt to chronically reduced c.o. so that t.p.r. decreases—**both systolic and diastolic BP fall**.

2. **Respiratory tract**

- **Propranolol increases bronchial resistance by blocking β2 receptors.**
- **In asthmatics,** however, the condition is consistently worsened and a severe attack may be precipitated.

3. **CNS**

- Propranolol **suppresses anxiety** in short term stressful situations,
- But this is due to peripheral rather than a specific central action.

4. **Local anaesthetic**

- **Propranolol is as potent a local anaesthetic as lidocaine,**
- but is not clinically used for this purpose because of its **irritant property.**

5. Metabolic

- Propranolol **blocks adrenergically induced lipolysis** and consequent increase in plasma free fatty acid levels.
- **It also inhibits glycogenolysis in heart, skeletal muscles and in liver (inconsistently)**
- **recovery from insulin action is delayed.**

6. Skeletal muscle

- Propranolol inhibits adrenergically provoked tremor. This is a peripheral action exerted directly on the muscle fibres (through β2 receptors).
- It tends to reduce exercise capacity by attenuating β2 mediated increase in blood flow to the exercising muscles, as well as by limiting glycogenolysis and lipolysis which provide fuel to working muscles.

7. Eye

Instillation of propranolol and some other β blockers reduces **secretion of aqueous humor, i.o.t. is lowered**. There is no consistent effect on pupil size or accommodation.

8. Uterus

Relaxation of uterus in response to isoprenaline and selective β_2 agonists is blocked by propranolol. However, normal uterine activity is not significantly affected.

Individual drugs account

Sotalol- Non selective β blocker

Timolol- β blocker preferred for treatment of **glaucoma** topically, and by orally given for **hypertension, AP, MI**.

Other glaucoma drugs:

Betaxolol, levobunolol, cartilol, metipranolol.

Pindolol - Prominent β blocker with intrinsic sympathomimetic activity, preferred as antihypertensive.

Metoprolol - Cardioselective drug (β1)**,** S(-)**Metoprolol: Active enantiomer used in half dose.**

Atenolol - Cardioselective drug (β1), S(-)**Atenolol : Active enantiomer used in half dose.**

Acebutalol- Cardioselective drug (β1)**,** partial agonistic activity, **membrane stabilizing properties.** Rapidly metabolized to active metabolite **diacetolol** (excreted via kidney have higher half-life)

Bisoprolol - Cardioselective drug (β1), used in CHF, AP, MI.

Esmolol ultrashort acting β blocker, **inactivated by AcE. Used in different types of arrhythmia, MI.**

NO PRODUCING β BLOCKERS: CELIPROLOL AND NEBIVOLOL

CELIPROLOL- NON SELECTIVE β blocker (blocks β1 and β2). Along with β mediated vasodilation NO production adds up to antihypertensive action.

NEBIVOLOL highly selective β blocker, used as antihypertensive and in CHF.

PHARMACOLOGICAL USES OF BETA BLOCKERS

1. ***Hypertension***

β blockers are relatively mild antihypertensives. all agents, irrespective of associated properties, are nearly equally effective.

2. ***Angina pectoris***

All β-blockers benefit angina of effort. Taken on a regular schedule they decrease frequency of attacks and increase exercise tolerance.

3. ***Cardiac arrhythmias***

- **β-blockers suppress extrasystoles and tachycardias, especially those mediated adrenergically (during anaesthesia, digitalis induced)—may be used i.v. for this purpose**.
- They control ventricular rate in atrial fibrillation and flutter, but only occasionally restore sinus rhythm.
- **Esmolol is an alternative drug for paroxysmal supraventricular tachycardia**

4. ***Myocardial infarction (MI)***

- ***Secondary prophylaxis of MI****:* Long-term use after recovery from MI has been found to decrease subsequent mortality i) By preventing reinfarction (ii) By preventing sudden ventricular fibrillation at the second attack of MI.
- ***Myocardial salvage during evolution of MI****:* Administered i.v. within 4–6 hours of an attack followed by continued oral therapy. β-blockers— (i) May limit infarct size by reducing O2

consumption— marginal tissue which is partially ischaemic may survive. (ii) May prevent arrhythmias including ventricular fibrillation.

5. ***Congestive heart failure***
   - The benefit may result from antagonism of deleterious effects of sympathetic overactivity on myocardium. Overactivation of cardiac β1 receptors has been found to exert toxic effects on the heart by accelerating myocyte apoptosis and promoting functionally unfavourable remodeling.
   - Certain β1 blockers, used appropriately along with other measures, is now established as standard therapy for most mild to moderate CHF patients.
6. ***Dissecting aortic aneurysm:*** β-blockers help by reducing cardiac contractile force and aortic pulsation.
7. ***Pheochromocytoma***

β-blockers may be used to control tachycardia and arrhythmia, but should never be administered unless an α blocker has been given before, otherwise dangerous rise in BP can occur. They suppress cardiomyopathy caused by excess CAs.

8. ***Thyrotoxicosis***

- Propranolol rapidly controls sympathetic symptoms (palpitation, nervousness, tremor, fixed stare, severe myopathy and sweating) without significantly affecting thyroid status.
- It inhibits peripheral conversion of T4 to T3 and is highly valuable during thyroid storm.
- Major use, however, is preoperatively and while awaiting response to antithyroid drugs/ radioactive iodine.

9. ***Migraine*** Propranolol is the most effective drug for chronic prophylaxis of migraine
10. ***Anxiety*** Propranolol exerts an apparent antianxiety effect, especially under conditions which provoke nervousness and panic, e.g. examination, unaccustomed public appearance
11. ***Essential tremor*** Nonselective β-blockers have now an established place in treating essential tremor. However, they do not benefit parkinsonian tremor.
12. ***Glaucoma*** Ocular β-blockers are widely used for chronic simple (wide angle) glaucoma; also used as adjuvant in angle closure glaucoma
13. ***Hypertrophic obstructive cardiomyopathy*** The subaortic region is hypertrophic. Forceful contraction of this region under sympathetic stimulation (exercise, emotion) increases outflow resistance which has incapacitating haemodynamic consequence.