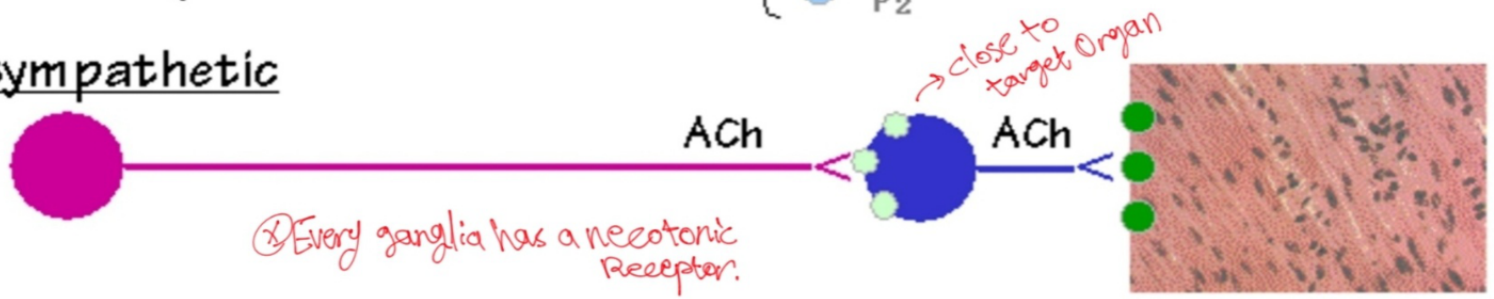

الطب و الجراحة
لجنة

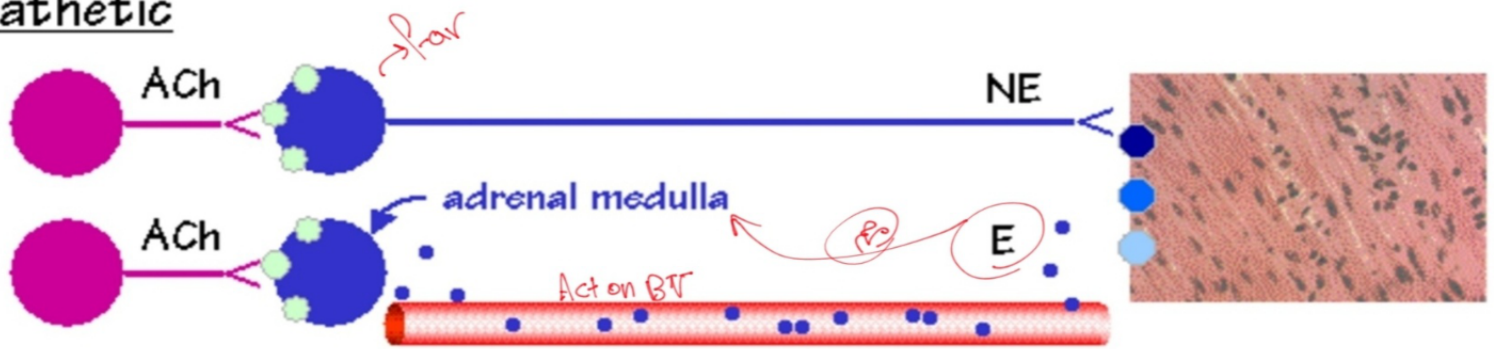
Remember:
- Parasymp. ⇒ CranioSacral Nerve Roots
- symp. ⇒ Thoracolumbar Nerve Roots.

cholinergic { nicotinic, muscarinic } adrenergic { α, β_1, β_2 }

Parasympathetic



Sympathetic



Somatic motor

Responses to Adrenergic Stimulation
(continued)

- Has both [redacted] and [redacted] effects.
- Responses due to different membrane receptor proteins. Major Mechanisms:
  - [redacted]: constricts (visceral) smooth muscles. ⇒ Mainly BV
  - [redacted]: contraction of smooth muscle. ⇒ Mainly GIT and Bladder.
  - [redacted]: increases HR and force of contraction. → Mainly in heart
  - [redacted]: relaxes bronchial (smooth muscles).
  - [redacted]: adipose tissue, function unknown

Drugs acting on autonomic ganglia

Increases activity

- Direct effect
  - Acetylcholine
  - Nicotine (Low doses)
- Indirect effect (ACE inhibitors)
  - Physostigmine
  - Neostgmine
  - Parathion
  - DFP

Decreases activity

- Ganglion blockers-
  - Hexamethonium
  - Macamylmamine
  - Pentolinum
  - Trymethaphan

Drugs acting on Postganglionic sympathetic nerve endings

Increases activity

- Release NE (TEA)
  - Tyramine
  - Ephedrine
  - Amphetamine

Decreases activity

- Block NE Synthesis
  - Metyrosine
- Block Storage
  - Reserpine
  - Guanethidine
- Prevent Release
  - Bretylium
- False transmitters
- Methyldopa

Drugs acting on Muscarinic receptors

Increases activity

- Acetylcholine

Decreases activity

- Atropine ⇒ Parasympathetic
- scopolamine

Drugs acting on Beta adrenergic receptor

Increases activity

- **β stimulators**
  - Isoproterenol
- **$\beta_2$stimulators**
  - Salbutamol
  - Terbutaline

- Decreases activity
- **β blockers**
  - Propranolol ⇒ Regulates HR
  - Metaprolol
- **β_1 blockers**
  - Atenolol
- **β_2 blockers**
  - Butoxamine

Drugs acting on Alpha adrenergic receptors

Increases activity

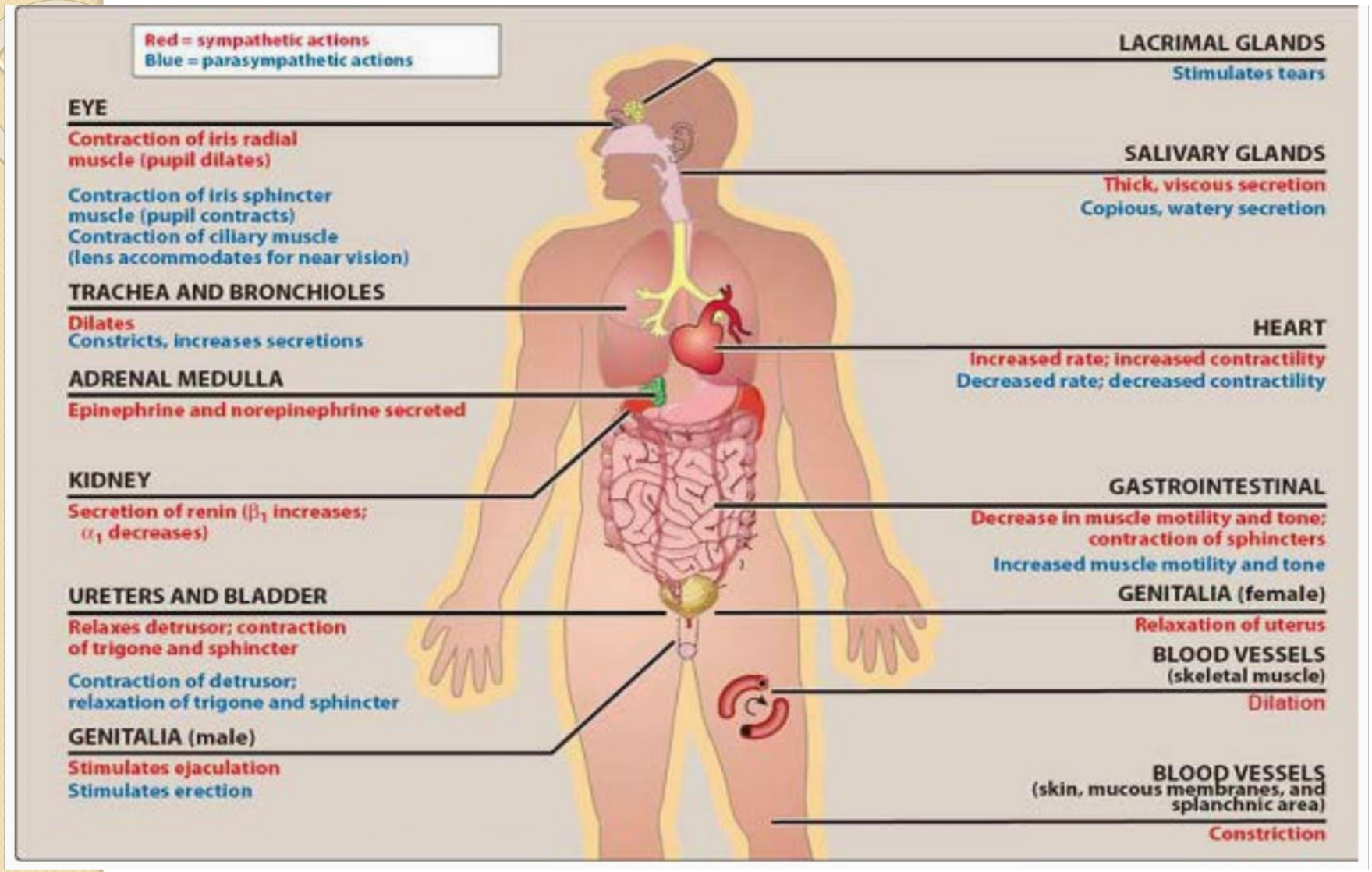
(α_1 stimulators)

- Methoxamine
- Phenylepinephrine

Decreases activity

(α blockers)

- Phenoxybenzamine
- Phentolamine
- Prazocin (α_1 blockers)
- Yohimbine ($\alpha_2$blockers)


Red = sympathetic actions
Blue = parasympathetic actions
EYE
Contraction of iris radial muscle (pupil dilates)
Contraction of iris sphincter muscle (pupil contracts)
Contraction of ciliary muscle (lens accommodates for near vision)
TRACHEA AND BRONCHIOLES
Dilates
Constricts, increases secretions
ADRENAL MEDULLA
Epinephrine and norepinephrine secreted
KIDNEY
Secretion of renin (β_1 increases; α_1 decreases)
URETERS AND BLADDER
Relaxes detrusor; contraction of trigone and sphincter
Contraction of detrusor; relaxation of trigone and sphincter
GENITALIA (male)
Stimulates ejaculation
Stimulates erection
LACRIMAL GLANDS
Stimulates tears
SALIVARY GLANDS
Thick, viscous secretion
Copious, watery secretion
HEART
Increased rate; increased contractility
Decreased rate; decreased contractility
GASTROINTESTINAL
Decrease in muscle motility and tone; contraction of sphincters
Increased muscle motility and tone
GENITALIA (female)
Relaxation of uterus
BLOOD VESSELS (skeletal muscle)
Dilation
BLOOD VESSELS (skin, mucous membranes, and splanchnic area)
Constriction

Autonomic drugs

1. Parasympathomimetics.
2. Parasympatholytics.
3. Sympathimetics.
4. Sympatholytic.
5. Ganglion stimulants & ganglion blockers.

Parasympathomimetics [Cholinomimetic drugs]

Acetylcholine (ACh) receptor stimulants and cholinesterase inhibitors together comprise a large group of drugs that **mimic** Ach (cholinomimetics or parasympathomimetics).

Cholinoceptor stimulants: they are either:

1-Direct-acting cholinomimetic agents bind to and activate muscarinic and/or nicotinic receptors: **1- Choline esters:**

***Ach** *** Methacholine** *** Carbachol** *** Bethanechol**

2- Cholinomimetic alkaloids: * Pilocarpine

Q/ What is pilocarpine?

II-*Indirect-acting agents* inhibit cholinesterases → increase the endogenous Ach in synaptic clefts and neuroeffector junction → stimulate cholinoceptors. The are classified into:

Reversible	Irreversible
▪ Physostigmine & neostigmine. ▪ Neostigmine substitutes: (edrophonium, pyridostigmine, ambenonium, benzpyrinium and demecarium)	▪ Organophosphorus compounds: - Echothiophate -Isoflurophate - Ware gases e.g. sarin &soman. - Thiophosphate insecticides e.g. parathion &malathion.

نحفظ اسامي؟ ماندري

Atropine ⇒ Muscarinic receptor blocker

Carbachol :

⇒ Work on the Nicotonic & Muscarinic Receptors.

⇒ Causes ⇒ Lid twitching + Miosis

- Small dose of Ach ⇒ Hypotension
- Atropin Then large dose of Ach ⇒ Hypertension.

Bethanecol :-

⇒ used in post-operative urinary retention and paralytic ileus.

⇒ has a little effect on the heart

Pilocarpine :

⇒ cholinomemitic Alkaloid

⇒ Tertiary amine

⇒ Well absorbed, crosses BBB, long duration, excerted in urine.

⇒ only Muscarinic Actions.

(1) Reversible cholinesterase Inhibitors

	Physostigmine	neostigmine
Source & chemistry	Natural plant alkaloid Tertiary amine	Synthetic Quaternary ammonium compound
Absorption & distribution	Complete oral absorption Passes BBB	Partial oral absorption . Cannot pass BBB
Metabolism	Both are metabolized by cholinesterase	
Actions	***1-Muscarinic*** (eye): Miosis, accommodation for near vision, ↓↓ IOP, lid twithches, lacrimation] ***2- Nicotinic*** ⟶ Muscle twitches (Indirect action only) ***3- CNS***: Stimulation (convulsions in high doses)	***1-Muscarinic*** (mainly GIT& urinary tract) ***2- Nicotinic*** ⟶ Muscle twitches (direct & Indirect action) ***3- CNS:*** no action

According to the binding with Ch.E. enzymes:

For the ch.E Inhibitor

1- Bind reversible by electrostatic bond with **anionic** site (Negative charge) → Edrophonium

2- Bind reversibly with both **anionic & esteratic** sites

Physostigmine, neostigmine.

3- Phosphorylation of the esteratic site → Organophosphorus compounds

إضافة الفوسفور

Clinical uses:

Physostigmine :

A) Eye drops:

1- Glaucoma.

2- Counteracts action of mydriatics after fundus examination.

3- To cut recent adhesion between iris and lens [alternatively with mydriatics].

B) Alzheimer dementia **but** newer drugs are better.

C) Atropine toxicity: It antagonizes central and peripheral action **but** not preferred due to CNS toxicity

Neostigmine : Uses to cure

1- Reversal of paralysis induced by non-depolarizing neuromuscular blockers during surgical operations.

2- Postoperative retention of urine (Catheterization is better alternative).

3- Postoperative paralytic ileus.

4- Myasthenia gravis. ⇒ Severe Weakness of the Muscle

5- Antidote to atropine toxicity.

6- Glaucoma.

✱ Remember ⇒ Neostigmine is used to Inhibit the Ch.E. Aims for More Ach.

Treatement of Myasthenia gravis:

⇒ Neostgimine OR pyridostigmine + Atropine

⇒ Adjuvant treatement ⇒ ephedrine + caffeine (Potintiates + facilitate $N/M_{transmission}$

⇒ To decrease Antibodies:

① Steroids ⇒ Prednisolone , ② Immunosappresent ⇒ azathioprine.

Alzheimer's disease (AD):

⇒ Mild to Moderate:

① Old drug ⇒ Tacrine , but causes hepatotoxcicity.

② New drugs ⇒ Donepezil , galantamine , Rivastigmine ⇒ More Selective drugs.
⇒ No Hepatotoxcicity!

⇒ Moderat to Severe:

① Memantine
- Inhibits glutamate induced excitotoxcicity
- Inhibits Neuronal damage.
- Improves Cognitive function.

Atropine:

⇒ To treat Organophosphate poisoning.

⇒ 1mg every 10 minutes for 24 hours.

(2) Irreversible cholinesterase Inhibitors

- Echothiophate &Isoflurophate ⟶ eye drops for glaucoma.
- Ware gases [e.g. sarin & soman].
- Thiophosphate insecticides [e.g. Parathion & Malathion]

Pharmacokinetics:

- All organophosphates (except for **echothiophate**) are well absorbed from the skin, lung, gut, and conjunctiva and distributed to all parts of the body, including CNS.
- The thiophosphate insecticides (parathion & malathion) are prodrugs. They are rapidly activated in insects and vertebrates. **Malathion** (not parathion)is rapidly metabolized by other pathways to **inactive products** in **birds** and **mammals** but **not in insects** (considered to be relatively safe).

N.B. Fish cannot detoxify malathion

5. **Cholinesterase reactivators [oximes]:** in cases of Ach toxicity.

   ❖**Pralidoxime (PAM):** [30mg/kg bolus dose then 8mg/kg/hr IV infusion until clinical improvement] can break the bond between organophosphates and the enzyme, so the enzyme becomes free and hydrolyzes Ach at the receptors.

   ❖**Diacetylmonoxime (DAM):** like pralidoxime but can cross BBB and reactivate central cholinesterase.

6. Diazepam for convulsions, and artificial ventilation for respiratory failure.

Note:

- Early after intoxication and formation of organophosphate-enzyme complex (ionic bond) → spontaneous reactivation of the enzyme can occurs that can be hastened by oximes.
- Within a few hours, the organophosphate-enzyme complex loses one alkyl group renders it no longer susceptible to reactivation → ageing. So cholinesterase reactivators should be administered as early as possible.

Cholinergic Antagonists.

Anti-Muscarinic Agents

Atropine :-

=> obtained from belladona Alkaloid

=> binds competitively and Prevents Ach from binding to Muscarinic receptors.

Scopolamine :-

=> Prevention of motion sickness

=> Antispasmodic Agent

Ipratropium + triotropium :-

=> bronchodialators in cases of (COPD), both chronic bronchitis and emphysema

Tropicamide + cyclopentolate :-

=> Ophthalmic Solations for Myadriasis and Cycloplegia

=> shorter duration than atropine

Ganglionic blockers

Mecamylamine :-

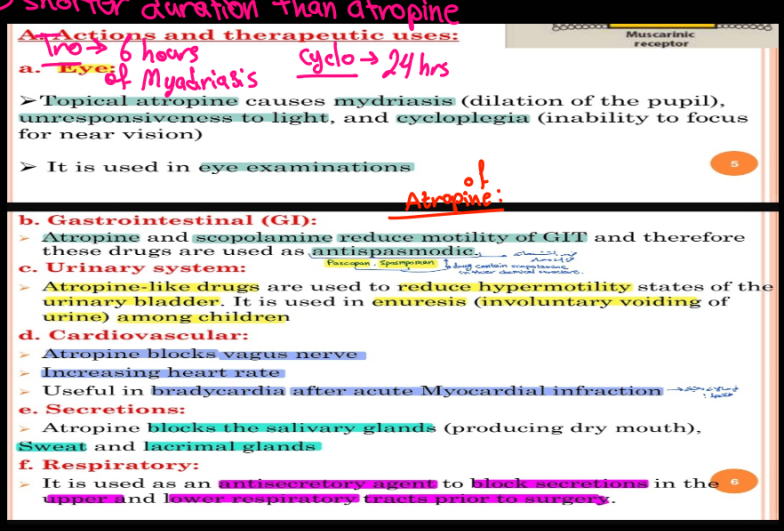
=> Produces a competitive Nicotonic blockade of the ganglia and is primarily used to LOWER BLOOD PRESSURE in Emergency situations.

NeuroMuscular blockers

1. Non-Depolarizing competitive blockers. (Antagonists) :-
   - (A) Pancuronium
   - (B) Atracurium
   - (C) Cisatracurium

   => Used to facilitate orthopaedic surgery.
2. Depolarizing Agents Agonists :-

   => Succinyl choline
   - used when rapid endotracheal intubation is required.
   - used during electroconvulsive shock treatement.



A. Actions and therapeutic uses:

Muscarinic receptor

Tro → 6 hours of Myadriasis

Cyclo → 24 hrs

a. Eye:

- Topical atropine causes mydriasis (dilation of the pupil), unresponsiveness to light, and cycloplegia (inability to focus for near vision)
- It is used in eye examinations

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Atropine :

b. Gastrointestinal (GI):

- Atropine and scopolamine reduce motility of GIT and therefore these drugs are used as antispasmodic.

c. Urinary system:

- Atropine-like drugs are used to reduce hypermotility states of the urinary bladder. It is used in enuresis (involuntary voiding of urine) among children

d. Cardiovascular:

- Atropine blocks vagus nerve
- Increasing heart rate
- Useful in bradycardia after acute Myocardial infraction

e. Secretions:

- Atropine blocks the salivary glands (producing dry mouth), Sweat and lacrimal glands

f. Respiratory:

- It is used as an antisecretory agent to block secretions in the upper and lower respiratory tracts prior to surgery.

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Classification of Sympathomimetics

- **Direct-acting:** (Works on adrenergic Receptor directly)
  - **Selective:** salbutamol (B2), dobutamine (B1) (selective → Mainly in Bronchus; increase cardiac contractility ⇒ used in acute Heart Failure; → in Heart)
  - **Non-selective:** adrenaline, noradrenaline (B & alpha receptors) (Both β + α)
- **Indirect-acting** (Enhance the release of NE.)
  - **Releasing agents** (amphetamine)
  - **Uptake inhibitors** (cocaine, tricyclic antidepressants TCAs) (inhibit pre take from synaptic. Keep it in the System.)
  - **MAO Inhibitors** (Metabolism of NE and E. → so Inhibiton means No Metabolism and keep it in the System.)
- **Mixed-acting** (ephedrine, pseudoephedrine)

Sympathomimetics

in emergency situations Adrenaline is amazing for shock.

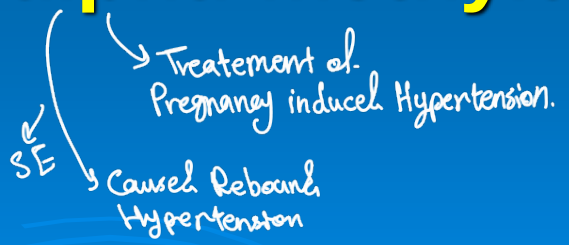
They are also classified into:

- **Catecholamines:** (adrenaline, NA, dopamine, dobutamine, isoprenaline)
- **Non-catecholamines:** (synthetic alpha-agonists & beta-agonists, e.g. phenylephrine, ephedrine, amphetamine)

Not given during emergency!

Alpha-stimulants

- **Pressor agents:**
  - **Phenylephrine** ⇒ ↑ Tension, Vascular constriction.
- **Mucosal decongestants:**
  - **Pseudoephedrine, Oxymetazoline**
- **Alpha 2-agonists:**
  - **Clonidine** & **alpha-methyldopa**



Alpha-stimulants

1- Pressor agents

- These are **non-catecholamines** that **increase peripheral vascular resistance (PVR)** & **arterial blood pressure (both SBP & DBP)**
- They **reduce renal blood flow** (RBF) **& splanchnic blood flow** due to **α1-vasoconstriction**

Phenylephrine

- Is a **direct acting**, synthetic adrenergic drug
- It has predominantly direct **α1-agonist** effect, **a vasoconstrictor** & It is used as:
- **Pressor** agent (Pressure)
- **Nasal decongestant** agent (vasoconstriction)
- **Mydriatic** agent (ophthalmic solutions)
- **Vasoconstrictor** agent with local anesthetics (LA) (increase the duration)

2. Mucosal decongestants: Pseudoephedrine, Oxymetazoline

- Oxymetazoline **(Otrivin)**
- Useful in **allergic rhinitis, common cold & sinusitis**
- **Oxymetazoline is used in Ophthalmic drops** for relief of redness of eye associated with swimming, colds or contact lens

⇒ Vasoconstriction in Sinuses

- Relieve Sinus congestion and pressure ⇒ Reduce the pain.

Alpha 2-agonists (Clonidine & methyldopa)

- **Centrally acting antihypertensive drugs**: **clonidine** & **methyldopa** (Aldomet)
- These act centrally to produce inhibition of sympathetic vasomotor centers, decreasing sympathetic outflow to the periphery
- Methyldopa is used in hypertension during pregnancy
- They are **rarely used** because of risk of **rebound hypertension on withdrawal** of therapy

Beta-adrenoceptors (receptors)

Two subgroups β_1, β_2

β_1-adrenoceptors:

- **Heart** ⟹ Increase HR, contractility & conductivity
  - ⇒ chronotropic effect
  - ⇒ Inotropic
  - ⇒ chronotropic effect.
- **Kidneys** ⟹ Increase renin release
  - ⇓
  - Ang I → Vasoconstrictor
  - ⇓
  - Ang II → Sodium + Water Retention.

β-Stimulants

1. **Selective β_2 agonists:**

   Salbutamol (Albuterol) (Ventolin)

   USA — tradename

- non-catecholamine
- can be given by **inhalation, orally** & **injection**
- **Short acting bronchodilator**
- Its t ½ is about **4 hours** — short duration
- Has **a rapid onset of action (acute asthmatic attacks)** — very effective — why?

⇒ used in treatment of ⇒ ① Acute bronchial asthma attacks.
② Premature labour or threatened abortion

Salmeterol & Formoterol

- is a **long acting bronchodilator** similar to salbutamol with **longer t ½ (12 hr)**
- **Have a delay onset of action**
- It is useful in **prophylaxis of bronchial asthma**
  - Repeated attacks in a short specific time. ex→ cold weather in winter.
- **Not useful for acute attacks** ⇒ because of the delay onset
- Not recommended as **monotherapy** & highly efficacious **when combine with corticosteroid**
  - Anti-infection
  - Mucus + contraction of smooth M may cause an inflammation.

2. Selective β1-agonist

Dobutamine

- **Is a synthetic, direct acting catecholamine**
- **Inotropic sympathomimetic** ⇒ ↑↑ contractility.
- is used in **congestive heart failure (CHF)** to **increase cardiac output**
- **Inotropic support after cardiac surgery**
- **Septic and cardiogenic shock**

3. Non-selective β-stimulants:

Isoprenaline (Isoproterenol)

- **A synthetic, direct acting drug**
- It is a **catecholamine** with **non-selective β1 & β2** agonistic activities
- It increases **SBP & HR** (**β1** effect) & **decreases DBP** (**β2** effect)
- It is **rarely** used **to increase heart rate** in **heart block** & **to stimulate heart in cardiac arrest**

Mixed Alpha & Beta agonists

Adrenaline (Epinephrine)

- It is an **endogenous catecholamine synthesized** in **adrenal medulla** & **certain areas in brain**
- **Commonly used therapy (drug of choice in emergency situations)**

Why? Because of the Rapid onset.

Pharmacodynamic effects

- **On blood vessels:** → Vasoconstriction

Response differs according to site of vessels:

- **Skin, mucous membrane & viscera arterioles contain $\alpha 1$ receptors** & show **vasoconstriction**
- **Skeletal muscle vessels** contain mainly β_2-receptors that show **vasodilatation**

Remember:-
- α_1 ⇒ Smooth. M constriction ✓
- β_2 ⇒ Smooth. M + Skeletal. M arterioles dilatation ✓

For Adrenaline:-
⇒ Veins shows ($\alpha 1$) Vasoconstrictors
⇒ Heart ⇒ ↑ contractility
↑ HR.

Therapeutic uses

"Adrenaline"

- **Cardiac arrest (cardiopulmonary resuscitation-CPR)**
- **Severe allergic reactions (anaphylactic shock & angioedema):**
  - Physiological antagonist to histamine & stabilizer of mast cells
- **Vasoconstrictor with LA**
- **Chronic open angle glaucoma (topically):** vasoconstriction; reduces aqueous humor production & IOP

Noradrenaline (Norepinephrine)

- It has **alpha agonist, β_1-agonist** & **weak β_2** agonist effects
- It **increases** both **SBP & DBP (potent α1 effect)**
- It is **mainly used to treat shock** as a **vasoconstrictor**

Dopamine

- It is an **alpha, beta & dopaminergic** agonist
- **Increases renal blood flow** due to **D1 vasodilatory** effect on **renal circulation**
- **At low dose, activates B1 receptors on heart, increases cardiac output, heart rate & BP**
- **At very high doses, activates alpha receptors, causes vasoconstriction**
- Is the drug of choice for **shock (cardiogenic & septic)** and is given by **continuous infusion to improve renal blood flow**

Indirect-acting sympathomimetics

Amphetamines

- Are important because can be **misused** as a **central psychostimulants** that **improve mood & alertness** منشطات
- **Acts by** Enhance **releasing endogenous NA** from adrenergic neurons after being taken up into neurons

Therapeutic uses of amphetamines

- **Narcolepsy** (excessive abnormal sleep in adults- daytime)
- **Attention deficit hyperkinetic disorder (ADHD)** in **children** (abnormal pathological hyperactivity): **amphetamines improve attention, reduce hyperkinesia)**

Direct & indirect sympathomimetics

Ephedrine

- **Mixed-action drugs** induce **release of NA from pre-synaptic terminals** and **they activate adrenergic receptor on postsynaptic membrane**
- **Non-catecholamine**

Ephedrine

- It is **non-selective agonist**, **stimulate both alpha & beta receptors** & its effects are **similar to that of adrenaline**
- **Ephedrine raises systolic & diastolic blood pressure** by **vasoconstriction & cardiac stimulation**
- **It causes bronchodilation**
- **Is give orally**

Therapeutic uses

- **Bronchial asthma** But NOT the Primary Choice!
- **Mydriatic agent** & **nasal mucosal decongestant**
- **Pressor agent** **in chronic orthostatic hypotension**
- **Heart block** **to increase heart rate**

Adrenergic Antagonists

1. Pharmacological actions of alpha blockers

1. **CVS**:
   Blockade of α_1 vasoconstrictor receptors produces **vasodilatation** & decrease in arterial blood **pressure**. This is associated with **stimulation** of the heart **rate.**

2. **Eye**:
   Blockade of α_1 receptors in the radial muscle of the iris leads to **miosis**.

3. **Headache**, **nasal congestion** (vasodilatation of the cranial & nasal vessels)

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Therapeutic uses

1. Hypertension
2. Hypertensive crisis ⇒ ارتفاع ضغط الدم
3. Pheochromocytoma hypertension ⇒ tumor in adrenal gland
4. Benign prostatic hypertrophy to relax bladder sphincter muscle & reduces urine retention
5. Peripheral vascular disease e.g. Raynaud's syndrome (spasm of the upper limb blood vessels on exposure to cold weather).
   ↳ cyanosis

Pharmacodynamics of beta blockers

1. **CVS**: These agents decrease heart rate, myocardial contractility, cardiac output & O2 consumption. They decrease renin release by kidneys.

2. **Bronchi:** producing bronchoconstriction & may precipitate in asthmatic attack.

3. **Eye:** producing a reduction in intraocular pressure (IOP)

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Therapeutic uses of beta blockers

1. **CVS** indications:
   - **Essential hypertension**
   - **Angina pectoris**: Beta-blockers are cardioprotective by reducing cardiac work & myocardial O_2 demand.
   - **Acute** myocardial infarction **(AMI)** to reduce infarction size & to prevent new infarction.
   - **Arrhythmias** like ectopic beats & tachycardia
2. **Glaucoma: timolol** eye drops reduces production of aqueous humour & the high IOP
3. **Hyperthyroidism** to reduce manifestations of sympathetic over-activity in the disease.
5. **CNS indications:**
   - **Migraine** prophylaxis
   - **Chronic anxiety** to control excessive sympathetic manifestations of anxiety

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Alpha blockers:

⇒

① Doxazosin:
- ⇒ Selective α1 blocker, Suitable for Once daily Administration
- ⇒ Useful in Hypertension, benign prostatic Hypertrophy.

② Phenoxybenzamine:
- ⇒ Irreversible, non selective oral long acting α-blocker.
- ⇒ Useful in treatement of phaeochromocytoma

③ Phentolamine:
- ⇒ non-selective, reversible, injectable α-blocker
- ⇒ Useful in Hypertensive crisis associated w/ high catecholamine levels in blood as in phaeochromocytoma.

Beta blockers:

① CardioSelective:-
⇒ Atenolol, Metoprolol, Carvedilol
↳ water soluble drug.

② Non-selective β-blockers:
⇒ Propranolol ⇒ Lipid Soluble drug.

③ Mixed α + β blockers:
⇒ Labetalol

β-blockers:

① Atenolol ⇒ Selective
② Propranol ⇒ Non-Selective
③ Timolol ⇒ Non-Selective
↳ Eyedrops
④ Metoprolol ⇒ selective
⑤ Pindolol ⇒ Non-Selective