Sympathomimetics
(Adrenergic agonist drugs)

- **Effects mediated by adrenergic receptor subtypes:**

• **α1 -receptors:** They are excitatory receptors present in smooth muscles cause contraction of smooth muscles.
e.g smooth muscles of blood vessels → vasoconstriction → ↑ TPR → hypertension and reflex bradycardia.
On smooth muscles of iris in the Eye→ Active Mydriasis.

Uses of alpha 1 agonist drugs:
1-Epstaxis to stop bleeding in **non-hypertensive** patients
2-Nasal decongestion (locally)
3- given with local anesthetics
4- Shock
5- As mydriatic agents

Unwanted effects: Increase in the total peripheral resistance (TPR), hypertension, reflex bradycardia and necrosis of tissue may occur when applied on peripheral small blood vessels.

- Examples for alpha1 agonist drugs:

Non selective drugs as adrenaline, noradrenaline, high doses of dopamine, etc.
Selective α1 agonist: Phenylephrine, etc.

• **α2 –receptors:** Present presynaptically, to regulate the release of NE from nerve terminal. Therefore α 2 agonists binds to these receptors causing suppression of further NE release.

e.g; Clonidine is an example of selective α2 agonist drug, used for treatment of hypertension and to overcome withdrawal symptoms of addictive drugs.

Unwanted effects: Lethergy & Sedation. (خمول &خدر).

• **β1-receptors:** They are mainly located in the heart, also found kidney.
- Activation of cardiac β1 receptors: → Increase cardiac work [↑ heart rate → tachycardia, increase conductivity and contractility] → ↑COP and the mean arterial blood pressure (↑B.P).

- Activation of β1 receptors in the kidney: → ↑Renin release → ↑angiotensin II → Vasoconstriction and ↑TPR (total peripheral resistance) → (↑B.P).

Unwanted effects; - Hypertension - Pulmonary oedema – Arrhythmia.

e.g: Non selective agonists: Adrenaline, Noradrenaline, Isoproterenol, Dopamine.
Selective β1 agonist: Dobutamine.

• **β2- receptors:** located in
smooth muscles of the bronchioles → (bronchodilation, gastrointestinal (GI)→ (reduce peristalsis and digestion),
in bladder wall → reduce urination and in uterine smooth muscles→ relaxation (tocolytic effect).
in liver and skeletal muscle→ enhance the glycogenolysis.
e.g: - Non selective agonists: Adrenaline, Isoproterenol.

- Selective agonist: Salbutamol ,Terbutaline , Ritodrine.

Clinical indications: Asthma, delay of Laboure (tocolytic)

Unwanted effects: Tachycardia, Tremor, hyperglycemia.

❖ Epinephrine:

It's catecholamine, given parenterally, preferred to be used by S/c or IV infusion.
Acts directly to activate all adrenergic receptors (β1,β2,β3, α1,α2) .
Adrenaline in small doses cause initial activation of β receptors result in vasodilatation and at higher therapeutic dose activate α receptors result in vasoconstriction.

• Pharmacological effects of adrenaline

1- Increase cardiac work and constrict the blood vessels in skin and mucous membranes and dilate coronary artery and blood vessels of skeletal muscles.
2- Relax smooth muscle of bronchi and relief Bronchospasm.
3- Active mydriasis and reduce IOP of open angle glaucoma
4- Metabolic effect; ↑ glycogenolysis result in hyperglycemia.
5- Relax smooth muscles of GIT, bladder & uterus.

• Clinical indications

1-Anaphylactic shock: (It's a physiological antagonist for histamine)
2- Bronchodilator for asthma (β2)
3- Combined with local anesthetics (prolong duration)
4- To control superficial bleeding in (non-hypertensive patient) (α1)
5- For Cardiac arrest (β1)
6- Intraocular surgery as mydriatic drug (α1)

• Side effects

1- Hypertension, arrhythmia, Cerebral hemorrhage (high dose)
2- Pulmonary oedema
3- Tremor
4- Metabolic disturbances (hyperglycemia)

❖ **Norepinephrine**:

Its Catecholamine drug, given by I.V infusion.

Has predominant effect on alpha receptors: α1=α2 > β1 but have no β2 effect.

❖ **Pharmacological Actions**

NE Produces effect like epinephrine except (Bronchodilation & metabolic effects). It has cardiac stimulant effect, causes increase of cardiac properties →↑↑ BP. (β1 effect) & produces vasoconstriction with reflex bradycardia (due to α1 effect).

NE has limited clinical use, can be given for shock with caution.

➢ Nurses must take care of patient status and not inject NE in small peripheral veins, with continuous monitoring of patient to avoid extravasation and tissue necrosis.

❖ **Dopamine:**

It's a Catecholamine drug, given by I.V infusion**.** It has dose-dependent receptor specificity:

- At low dose or low infusion rate, dopamine acts on (D1) and dilates renal blood vessels, coronary arteries & mesenteric blood vessels result in improvement of circulation and increase blood flow throughout the body.

- At moderate therapeutic dose result in renal vasodilatation (D1) + increase cardiac work (β1).

- High therapeutic dose or infusion rate dopamine activates (α1) receptors result in vasoconstriction & decrease renal blood flow.

❖ **Dobutamine:** Is a selective β1 catechol, given by IV infusion. Stimulate the heart (increases contractility and cardiac output), useful for hypotensive patients with heart failure.

❖ **Naphazoline, Oxymetazoline**: non selective alpha agonist used as decongestant.

❖ **Albuterol:** selective β2 agonist used for acute asthma.

❖ **Salmeterol and formoterol:** long acting selective β2 used for chronic asthma.

II- Indirect acting sympathomimetics:
e.g: Amphetamine: act by increasing the release of NE. The pharmacological action like norepinephrine. In addition to peripheral effects amphetamine has central effect causing anxiety, insomnia and weight loss, however, its effect showed tachyphylaxis.

III- Mixed acting:
e.g; Ephedrine: these are natural compounds, act by both indirect and direct mechanisms to activate (α &β) receptors centrally and peripherally result in an increases B.P, bronchodilation, C.N.S stimulation and nasal decongestion.

II: Adrenergic Antagonist drugs
Adrenoceptor Blockers (Sympatholytic)
These are drugs which reduce the sympathetic nerve stimulation or block sympathetic receptors producing an opposite effect of *adrenergic agonists.*

The **adrenergic antagonists** can be divided into two major groups:
(1) Alpha blockers subdivided into two subgroups*;*
- Non selective blockers as (phenoxybenzamine, and phentolamine) they block both α1 and α2.
- Selective α1 blockers as doxazosin, prazosin, Tamsulosin.

(2) beta- blockers which classified into:

- non-Selective block [β1, β2] e.g.; Propranolol, Timolol.

or [Block β & α] e.g.; Labetalol, Carvedilol.

- Selective [block β1] e.g.; Atenolol, Metoprolol, Bisoprolol.

Alpha-Blockers

- **Pharmacokinetics:**

These drugs available as oral and parenteral medications, they bind to plasma protein, metabolized in liver, and excreted with bile and urine therefore the patient need assessment for hepatic and renal functions before using such drugs.

- **Mechanism of action**

These drugs have affinity for binding alpha-adrenergic receptor and antagonize the effect of norepinephrine and other adrenergic agonist drugs on these receptors.

- **Pharmacological Effects**:

-Blocking of α1 receptors present in blood vessels → vasodilatation, reduced B.P → Reflex Tachycardia.

- Blocking of presynaptic α2 receptor → ↑ NE release → ↑ cardiac work → Tachycardia.

- Selective alpha 1 blockers more effective than non-selective as antihypertensive medications.

Clinical indications of alpha blockers:

- Essential Hypertension: Selective α1 blockers as e.g., Doxazosin used to lower blood pressure.
- Peripheral vascular disease (PVD): in which there is vasospasm in blood vessels of toe and fingers. Alpha blockers can suppress the vasoconstriction.
- Benign prostatic hyperplasia (BPH): Blocking of alpha receptors present in the prostate and bladder tissue by selective α1 blockers as e.g., Tamsulosin.
- Pheochromocytoma: it's a tumor of adrenal medulla result in excessive secretion of catecholamines (epinephrine, norepinephrine) which rise the B.P.

Non selective alpha- blockers can be used to suppress hypertension e.g.; phenoxybenzamine and phentolamine.

- Reverse toxicity of alpha agonists by (nonselective e.g., Phentolamine)

✓ **Adverse effects:**

Most of adverse effects are related to the vasodilator effect of alpha blockers
including**:**

- **First dose effect:**
- Orthostatic or postural hypotension with reflex tachycardia.
- Headache due to cranial vasodilatation.
- Decrease ejaculation in male.
- Nasal congestion.

Specific considerations of alpha blockers;
- With α1 blockers, first dose syncope may occur from hypotension.
✓ Therefore you have to start treatment with low dose given to the patient at bed time. and monitor patient during treatment because long term use of alpha1 blockers may cause fluid retention and edema.

Beta-Blockers

✓ **Mechanism of action**

They are competitive antagonist on beta receptors, suppress or inhibit their effects on these receptors.

• Pharmacological effects:

Cardio selective or β1 receptor blockers: e.g. Atenolol, Bisoprolol, Metoprolol. → reduce myocardial stimulation & decrease all cardiac properties (HR, slow conductivity through AV node, reduce contractility, COP & BP).

Blocking of β2 receptor → ↑ bronchospasm and the tone of other smooth muscles.

Effect of beta blocker include:

- **heart:** Reduce cardiac work [HR, conduction, force of contraction, COP, oxygen need] and ↓BP.
- **Lung**: Bronchoconstriction
- **Eye:** Decrease aqueous humor formation (Reduce IOP)
- **Kidney:** ↓ renin secretion
- **Metabolism:** hypoglycemia and mask early signs of hypoglycemia (tachycardia, Sweating) & moreover beta blocker cause increase VLDL and decrease HDL.

• Indications

They are indicated mainly for cardiovascular disorders including;

• Hypertension
• Chronic stable angina (decrease myocardial oxygen consumption)
• Tachycardia, dysrhythmias & thyrotoxicosis, because these drugs reduce the conduction through the AV node.
• For myocardial infarction (MI) as cardioprotective inhibit sympathetic stimulation to the heart.
• Glaucoma ; using topical drugs as betaxolol, Timolol.
• Migraine headache (propranolol which is a lipophilic drug easily cross BBB)

• Side effects related to beta1 blockers:

Bradycardia, Reduced C. O. P., Precipitation of heart failure,
A. V heart block, Rebound hypertension & cardiac excitation with sudden stop.

• Side effects of beta2-blockers:

• Bronchoconstriction, Metabolic disturbances, Inhibition of glycogenolysis (hypoglycemia), ↓ HDL, cold extremities, and decrease ejaculation.

• Contraindications

1. Chronic heart failure
2. Pulmonary edema.
3. Cardiogenic shock.
4. Bradycardia
5. AV or Heart block