

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

**Noradrenergic receptors blockers
(antagonists)**

By

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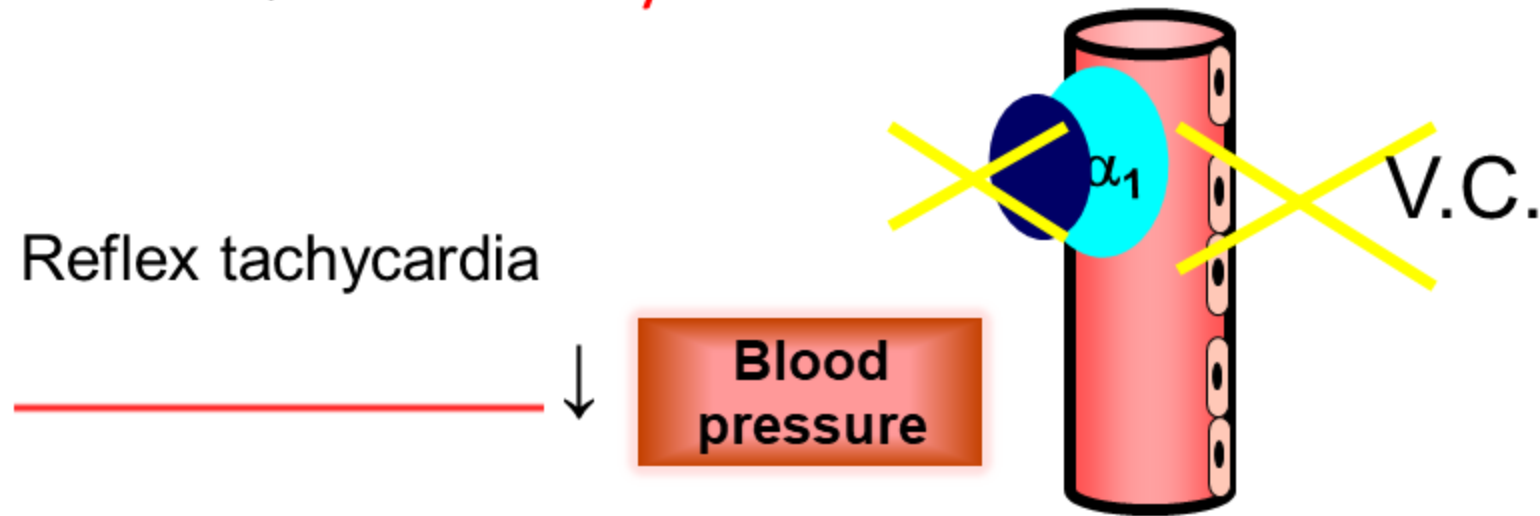
2023

1- α adrenergic blockers

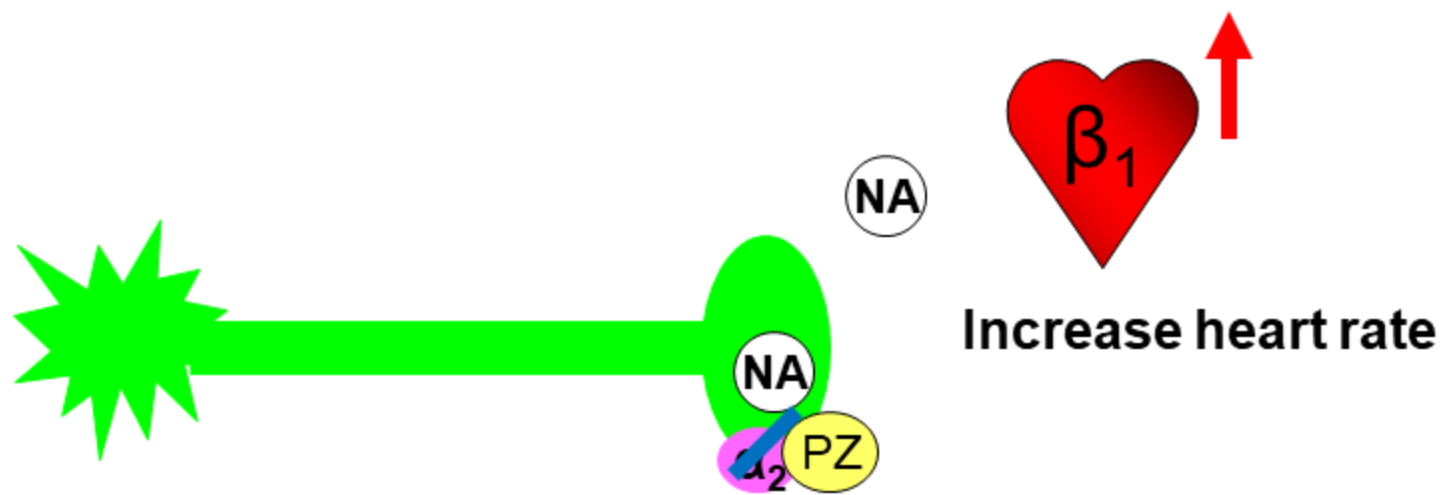
Pharmacological actions:

Blocking α_1 receptors will relax smooth muscles of blood vessels leading to **vasodilatation** and decrease peripheral resistance and **hypotension**.

- **Hypotension** \rightarrow **reflex tachycardia**.



Blocking of the presynaptic α_2 receptors will **increase norepinephrine release** leading to **tachycardia** (beta 1 effect)



Prostates: Blockade of α_1 receptors will relax the prostatic smooth muscles and can improve the urinary obstructive symptoms of benign prostatic hyperplasia (BPH).

N.B. Prostate exhibits a high proportion of α_{1A} receptors.

N.B. Blood vessels contain more α_{1B} receptors

A) Non-selective α -blockers.

1- *Competitive blockers*: Phentolamine

2- *Non-competitive blockers*: irreversible antagonist e.g., phenoxybenzamine .

Uses: both drugs are used for short-term in hypertension with pheochromocytoma (adrenaline secreting tumor of the adrenal medulla) .

Adverse effects:

1. **Postural hypotension**: Dizziness, vertigo and syncope after the initial dose.
2. **Marked tachycardia** (overcome by concurrent use of β - blocker).
3. **Nasal congestion and pulsating headache.**
4. **Decreased libido and sexual dysfunction.**

B) Selective α_1 blockers

Prazosin, terazosin, doxazosin, and tamsulosin.

Uses:

- 1- Mild to moderate hypertension (Prazosin, terazosin can be used; however, Doxazosin is the longest acting of these drugs (excreted in feces).
- 2- Congestive heart failure as they decrease preload and afterload.
- 3- Decrease obstructive symptoms in benign prostatic hyperplasia (BPH); all can be used but alfuzosin and *tamsulosin* are better as more selective for α_{1A} -receptors (present on prostatic smooth m.), causing *less vasodilator side effects* as hypotension and headache (blood vessels contain alpha 1b receptors).

Common advantages of all selective α_1 - blockers

- a) Less tachycardia (compared to non selective alpha blockers).
- b) Beneficial favorable effect on plasma lipids.

Adverse effects of Selective α_1 blockers

- **First dose phenomena:** Dizziness, vertigo and syncope due to marked postural hypotension; 30-90 min after the initial dose avoided by using low doses and at bedtime.
- **Reflex Tachycardia avoided by β - blocker.**
- **Nasal congestion avoided by topical nasal decongestants.**
- **Fluid retention (prazosin) avoided by diuretic**
- **Decreased libido and sexual dysfunctions.**



Orthostatic hypotension



Tachycardia



Vertigo



Sexual dysfunction

Selective Alpha-2 Receptor Blocker

MOA: Antagonist at α_2 -prejunctional receptors in the CNS, increasing sympathetic outflow.

Clinical uses:

1-Yohimbine: treatment of postural hypotension and sexual dysfunctions induced by clonidine.

2- Mirtazapine: used as antidepressant drug.

N.B. ergot alkaloids (like ergotamine) has weak alpha blocking actions and a direct potent smooth muscle stimulatory actions. They produce vasoconstriction (treat acute migraine) and uterine contraction (treat postpartum hemorrhage)

β - Adrenergic Receptors Blockers

Beta 1 blocking

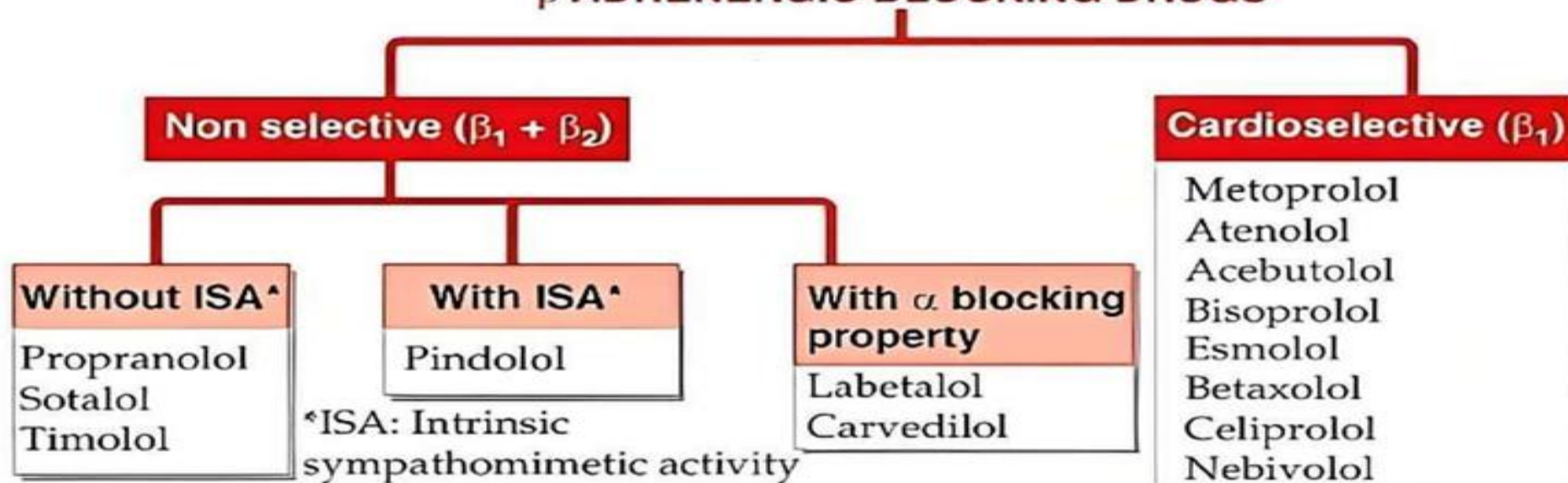
- 1- Decrease heart Rate**
- 2- Decrease cardiac contractility**
- 3- Decrease AV conduction**
- 4- Decrease renin secretion from kidney**

Beta 2 blocking

- 1- Bronchoconstriction**
- 2- vasoconstriction**
- 3- Hypoglycemia**
- 4- prevent skeletal muscle tremors**

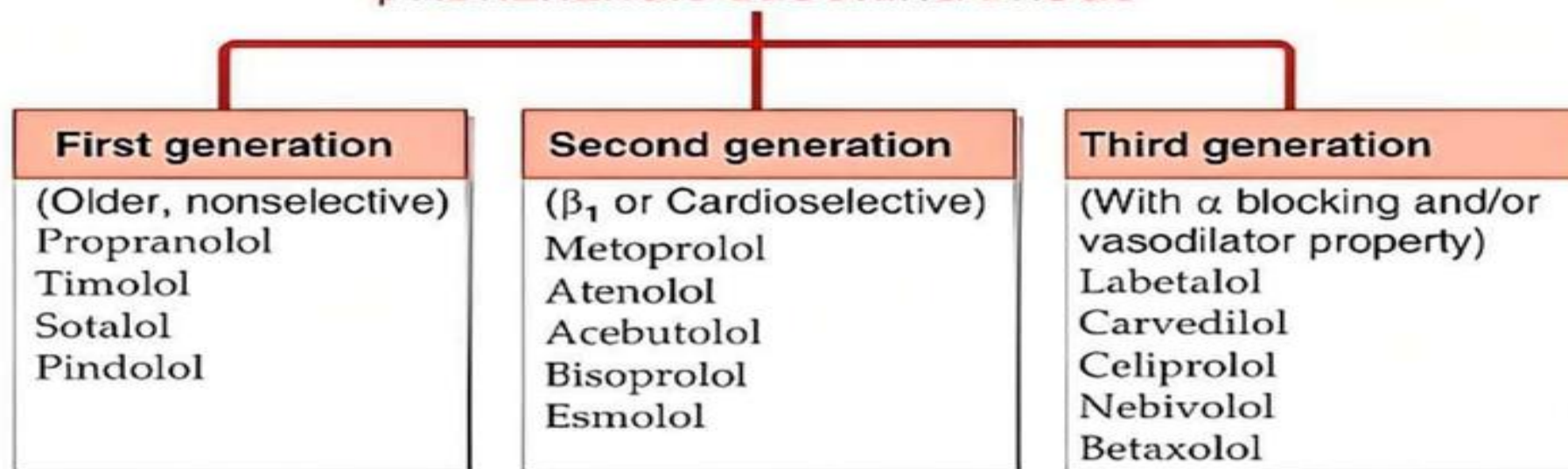
**Beta 3
blocking
Inhibit
lipolysis**

β ADRENERGIC BLOCKING DRUGS



GENERATIONWISE CLASSIFICATION

β ADRENERGIC BLOCKING DRUGS



1- Heart : Blocking β_1 results in:

- **-ve Inotropic (decrease cardiac contraction)**
- **-ve Chronotropic (decreased heart rate)**
- **-ve Dromotropic (Decreased atrio-ventricular conduction)**
 - **↓ cardiac output (COP) → ↓ BP (antihypertensive)**
 - **↓ Cardiac work & ↓ O₂ consumption (antianginal)**
 - **↓ Automaticity, & ↓ conductivity in SA and AV nodes**
→ **↓ HR (Antiarrhythmic).**

2- Blood vessels (β_2 blocking):

- Blocks V.D. effect (due to β_2 blocking) \rightarrow Unopposed α \rightarrow V.C. \rightarrow \downarrow blood flow to various tissues.
 - So, not used in vasospastic angina and peripheral vascular disease.
 - ✓ \downarrow I.O.P.: \downarrow secretion of aqueous humor in the eye.
 - ✓ Constrict blood vessels in hemangiomas

3- Bronchi (β_2) \rightarrow Bronchospasm

- Not used in patients with chronic obstructive COPD or BA

4- Metabolic effects of BBs

➤ **Non-selective β -blockers:**

1- **hypoglycemia**: blocking hepatic $\beta_2 \rightarrow \downarrow$ Glycogenolysis and augments the hypoglycemic action of insulin.

2- **Masking hypoglycemic reactions** “symptoms” (blocking β_1); **Beta blockers mask the signs of hypoglycemia (tachycardia, anxiety and tremors).**

➤ **Selective β_1 blockers: Better tolerated in diabetic patients. However, still masking hypoglycemic reactions particularly tachycardia and palpitation.**

➤ **Beta blockers increase blood lipids.**

Adverse Effects & Contraindications

1. Bronchoconstriction

Nonselective β blockers are potentially dangerous in asthma and COPD (as severe bronchospasm may cause asphyxia).

So, Non- selective BBs are contraindicated in **asthmatics**.

2. Rebound effects:

Never stop suddenly (can worsen **angina**, **hypertension** or precipitate **arrhythmia**) due to **up regulation of receptors**; withdraw gradually (1week).

3. Bradycardia and heart block.

4. Sexual impairment: impotence (psychogenic)

5. Disturbances in metabolism:

Mask manifestations of hypoglycemic reactions in diabetes and augment the **hypoglycemia**. They used cautiously in **diabetics** (especially those treated by insulin).

6. Worsen acute **heart failure**: by -ve inotropic effect.

7-**C.N.S**: Sedation, **sleep disturbance**, **depression**, fatigue, **night mares**, weakness (with lipid soluble as propranolol).

8- Unlike alpha blockers, most beta blockers elevated Low density lipoproteins (LDL).

1- Propranolol, Nadolol, Timolol

- **Non-selective beta blocker (first generation)**
 - **Chronic use is associated with hyperlipidemia (\uparrow LDL-C and/or triglycerides (\uparrow TGs)).**
 - **They are hazardous in *bronchial asthma, diabetes, peripheral vascular disease & hyperlipidemia.***
1. **Propranolol:**
 - It is the prototype of this class;
 - It is highly lipid soluble so more crossing BBB and produces sedation.
 2. **Nadolol: has the longest half-life (24h) and no CNS entry.**
 3. **Timolol: is used mainly in glaucoma (topically in eyes).**

2- Atenolol, Metoprolol, Bisoprolol:

- **Cardioselective β -blockers (second generation)**
- **Less effect on blood vessels, bronchioles, and metabolism than first generation.**
- **Atenolol has no CNS entry.**

Advantages:

- ***Safer in asthma, diabetes, and peripheral vascular disease.***

3- Pindolol and acebutolol

- BBs with intrinsic sympathomimetic activity (ISA)
- Less bradycardia compared to propranolol.
- Most suitable BBs for **patients with bradycardia or heart block**
- Used in hypertensive patients with moderate bradycardia

4- Carvedilol and labetalol

- Have combined α_1 & β -blocking activity (third generation-non selective Vasodilator BBs).

Labetalol :

- It is used I.V. in hypertensive emergencies and orally in chronic hypertension.
- It is safe to be used in **severe hypertension of pregnancy**

Carvedilol :

- It has an additional **antioxidant** property
- Useful in chronic stabilized heart failure.

5- Esmolol

- It is ultra-short acting BB
- Rapidly metabolized by esterases of RBCs with $t_{1/2}$ **10 minutes**
- Useful in **arrhythmias associated with cardiac surgery.**

6- Nebivolol Highly selective β_1 – and α_1 receptor blockers of 3rd generation BB.

- Causes vasodilation through increasing the production of endothelial NO.
- It is used whenever the erectile sexual dysfunction is associated with cardiac disease because it improves both conditions (e.g., hypertension and erectile dysfunction).

Therapeutic uses of BBs

1- Cardiovascular uses

- A. *Mild-moderate hypertension:*** all BB except esmolol (ultrashort).
- B. *Chronic stable angina:*** All except BBs with ISA.
- C. *Supraventricular arrhythmias:*** Correct and treat only tachycardia; protect the ventricle.
- D. *Prophylactic after myocardial infarction:*** to decrease the incidence of sudden death. (Propranolol, metoprolol or timolol are used).
- E. *Chronic heart failure:*** Low dose of carvedilol, metoprolol or bisoprolol can decrease the mortality rate in patients with heart failure.
 - **Carvedilol** is preferred because it has antiarrhythmic, antiremodeling and antioxidant effects.

2- Endocrinal uses:

- A. Hyperthyroidism:** **propranolol** is used to control tachycardia & inhibits the conversion of T_4 to T_3 which is the most active form.
- B. Pheochromocytoma:** To control the associated arrhythmia, but it must be given after α -blockers to avoid marked increase in BP.

3- Hepatic uses:

Prevention of **oesophageal variceal** bleeding in patients with portal hypertension caused by liver cirrhosis (**Carvedilol** and **propranolol** can be used).

4- Neurological uses: Propranolol can be used in the following conditions.

1. Tremors
2. Alcohol withdrawal manifestations
3. Acute panic symptoms as tachycardia.
4. anxiety associated with psychosomatic disorders.
5. Prophylactic uses in migraine.

5- Topical uses:

- Eye drops *timolol*, *betaxolol* and *carteolol* reduces intraocular pressure and are used in open angle glaucoma.
- **Note:** sufficient amount of BBs may be absorbed from the eye to cause serious systemic adverse effects.
- Topical propranolol cream can be used for treatment of infantile haemangioma (as it constricts blood vessels).

Characteristics of Some Beta Blockers

Drugs	β 1-Selective	ISA	Sedation	Blood Lipids
Acebutolol	+	++	+	-
Atenolol	+	-	-	↑↑
Metoprolol	+	-	+	↑↑
Pindolol	-	++	+	-
Propranolol	-	-	+++	↑↑
Timolol	-	-	++	↑↑



Thank
you!!