

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

Adrenoceptors blockers (antagonists)

By

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Alpha- blockers

Pharmacological actions:

1- Blocking α_1 receptors produce vasodilatation and hypotension occurs. Hypotension \rightarrow reflex tachycardia.

2- Blocking of the presynaptic α_2 receptors will **increase**

Norepinephrine release leading to **tachycardia** (beta 1 effect).

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

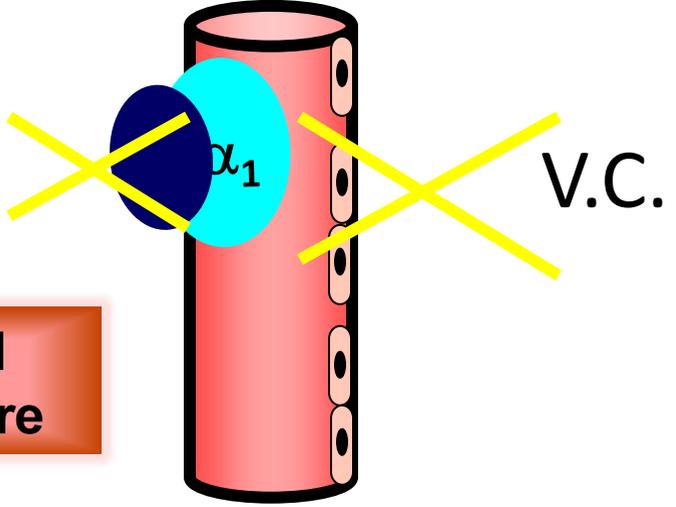
N.B. **Prostate** exhibits a high proportion of **α_{1A} receptors**.

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

Reflex tachycardia



Blood pressure



Non-selective α -blockers

1- *Competitive blockers*: Phentolamine

2- *Non-competitive irreversible blockers*: phenoxybenzamine .

- Used for short-term control of hypertension in **pheochromocytoma** (adrenaline secreting tumor of the adrenal medulla) .
- Phentolamine can treat marked vasospasm of injected sympathomimetics with local anesthetics
- Phentolamine was used for treatment of erectile dysfunction (intracavernous injection)

Adverse effects:

1. **Postural hypotension**: Dizziness & 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**.

Selective α_1 blockers (zosins)

Prazosin, terazosin, doxazosin, alfuzosin, and **tamsulosin** are used in

1- Mild to moderate **hypertension** (Prazosin, terazosin), Doxazosin is the longest acting of these drugs.

2- Congestive **heart failure**.

3- Decrease obstructive symptoms in **benign prostatic hyperplasia** (BPH);

All selective alpha 1 blockers can be used but **alfuzosin** and tamsulosin are more selective for α_{1A} receptors (prostatic smooth m.), causing less vasodilator side effects as hypotension and headache.

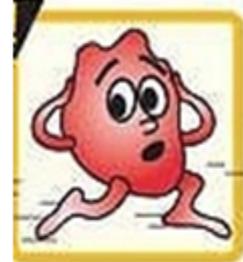
☐ Selective α_1 - blockers has advantages of producing **Less tachycardia** (compared to non-selective alpha blockers).

Adverse effects of Selective α_1 blockers

1. **First dose phenomena:** Dizziness, vertigo and syncope due to marked orthostatic hypotension; 30-90 min after the initial dose avoided by using low doses and at bedtime.
2. **Reflex Tachycardia** avoided by β - blocker.
3. **Nasal congestion** avoided by topical nasal decongestants.
4. **Fluid retention (prazosin)** avoided by diuretic
5. **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 hypotension and sexual dysfunctions induced by clonidine (alpha 2 agonist).
- 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 (olols)

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**

1- Heart : Blocking of β_1 lead to:

- \downarrow HR & \downarrow conductivity (**Antiarrhythmic** effects).
- \downarrow Cardiac work & \downarrow O_2 consumption (**antianginal**).

2- Blood vessels (β_2 blocking):

- β_2 blocking \rightarrow Unopposed $\alpha \rightarrow$ **Vasoconstriction**. So, beta blockers should not used in vasospastic angina and peripheral vascular disease.

✓ I.O.P.: \downarrow secretion of aqueous humor in the eye.

✓ Beta blockers constrict blood vessels in hemangiomas

3- Bronchi (blocking of β_2) \rightarrow Bronchospasm occurs

- ☐ Beta blockers should be avoided in patients with bronchial asthma.

4- Metabolic effects of Beta blockers

➤ Non-selective β -blockers:

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

❑ Beta blockers delay the recovery from hypoglycemia

2- **Masking hypoglycemic manifestations**

Hypoglycemia produces sympathetic stimulation manifested by (tachycardia, anxiety and tremors); β -blockers mask these manifestations

- **Selective β_1 blockers: Better tolerated in diabetic patients. However, still masking hypoglycemic reactions particularly tachycardia and palpitation.**
- **Beta blockers increase blood lipids** (especially triglycerides).

Adverse Effects & Contraindications

1. Bronchoconstriction

Non-selective β blockers 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

3. Bradycardia and heart block.

4. Sexual dysfunction (psychogenic)

5. Worsen acute **heart failure**: by decreasing cardiac contractility.

6- Unlike alpha blockers, most beta blockers **elevate plasma lipids**.

7. Hypoglycemia

Mask manifestations of hypoglycemic reactions in diabetes and augment the **hypoglycemia** and delay the recovery from hypoglycemia.

They used cautiously in **diabetics** (especially those treated by insulin).

8. C.N.S (more with lipid soluble as **propranolol**): Sedation, **sleep disturbance**, **depression**, fatigue, **nightmares**, weakness

1- Propranolol, Nadolol, Timolol

- **Non-selective beta blocker (first generation)**
- Chronic use is associated with hyperlipidemia
- They are hazardous in *bronchial asthma, diabetes, peripheral vascular disease & hyperlipidemia.*

1. Propranolol:

It is **highly lipid soluble** (cross to the brain) and may produce **sedation**.

2. **Nadolol**: has the **longest half-life** (24h) and **no CNS entry**.

3. **Timolol**: is used mainly in **glaucoma** (topically in **eyes**).

Second generation

(Atenolol, Metoprolol, Bisoprolol)

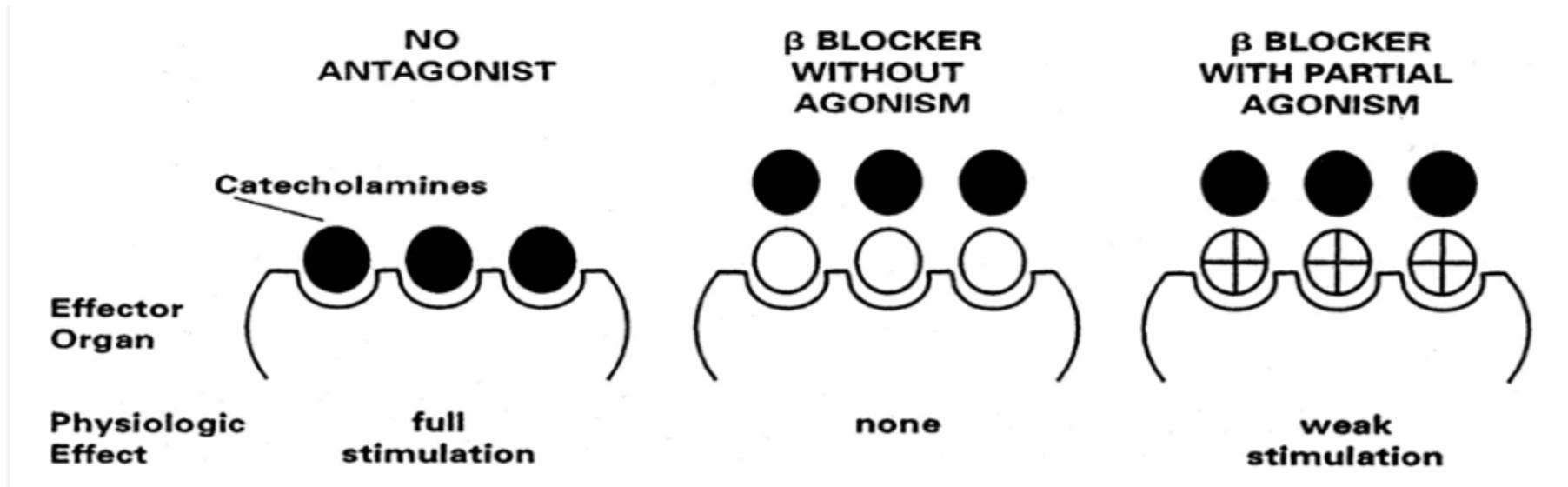
- These are selective β_1 -blockers (Cardio-selective)
They have less effects on blood vessels, bronchioles & metabolism than first generation.
- **Atenolol has no CNS entry.**

Advantages:

- **Safer** than first generation (non-selective beta blocker) in asthma, diabetes, and peripheral vascular disease.

Pindolol and acebutolol

- Beta blockers with intrinsic sympathomimetic activity (partial agonists)
- Produce Less bradycardia compared to propranolol.
- Used in hypertensive patients with bradycardia or heart block



Third generation beta blockers

- Most of these drugs have combined α_1 & β -blocking activity .
- They are called Vasodilator beta blockers.

1- Labetalol: used I.V. in hypertensive emergencies and orally in **severe hypertension of pregnancy**.

2- Nebivolol: Causes vasodilatation by \uparrow endothelial Nitric Oxide.

- Advantage: No sexual dysfunction

3- Carvedilol :

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

4- Esmolol (selective beta 1)

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

Therapeutic uses of Beta blockers

1- Cardiovascular uses

- A. **Mild-moderate hypertension:** all except esmolol (ultrashort).
- B. **Chronic stable angina:** All except Bet blockers with ISA.
- C. **Tachycardia** and **arrhythmias:** All except Bet blockers with ISA.

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.

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 with tachycardia.
4. Psychosomatic anxiety 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:** eye drops containing beta blockers may be absorbed from the eye to cause serious systemic adverse effects.
- Topical propranolol cream can be used for treatment of infantile haemangioma and rosecea (as it constricts blood vessels).

Characteristics of Some Beta Blockers

Drugs	β_1 -Selective	ISA	Sedation	Blood Lipids
Acebutolol	+	++	+	-
Atenolol	+	-	-	↑↑
Metoprolol	+	-	+	↑↑
Pindolol	-	++	+	-
Propranolol	-	-	+++	↑↑
Timolol	-	-	++	↑↑

A white, hand-drawn style thought bubble sticker is pinned to a brown corkboard. The bubble has a small tail pointing downwards and to the left. Inside the bubble, the words "Thank you!!" are written in a bold, black, sans-serif font. "Thank" is on the top line, and "you!!" is on the bottom line, slightly indented to the right.

Thank
you!!