

بِسْمِ اللَّهِ الرَّحْمَنِ الرَّحِيمِ

**Adrenergic receptors blockers
(antagonists)**

By

Dr. Mohammad Salem Hareedy

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1- what's the pharmacological action of α blocker?
↳ α_1
↳ α_2

1- α adrenergic blockers ✓

↳ most prominent side effect = tachycardia.

Pharmacological actions:

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

❑ Hypotension → reflex tachycardia.

❑ Blocking of the pre-synaptic 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 → relax prostate without tachycardia and hypotension.

1- what're the type of Non-selective blocker?

→ A) Non-selective α -blockers.

2- what's the therapeutic use?

3- what're the adverse effects?

1- Competitive blockers: Phentolamine فينتولامين

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

فينتولامين نسي البنت تبعته أسيه؟!



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

maligient tumor of adrenal medulla → increase secretion of Adrenaline.
↑ pulsation ← ↑ B.p ←

Adverse effects:

1. Postural hypotension: Dizziness, vertigo and syncope after the initial dose.
توخية دوار واغماء

2. Marked tachycardia (overcome by concurrent use of β -blocker).

3. Nasal congestion and pulsating headache. due to vasodilation of B.v.

4. Decreased libido and sexual dysfunction. in males

1- what're the involved drug?
2- what're the therapeutic indication?

3- what's the advantage? 4- what're the adverse effect?

B) Selective α_1 blockers

↓ tachy cardia
↓ NE release.

Prazosin, terazosin, doxazosin, and tamsulosin. *المداوية التي تترافق بها بشكل تام.*

Uses:
→ long duration / so it's the best choice for hypertension.

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).
First line treatment in treat large prostat.
↳ less hypotension, tachy cardia.

Common advantages of all selective α_1 - blockers

a) ✓ Less tachycardia (compared to non selective alpha blockers).

b) ✓ Beneficial favorable effect on plasma lipids. ✓

↳ protect the patient from hyperlipidemia.

20/0
Adverse effects of Selective α_1 blockers

→ severe postural hypotension.

① **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.**

no control the hypotension.

② **Reflex Tachycardia avoided by β -blocker.**

③ **Nasal congestion avoided by topical nasal decongestants.**

↳ xylometazolin.

④ **Fluid retention (prazosin) avoided by diuretic (fluid retention).**

⑤ **Decreased libido and sexual dysfunctions.**

→ 1- what's the mechanism of action?

→ 2- what're the therapeutic uses?



Orthostatic hypotension



Tachycardia



Vertigo



Sexual dysfunction

Selective Alpha-2 Receptor Blocker

↳ increasing the Norepinephrine.

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. (α₂ 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

Beta 1 blocking

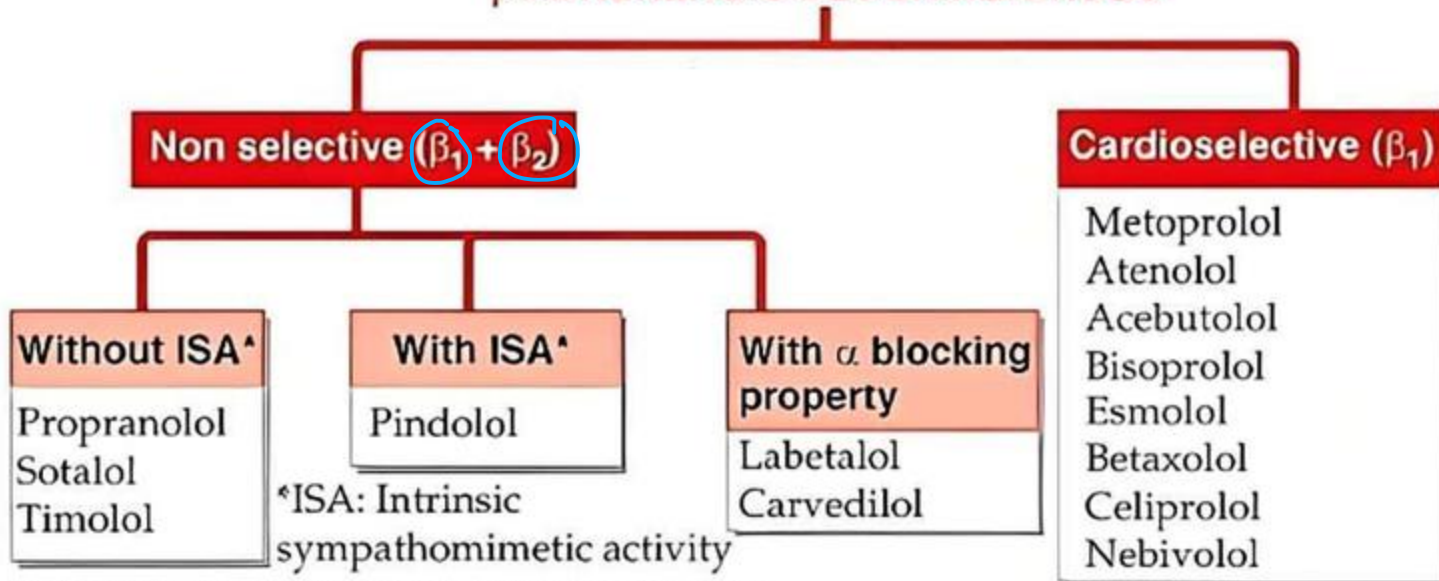
- 1- Decrease heart Rate
- 2- Decrease cardiac contractility
- 3- Decrease AV conduction
- 4- Decrease renin secretion from kidney

Beta 2 blocking

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

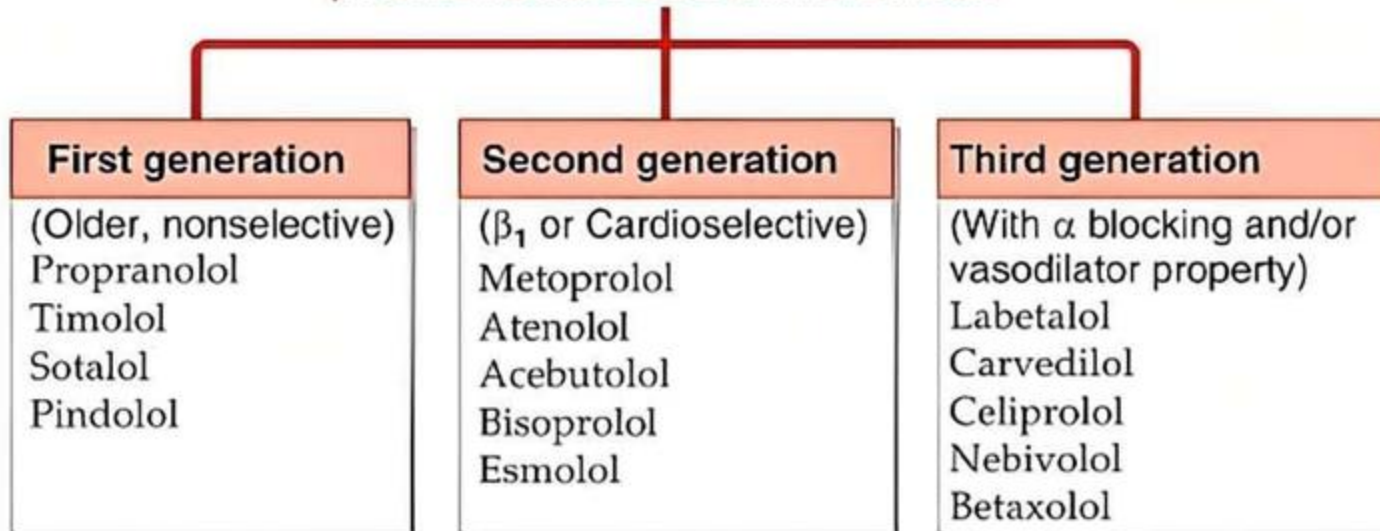
Beta 3
blocking
Inhibit
lipolysis

β ADRENERGIC BLOCKING DRUGS



GENERATIONWISE CLASSIFICATION

β ADRENERGIC BLOCKING DRUGS



1- Heart : Blocking β_1 results in:

→ 1- what's the effect of it?
→ 2- what's the use of it?

- -ve Inotropic (decrease cardiac contraction)
weak
- -ve Chronotropic (decreased heart rate)
- -ve Dromotropic (Decreased atrio-ventricular conduction)
التأخر في التوصيل الكهربائي
 - ↓ 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):

→ 1- what's the effect of it?
→ 2- what's the contraindication?

- Blocks V.D. effect (due to β_2 blocking) → Unopposed α → V.C. → ↓ blood flow to various tissues.

❑ So, not used in vasospastic angina and peripheral vascular disease. due to increase vasoconstriction.

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

✓ Constrict blood vessels in hemangiomas

الرحمة الدموية
→ Bv dilated



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3- Bronchi (β_2) → Bronchospasm

❑ Not used in patients with chronic obstructive COPD or BA

4- Metabolic effects of BBs

1- what're the effects of them?

➤ Non-selective β -blockers:

1- **hypoglycemia**: blocking hepatic β_2 → ↓ Glycogenolysis and augments the hypoglycemic action of insulin.

adrenaline → liver → glucose
↘ sweating

palpitation ← heart

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 → in asthma patient.

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

So, Non-selective BBs are contraindicated in asthmatics.

↳ Use selective β_2 blocker in asthma

2. Rebound effects:

→ Never stop suddenly (can worsen ^aangina, ^bhypertension or precipitate arrhythmia) due to up regulation of receptors; withdraw gradually (1 week).

Not stop suddenly X ↓

3. Bradycardia and heart block. ↑ dose → direct inhibition to heart.

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). *used selective.*

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

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

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

1- what does the non-selective β -blocker have? 2- what're the contraindications abt it? 3- what're the features of each one?

1- Propranolol, Nadolol, Timolol

Nada pro has time.

- **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^①, diabetes^②, peripheral vascular disease^③ & hyperlipidemia^④. *bronchospasm, hyperglycemia*

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).

1- what does the cardio selective induced?

2- what's special about them?

3- what's the advantage?

2- **Atenolol**, Metoprolol, Bisoprolol:

B1

- **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.**

1- what's special about them?

2- what's the advantage of it?

3- what's the therapeutic use?

3- Pindolol and acebutolol

↪ partial agonist / prevent adrenaline from binding
↪ no action

- 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

سنوات

1- what does they involved? what's special about them?

دلیل ہے

دوبہلا

2- what're the therapeutic use?

4- Carvedilol and labetalol

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

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

↳ as α -methyl dopa

Carvedilol :

- ^{a-} It has an additional antioxidant property
- ^{b-} Useful in chronic stabilized heart failure.

5- Esmolol

→ 1- why does it have short acting effect?
→ 2- what's the indication of it?

- 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.

↳ if we used propofol (IV) → ✓ it'll help but the heart will be weak for 6-8 H.

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

- 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

:- due to short $T_{1/2}$

- 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.

↳ it is important (in) retained of histology of heart!

2- Endocrinal uses:

A. Hyperthyroidism: propranolol is used to control tachycardia & inhibits the conversion of T₄ to T₃ which is the most active form. *Thyroxin... inactive form of thyroidism*

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 (to decrease anxiety).
3. Acute panic symptoms with 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).

non-selective β -blockers
highly lipid soluble
→ pt may used adverse effect

Characteristics of Some Beta Blockers



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