

β - Adrenoceptors blockers



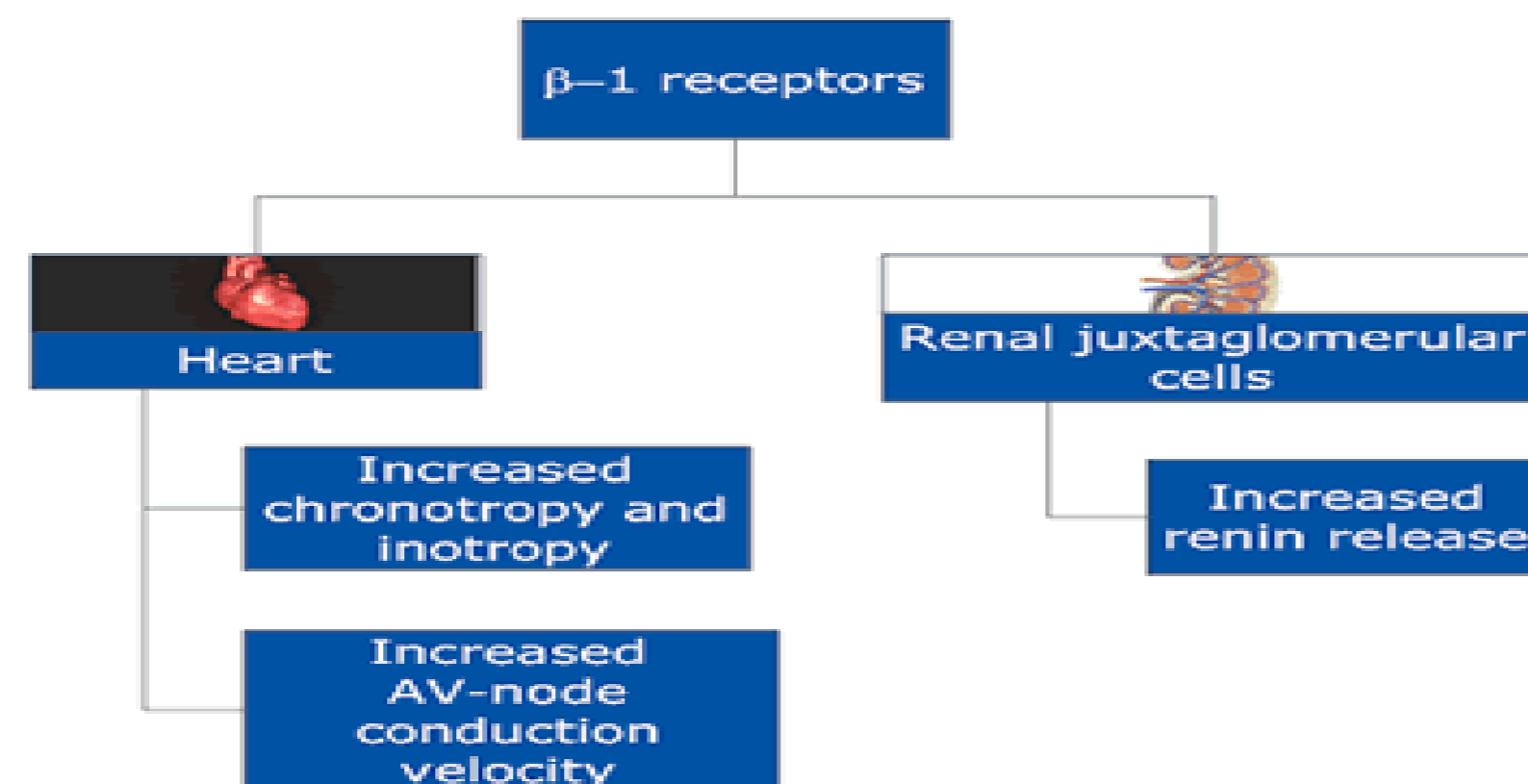
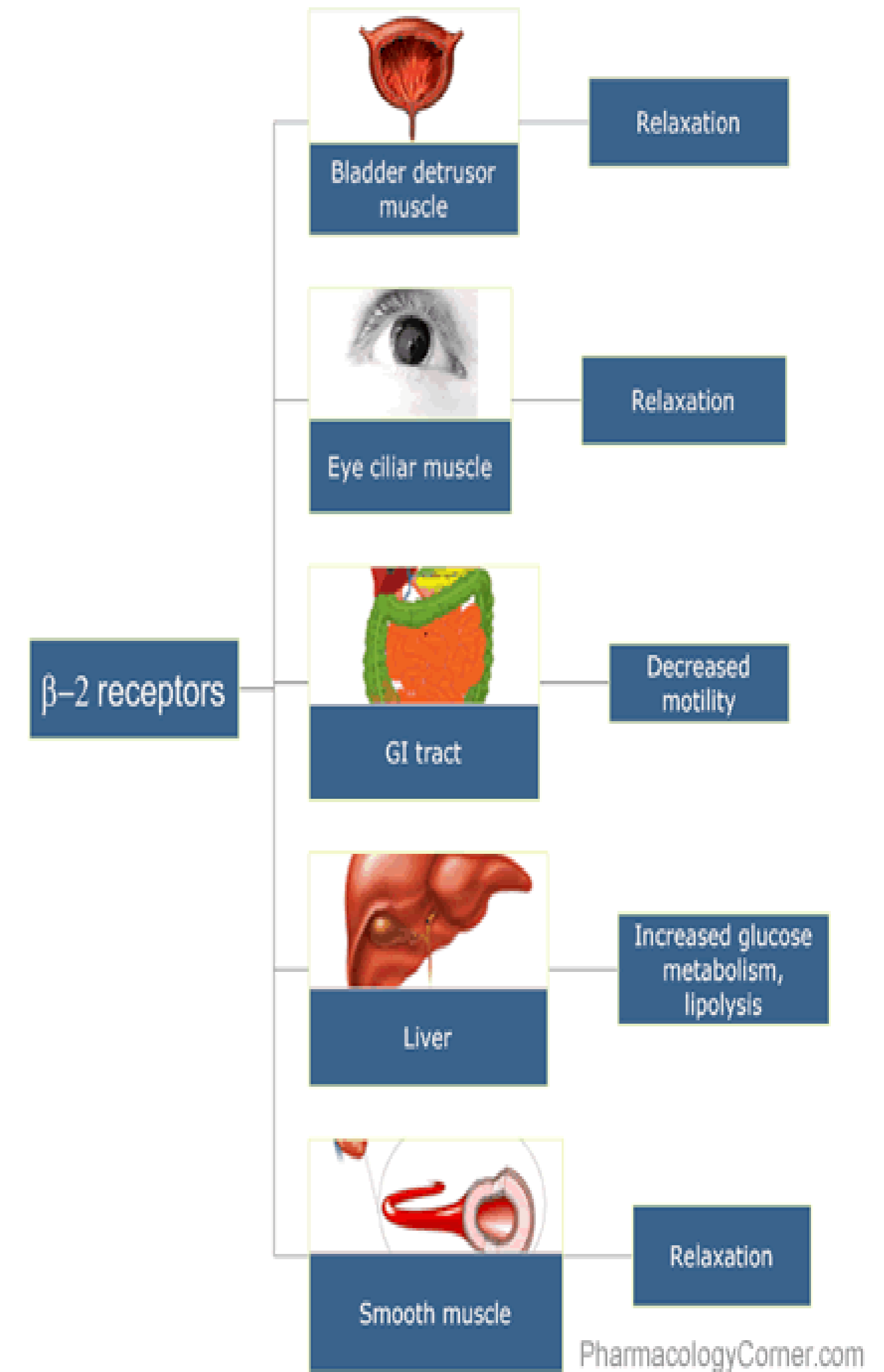
OBJECTIVES:

- Describe the different classifications for drugs that can block sympathetic nervous system.
- Describe the kinetics, dynamics, uses and side effects of alpha adrenergic drugs.
- Identify Difference between selective and non selective beta blockers.
- Identify the different classifications for beta receptors blockers.
- Describe the kinetics, dynamics, uses and side effects of beta adrenergic drugs.
- Know the preferable drug for diseases such as hypertension, glaucoma, arrhythmia, myocardial infarction, anxiety, migraine and ect....

- Titles
- Very important
- Extra information
- Doctor's notes

β-Adrenergic receptors

	Beta 1	Beta 2	Beta 3
Site	Heart	Smooth muscle	Adipose tissue
Action	<ul style="list-style-type: none"> • Increase heart Rate (Positive chronotropic effect). • Increase in contractility (Positive inotropic action). • Increase in conduction velocity (Positive dromotropic). 	<ul style="list-style-type: none"> • Relaxation of smooth muscles. • Hyperglycemia due to: <ul style="list-style-type: none"> ○ ↑ Release of glucagon from pancreas. ○ Glycogenolysis & gluconeogenesis in liver (With α1) 	<ul style="list-style-type: none"> ↑ Lipolysis.



Classification of β - Adrenoceptors Blockers

According to the selectivity

many side effect لها non selective لانها هالدرقز (TSP) تنسب
 T → Timolol
 S → Sotalol
 P → Propranolol

هل قابلت (meto =meet) اللى اسمو(Esmo)بيسو(Biso) الساعة ١٠ (At ten =Aten) وبما اني حددت وقت
 Did you meto elly Esmo Biso Aten

Non-Selective

Mixed α , β blockers

Selective

Propranolol**

Sotalol

Timolol*

Labetalol = L(α)(beta)LOL → so Mixed α , β blockers

Labetalol is an example of ISA effect
 رجع عيسى (ISA)
 لبيته (LABETAlol)

Labetalol***

CARvedilol → car needs benzene(lipid soluble).

CarveDILOL → DI mean two so mixed blocker..

Carvedilol*

Atenolol

Bisoprolol

Esmolol

Metoprolol*

According to presence of membrane stabilizing effects i.e. Propranolol, labetalol.

برب البيت انه ثابت

*** It has Intrinsic Sympathomimetic Activity (ISA) , which mean it gives initial agonist action.**

***They produce local anesthesia by removing the pain by blocking the NA channels which leads stabilization to the cell membrane of the nerve, so it won't respond to the stimulation**

(No pain sensation) (Quinidine-like action Antiarrhythmic action)

***Lipid soluble**

Pharmacokinetic of β -blockers

- Most of them are lipid soluble:
 - Well absorbed orally.
 - Are rapidly distributed.
 - Cross readily BBB.
 - CNS depressant effects i.e. Sedative effect \rightarrow \downarrow Anxiety.
 - Short $t_{1/2}$.
 - Metoprolol, propranolol, timolol, labetalol, carvedilol.

Tim(Timolol) came Labeta (Labetalol) by the car (Carvedilol) to prepare(propranolol) the meat (Metoprolol) with oil (Lipid soluble).

- Some of them are hydrophilic:
 - Irregular Oral absorption.
 - Doesn't cross readily BBB.
 - Long $t_{1/2}$.
 - Low CNS side effects.
 - Atenolol, Bisoprolol, Esmolol, Sotalol.

- Most of them have half-life from 3-10 hrs

لما نعطي الانجيكتشن (IV) نسمي ونقول اسم الله (Esmolol) عليك
وكل شيء يتيسر و يصير بسرعة (rapid action 10min)

except **Esmolol (10 min. given intravenously)**.

(Because it gets removed by esterase enzyme in the blood that's why its name start with ESM which refer to ester methyl)

- Most of them metabolized in liver & excreted in urine.

Pharmacological actions of β -Adrenergic blockers

- **Metabolic effects:**

- Hypoglycemia **due to:**

- \downarrow glycogenolysis in liver

- \downarrow glucagon secretion in pancreas

- \downarrow lipolysis in adipocytes

- Na^+ retention 2ndry to \downarrow BP \rightarrow \downarrow renal perfusion.

- All β -Adrenergic blockers mask (hide) hypoglycemic manifestations (**familiar symptoms**) in diabetic patients \rightarrow **COMA**

- **Anti-arrhythmic effects:**

- \downarrow excitability, \downarrow automaticity & \downarrow conductivity, **due to:**

- its sympathetic blocking.

- **Respiratory tract: β_2**

- Bronchoconstriction

\rightarrow **Contraindicated in asthmatic patients.**

- **Eye:**

- \downarrow Aqueous humor production from ciliary body

- \downarrow Reduce intraocular pressure (IOP)

- **e.g. timolol as eye drops**

يله جاء وقت قطرة العين It is the time(timolol) for eye drops

Con. Pharmacological actions of β -Adrenergic blockers

- **Cardiovascular system:**

- Negative (inotropic, chronotropic, dromotropic) \rightarrow \downarrow CO

- **Blood vessels: β_2**

- \uparrow peripheral resistance (PR) by blocking vasodilatory effect β_2
- \downarrow blood flow to organs \rightarrow cold extremities
- contraindicated in peripheral diseases like **Reynaud's disease** (Cold and numb feeling in fingers and toes due to vasospasm in response to cold or stress)

- **Blood pressure:**

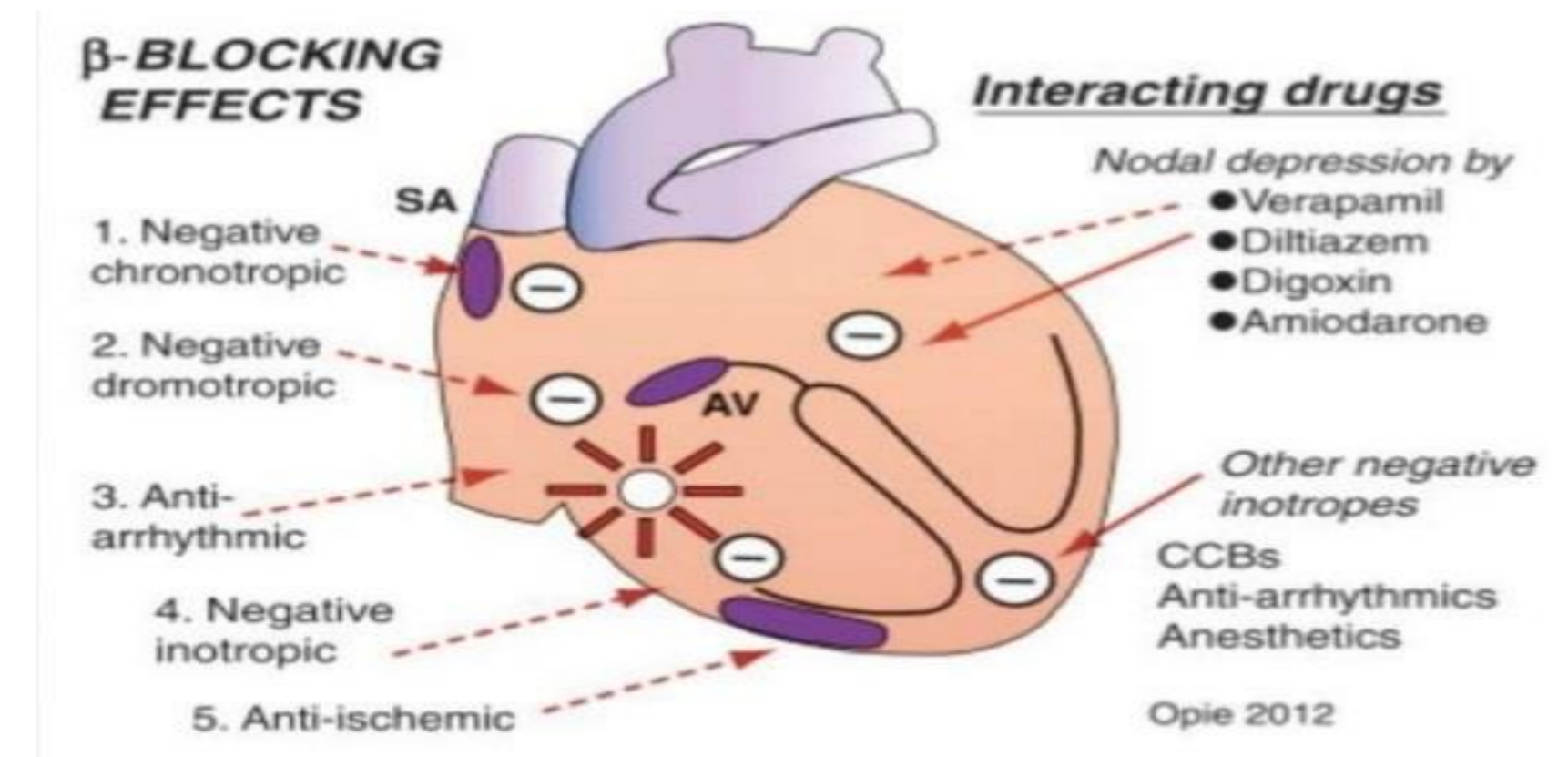
- Antihypertensive \rightarrow \downarrow BP in hypertensive patients **due to its effects on:**
 - Inhibiting heart properties \rightarrow \downarrow cardiac output (β_1)
 - β Blockade \downarrow renin secretion \downarrow Ang II & aldosterone secretion (β_1).
 - Presynaptic inhibition of NE release from adrenergic nerves

- **Intestine:**

- \uparrow Intestinal motility

- **Antianginal effects (ischemic heart disease):**

- \downarrow Heart rate (bradycardia)
- \downarrow force of contraction
- \downarrow cardiac work
- \downarrow Oxygen consumption due to bradycardia



Angina is chest pain or discomfort caused when your heart muscle doesn't get enough oxygen-rich blood. It may feel like pressure or squeezing in your chest. The discomfort also can occur in your shoulders, arms, neck, jaw, or back. Angina pain may even feel like indigestion. But, angina is not a disease. It is a symptom of an underlying heart problem, usually coronary heart disease (CHD).

Clinical Uses of β -receptor blockers

• Cardiovascular disorders

- Hypertension
- Arrhythmia
- Angina pectoris
- Myocardial infarction (used as secondary prophylactic)
- Congestive heart failure (used with another drug)

• Pheochromocytoma

• Chronic glaucoma

• Hyperthyroidism (thyrotoxicosis)

(increase in thyroid hormone which may lead to tachycardia)

• Migraine prophylaxis

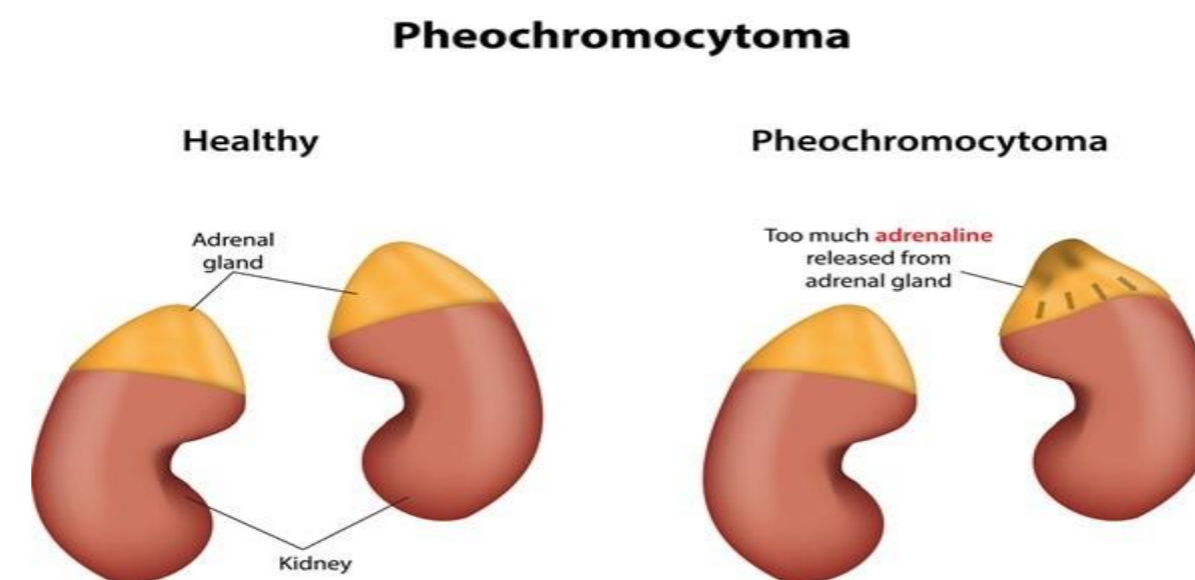
• Anxiety التوتر

Pheochromocytoma:

used with α -blockers (never alone)*
 α -blockers lower the elevated blood pressure.

β -blockers protect the heart from NE.

* (ما يستخدم لحاله عشان مايصير ارتفاع حاد في ضغط الدم، في المقابل نقدر نستخدم الفا لحاله بدون بيتا)



In Hypertension:

Propranolol, atenolol, bisoprolol : β blockers

Labetalol (I.V.): α , β blockers, Used in

***hypertensive pregnant & hypertensive crisis.**

*Remember: α -methyl dopa does this too

In cardiac arrhythmias:

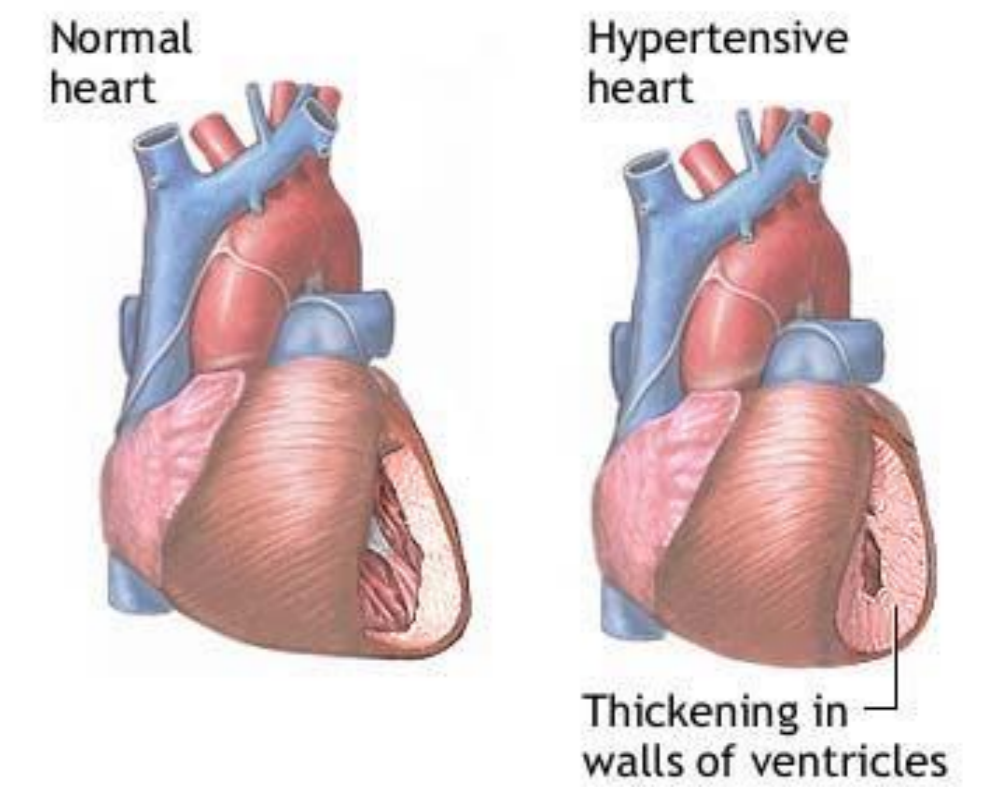
In supraventricular & ventricular arrhythmias.

Bisoprolol and carvedilol* are preferred

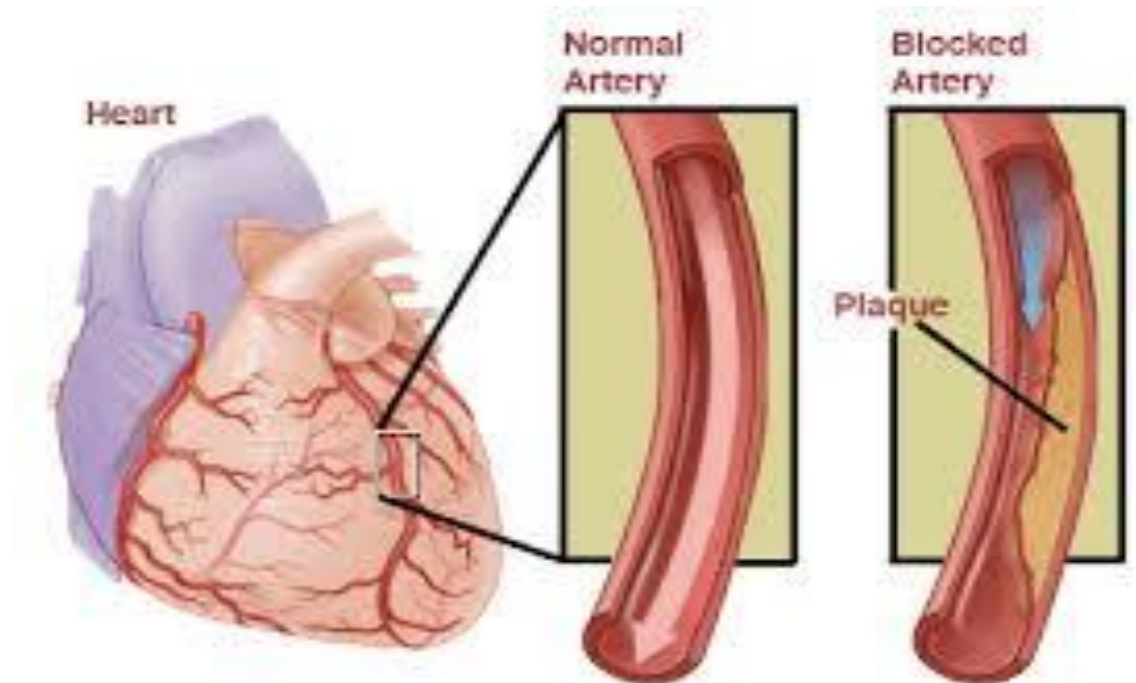
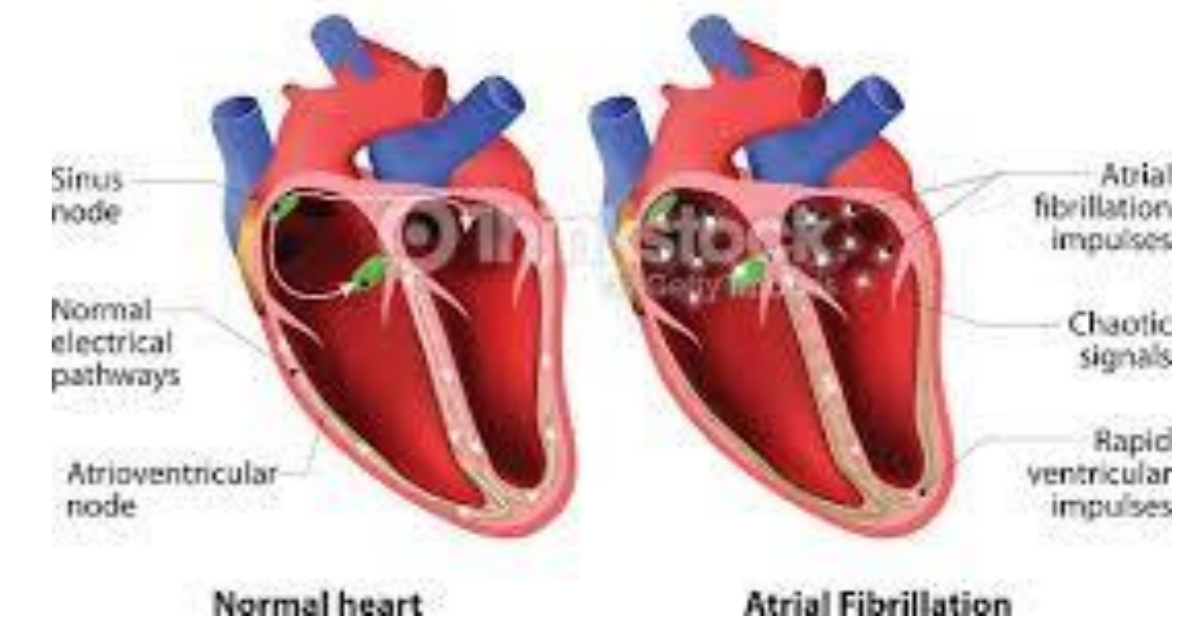
(مضاد للأكسدة ويستخدم أيضا ك antiaging)

Angina pectoris:

- \downarrow heart rate, \downarrow cardiac work & oxygen demand.
- \downarrow the frequency of angina episodes.



Cardiac arrhythmia



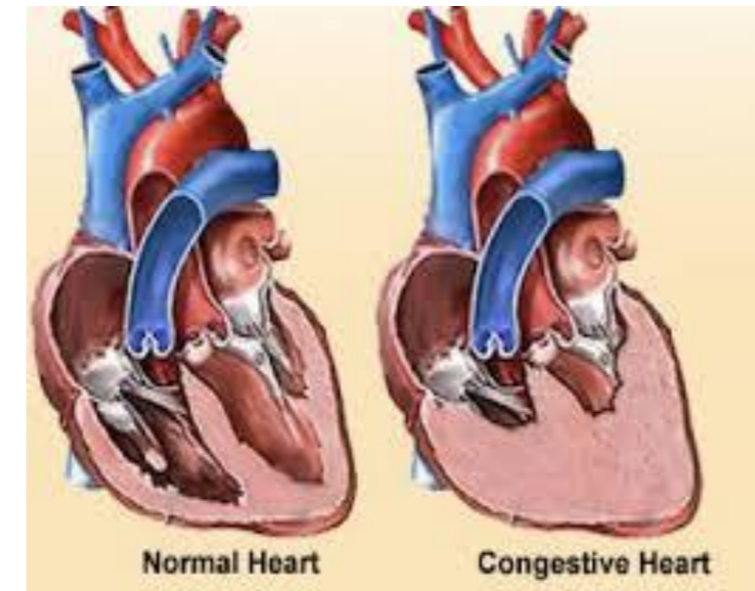
Con. Clinical Uses of β -receptor blockers

All the pictures are extra

Congestive heart failure:

e.g. **carvedilol**:

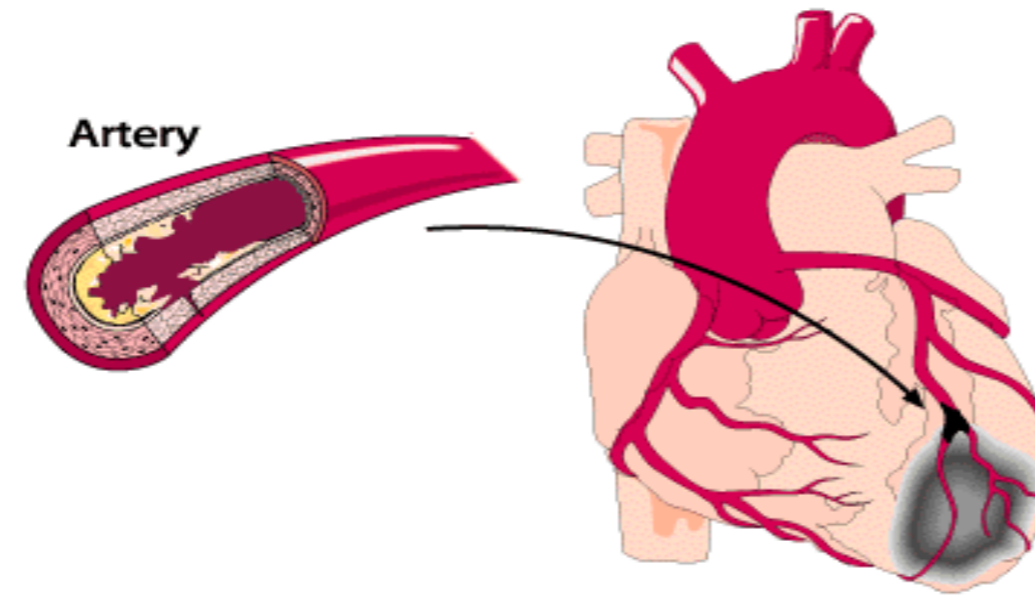
antioxidant and non selective α, β blocker
 \downarrow myocardial remodeling & \downarrow risk of sudden death.



Myocardial infarction*:

Have cardio-protective effect.

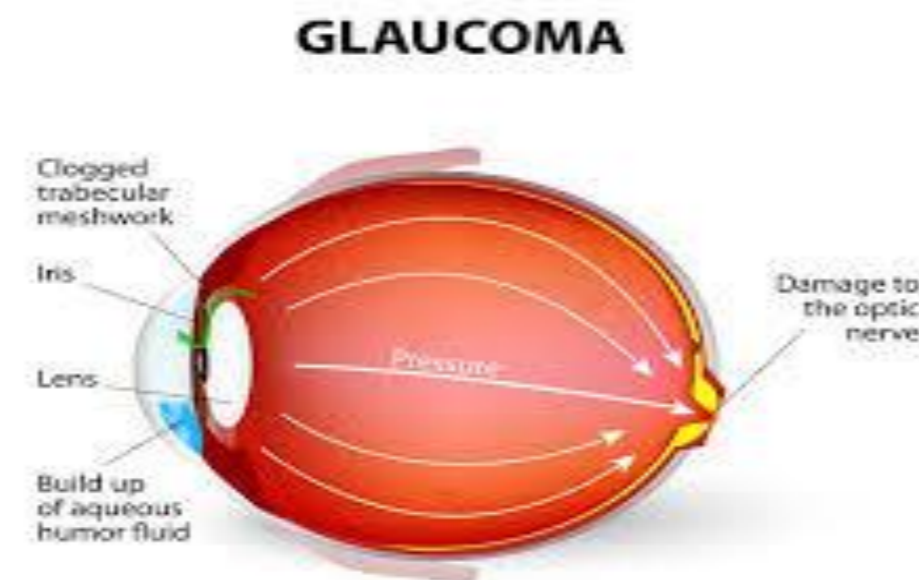
- \downarrow infarct size
- \downarrow morbidity & mortality \rightarrow
- \downarrow myocardial O₂ demand.
- Anti-arrhythmic action.
- \downarrow incidence of sudden death.



* (عادة يصيب مرضى السكر، اللي ضغطهم مرتفع وما ياخذون ادوية واللي عندهم مشكلة في تخثر الدم)

In glaucoma

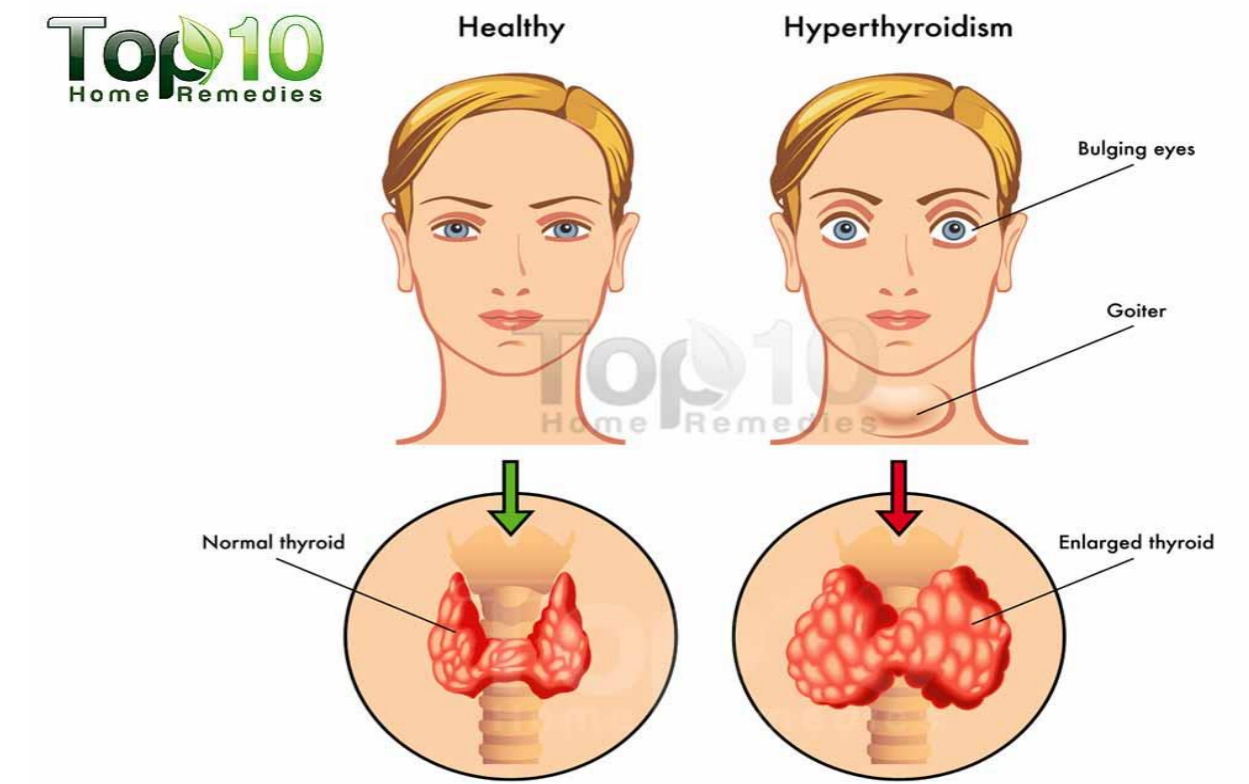
e.g. **Timolol** as eye drops



يله جاء وقت قطرة العين It is the time (timolol) for eye drops

In Hyperthyroidism

- \circ Protect the heart against sympathetic over stimulation
- \circ Controls symptoms; tachycardia, tremors, sweating.

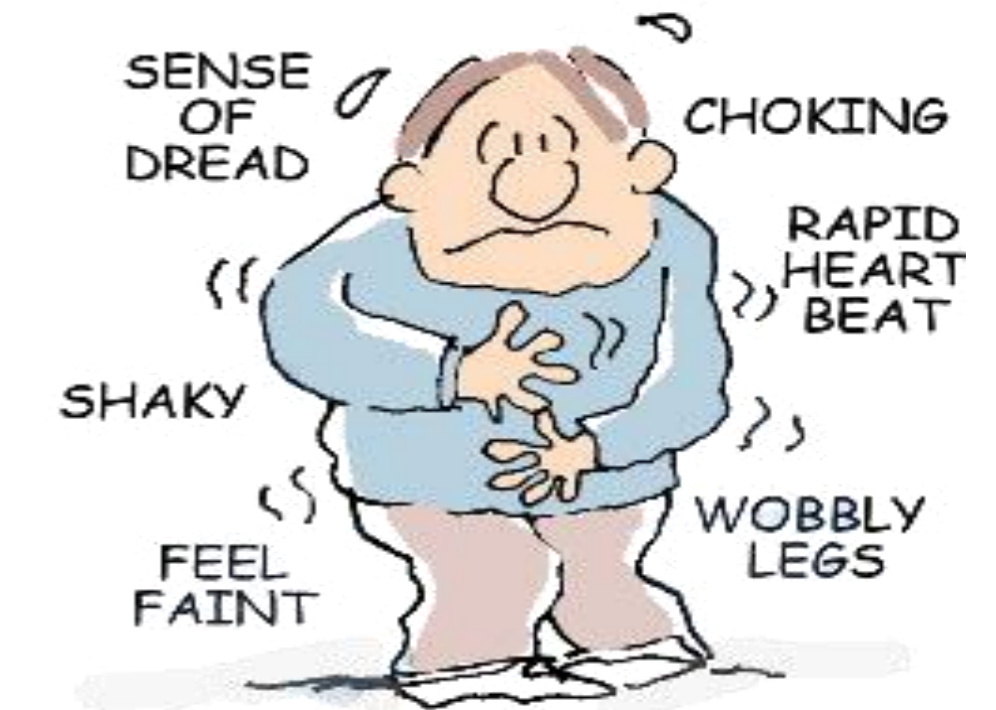


In anxiety (Social and performance type)

e.g. **Propranolol**

Controls symptoms; tachycardia, tremors, sweating.

تخيلوا شخص عنده رهاب اجتماعي او رهاب مسرح وكل ما سنحت له الفرصة يقول برب (PROPranolol) عشان يتهرب منهم.



Migraine:

Prophylactic

- \downarrow reduce episodes of chronic migraine
- \downarrow catecholamine-induced vasodilatation in the brain vasculature

e.g. **propranolol**

شخص عنده مرض الشقيقة ومن ألمها يمشي ويقول بربك هذا ألم يستحمل!



Adverse Effects of β - Adrenoceptors blockers

Due to blockade of β_1 - receptor:

- Bradycardia, hypotension, heart failure

Due to blockade of β_2 - receptor:

only with non-selective β blockers

- Hypoglycemia
- Bronchoconstriction (# Asthma, emphysema).
- Cold extremities & intermittent claudication (cramping pain in the leg is induced by exercise, due to obstruction of the arteries.) → by vasoconstriction(# Reynaud's disease)
- Erectile dysfunction & impotence
- ↑ TG hypertriglycerides
- All β -Adrenergic blockers mask hypoglycemic manifestations i.e. tachycardia, sweating,... → COMA

- Depression, and hallucinations.
- Gastrointestinal disturbances.
- Sodium retention

Precautions

Sudden stoppage will give rise to a withdrawal syndrome*:

Rebound angina, arrhythmia, myocardial infarction &

Hypertension **WHY ?** → ****Up-regulation of β -receptors.**

To prevent withdrawal manifestations → drug withdrawn gradually.

* (لازم اذا جاء يوقف الدواء يكون تدريجي عشان ما يصير عنده اعراض الانسحاب)

** (زي الواحد لما يكون مكبوت أو مسجون وفجأة يفكون عنه يبدأ يسوي كل شيء بالهبل وبيزادة ، نفس الفكرة هنا بيتا ريسبتور يكون مكبوت بالبلوكرز فلما أوقف الدرق فجأة يبدأ يتحرر ويطلع أو يعرض ريسبتورز بالهبل او بزيادة).

Contraindications of β - Adrenoceptors blockers

- Heart Block (beta blockers can precipitate heart block).
- Bronchial Asthma (safer with cardio-selective* β -blockers).
- Peripheral vascular disease (safer with cardio-selective β -blockers).
- Diabetic patients → Masking of hypoglycemia / GIVEN CAUSIOUSLY
- Hypotension
- Alone in pheochromocytoma (must be given with an α -blockers).

* (يعني خاص ب البيتا 1)

Propranolol

- Non-selective competitive blocker of β_1 & β_2
- It also has a membrane stabilizing action (quinidine-like) with a local anesthetic effect and may cause some sedating effect too.

Kinetics:

- Its **lipid soluble** so that it's completely absorbed but **70% could be destroyed during 1st pass hepatic metabolism.**
- 90-95% is protein bounded.
- Can cross the BBB. Because its lipid soluble
- Given p.o (Per os =by mouth or orally) or parenteral.

Dynamics:

- Beta-blocking effect:
 - Membrane stabilization: it blocks **Na channels** which leads to direct depressant of the myocardium (anti-arrhythmic effect).
 - CNS effect: **has sedative effect.** Also it decreases the tremor and anxiety thus used to protect against social anxiety and performance anxiety.

Uses:

1. Hypertension.
2. Arrhythmia.
3. Angina.
4. Myocardial infarction.
5. Migraine as a prophylactic therapy.
6. Pheochromocytoma (used in combination with alpha blocker and never used alone.
7. Chronic glaucoma.
8. Tremors.
9. Anxiety specially social and performance type.
10. Hyperthyroidism.

Cont.... Propranolol

Actions:

1. Heart: **by blocking β_1**
 - Inhibit heart properties which leads to **decrease in cardiac output**.
 - Has anti-ischemic action. (decrease cardiac work thus **prevent more oxygen consumption**.)
 - Has anti-arrhythmic effect. Decreases **excitability, automaticity** and **conductivity** by membrane stabilizing action.
2. Blood pressure by block **beta 1 and 2:**
 - Has anti-hypertensive action by many ways:
 - **Decrease cardiac output** by inhibiting heart properties.
 - **Decrease renin and RASS system**.
 - Presynaptic inhibition of nor-epinephrine release from adrenergic nerves.
 - Inhibiting sympathetic outflow in CNS.
3. Blood vessels by blocking **Beta2:**
 - Vasoconstriction which leads to decrease blood flow mainly to muscles and the other organs (causes cold extremities).
 - **Blood flow to the brain is not affected at all.**
4. Bronchi by blocking **Beta2:**
 - Bronchospasm specially in susceptible patients. As in asthma and COPD.
5. Intestine by blocking **Beta2:**
 - Increase intestinal motility.
6. Metabolism by blocking mainly **Beta2:**
 - In liver:: decrease **glycogenolysis** thus causing **hypoglycemia**.
 - In pancreas: decrease **glucagon secretion**.
 - In adipocytes: decrease **lipolysis**.
 - In skeletal muscles: decrease **glycolysis**.
7. On peripheral and central nervous system:
 - Has local anesthetic effect which then decreases tremor and anxiety.

Labetalol

- Blocks alpha1 and beta. Labetalol = L(α)(beta)LOL → so Mixed α, β blockers
- Rapid acting and non-selective with ISA. رجع عيسى (ISA) لبيته
- Local anesthetic effect.
- Do not alter serum lipid or blood glucose.
- Given p.o or IV.

Used in:

- Severe hypertension in pheochromocytoma.
- Hypertension crisis (e.g. during abrupt withdrawal of clonidine).
- **Used in pregnancy-induced hypertension.**

ADRs:

- Orthostatic hypotension.
- **Sedation.**
- Dizziness.

Carvedilol

- Block Alpha1 and Beta. CarveDILOL → DI mean two so mixed blocker..
- Non selective with no ISA and no local anesthetic effect.
- **Has anti-oxidant action.**
- Favorable metabolic action.

Used in:

- **Effectively in congestive heart failure** by reversing its pathophysiological changes.

ADRs:

- Edema.

Selective beta1-receptor blockers

- Selectivity in low doses but lost at high doses.
- Such as (**Atenolol / bisoprolol / Esmolol / Metoprolol**)
- No change in lipid or glucose.
- **No bronchoconstriction.**
- **Are preferable in patients with:**
 1. Asthma and COPD.
 2. Raynaud's phenomenon and PVD.
 3. Diabetics and other dyslipidemias.
 4. Variant angina.

Drug	features	Uses
Propranolol	<ul style="list-style-type: none"> • Non-selective. • B₁, B₂ blocker. 	Migraine prophylaxis.
		Hyperthyroidism (thyrotoxicosis).
		Relieve anxiety (specially social and performance types).
Timolol	<ul style="list-style-type: none"> • Non-selective. • B₁, B₂ blocker. 	Glaucoma.
Atenolol	<ul style="list-style-type: none"> • Selective . • B₁ blocker. 	Myocardial infarction.
bisoprolol		Hypertension.
Metoprolol		
Esmolol	<ul style="list-style-type: none"> • Selective. • B₁ blocker. • Ultra short acting. 	Cardiac arrhythmia.
Carvedilol	<ul style="list-style-type: none"> • Non selective. • α, B blocker. 	Congestive heart failure.
Labetalol	<ul style="list-style-type: none"> • Non-selective. • α, B blocker. 	Hypertension in pregnancy.
		Hypertension emergency.



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