

Alpha Adrenoceptor Antagonists Beta Adrenoceptor Antagonists Ganglion- Blocking Drugs

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Alpha-Receptor Antagonist Drugs

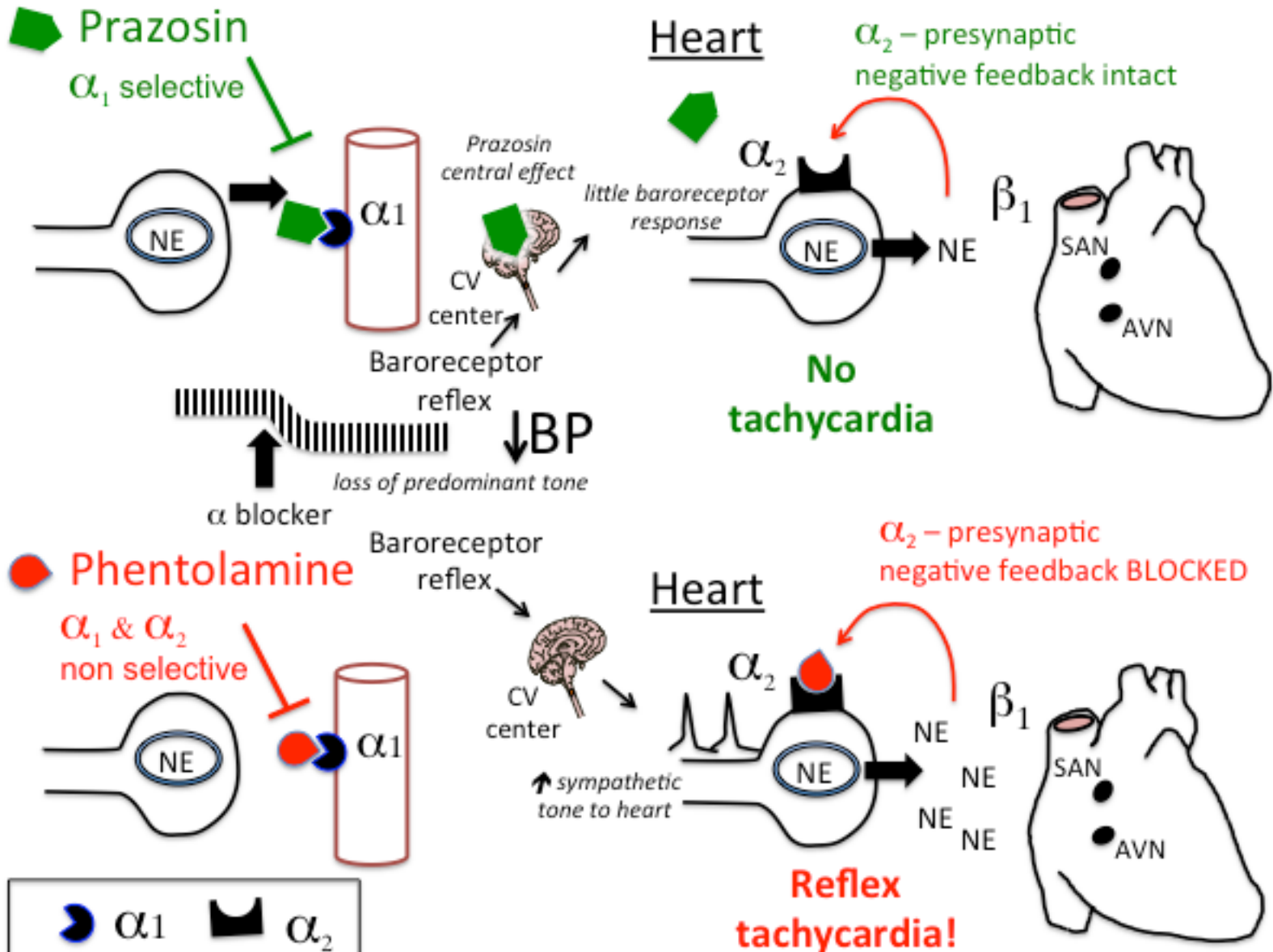
Pharmacologic Effects

Cardiovascular Effects

- ↓ peripheral vascular resistance and blood pressure.
- Prevent the pressor effects of α agonists
- often cause **orthostatic hypotension** and reflex tachycardia; nonselective ($\alpha_1 = \alpha_2$) blockers cause **tachycardia** if blood pressure is lowered below normal.



Effects of selective & Non selective alpha blockers on HR



Other Effects

- **miosis** and **nasal stuffiness**.
- **Alpha1** receptors are expressed in the base of the bladder and the prostate, and their blockade decreases resistance to the flow of urine and reduce urinary urgency.
- Alpha blockers are used for the treatment of urinary retention due to prostatic hyperplasia .



Non selective alpha blockers

Phenoxybenzamine

Binds covalently to α receptors, causing irreversible blockade of long duration (14–48 h).

Blocks α_1 & to less extent α_2 receptors.

Also **inhibits reuptake of NE** and blocks histamine (H1), ACh, and serotonin receptors.

Causes **little fall in BP in normal supine individuals**, it reduces BP when sympathetic tone is high, e.g., as a result of **upright posture**.

Absorbed poorly but usually given orally.

Uses: treatment of **pheochromocytoma**, Peripheral vascular diseases

Adverse effects

Orthostatic hypotension, tachycardia, Nasal stuffiness and inhibition of ejaculation.



Phentolamine

- Rapidly acting α blocker with short duration $t_{1/2}$ 19 min.
- Competitive α_1 and α_2 antagonist.
- Reduces peripheral resistance (α_1) and causes **cardiac stimulation** (α_2 receptors blockade enhances release of NE) .
- minor inhibitory effects at 5HT receptors and agonist effects at muscarinic (salivary, sweat, lacrimal) and H1 and H2 receptors (Increase acid secretion).
- Uses: Diagnostic of pheochromocytoma, control of hypertension due to clonidine withdrawal, Cheese reaction.
- To counteract vasoconstriction due to alpha agonists..
- **Adverse effects: severe tachycardia, arrhythmias, and myocardial ischemia.**



Selective α 1 blockers

Prazosin

- **Highly selective α 1 blocker** & less potent at α 2 receptors.
- Relaxes **both arterial and venous vascular** sm muscle & smooth muscle in the **prostate**, due to blockade of α 1 receptors with **no or little tachycardia**
- Extensively metabolized, only 50% is available after oral administration. The half-life is **3** hours.
- Favorable effect on plasma lipids: increase HDL/LDL ratio.
- **Uses** Antihypertensive , Benign prostatic hyperplasia (BPH) Blocks α 1 in bladder trigone & prostate & decreases tone & Improves urine flow .
- **Adverse effects:** First dose phenomenon i.e. postural hypotension with initial doses.



Terazosin

High bioavailability. The half-life is 9–12 hours.

Doxazosin

Has a longer half-life of about 22 hours.

Tamsulosin

Uroselective α 1A blocker. α 1A are predominant in bladder base & prostate.

30 times high affinity for α 1A

High bioavailability and a half-life of 9–15 hours.

It is used to treat **BPH**.

No effect on BP and heart rate.

Side Effects: Dizziness & retrograde ejaculation.



Yohimbine

- An indole alkaloid, is **α 2-selective antagonist**. Blocks other receptors also – 5HT, DA
- Increases ADH release
- Enhances sexual activity – aphrodisiac
- Sometimes used in the treatment of **orthostatic hypotension** because it promotes NE release through blockade of presynaptic α 2 receptors.
- Was widely used to improve male **erectile dysfunction** but has been superseded by phosphodiesterase-5 inhibitors like **sildenafil (viagra)**.



Uses of the Alpha-Receptor–Blocking Drugs

1- Pheochromocytoma

Causes intermittent or sustained hypertension, headaches, palpitations & increased sweating.

Phenoxybenzamine (orally) preoperative to control hypertension & for the **chronic treatment of inoperable or metastatic pheochromocytoma.**

Beta-receptor antagonists used to reverse the cardiac effects. **Should not be used prior to establishing effective α -receptor blockade.**

Metyrosine

α -methyltyrosine, a competitive inhibitor of **tyrosine hydroxylase**.

Used in **inoperable or metastatic pheochromocytoma**.

Can cause **extrapyramidal effects** due to reduced dopamine levels

2-Hypertensive Emergencies

Labetalol (α and β blocker) is used in Hypertensive Emergencies

3-Treatment of overdose of α_1 agonis
(phentolamine).

4-Chronic Hypertension

α 1-selective antagonists in mild to moderate systemic hypertension.

Not recommended as monotherapy because other drugs are more effective in preventing heart failure.

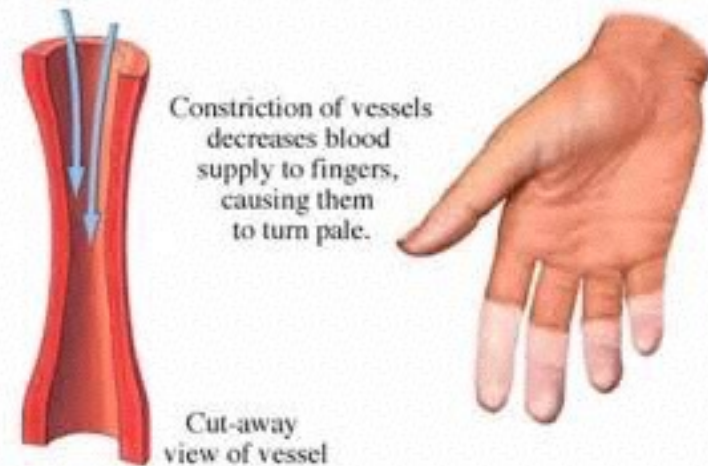
Their major adverse effect is **orthostatic hypotension**, (First-Dose Phenomenon).

5-Peripheral Vascular Disease

Raynaud's phenomenon

(excessive reversible vasospasm in the peripheral circulation).

Prazosin or **phenoxybenzamine** are used but **calcium channel blockers** are preferable for most patients.



6-Urinary Obstruction

Benign prostatic hyperplasia (BPH) is common in elderly men.

Block alpha1 receptors → reduced contraction of smooth muscle in the bladder neck and prostatic capsule → Reduce urinary urgency and improves urine flow.

Prazosin, doxazosin, and terazosin are all effective.

Tamsulosin is **α 1A-receptor antagonists** preferred in patients who have orthostatic hypotension with other α 1-receptor antagonists.

β - Adrenoceptor Antagonists

First generation: non selective (β_1 and β_2) .

Second generation: Cardioselective (β_1)

Third generation: Vasodilator β blockers.

The **selectivity is dose-related; it tends to diminish at higher drug concentrations.**

Other major differences relate to their **lipid solubility** and **local anesthetic (membrane-stabilizing)** effects. However, the concentration in plasma is **too low** for the anesthetic effects.

Most drugs are well absorbed after oral administration; peak concentrations **1–3** hours after ingestion.

- Lipophilic β blockers
 - **propranolol, metoprolol, oxprenolol, carevdilol**
 - readily absorbed from GI, metabolized in liver
 - large volume of distribution, and penetrate BBB well
 - hepatic failure prolongs their $t_{1/2}$.
- Hydrophilic β blockers
 - **acebutolol, atenolol, bisoprolol,, nadolol. sotalol**
 - less readily absorbed, not extensively metabolized
 - long plasma half-lives which are prolonged in renal failure.

Pharmacodynamics

Effects on the Cardiovascular System

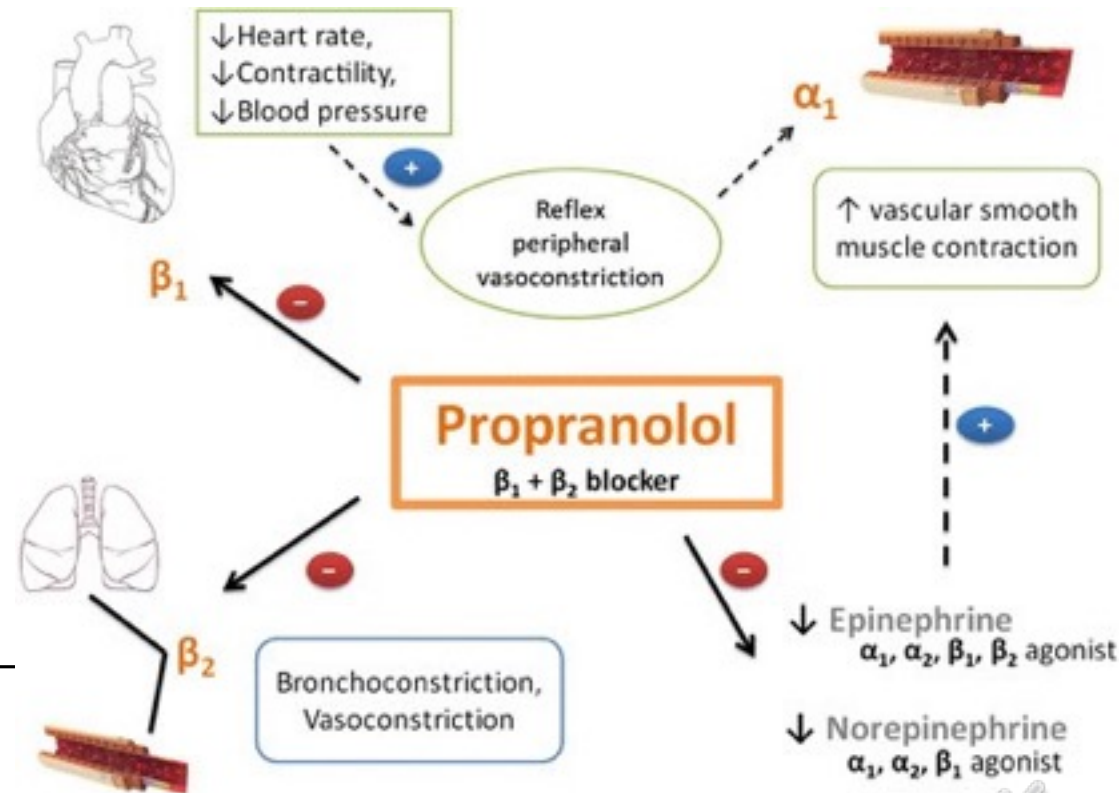
Very valuable in **hypertension, angina** and **chronic heart failure** and **following myocardial infarction (MI)**.

Heart: ↓ HR, ↓ SV, ↓ COP. ↓ AV conduction. ↓ cardiac work & O₂ consumption.

Blood vessels: ↓ BP both diastolic and systolic after continuous treatment.

Do not cause hypotension in healthy individuals with normal BP.

Nonselective and β₁-block –
Also, an inverse agonist (↓ resting Heart Rate)



Effects on the Respiratory Tract

Increase in airway resistance, particularly in patients with asthma.

β 1 blockers are safer than nonselective β blockers.

β 1-selective blocker are not sufficiently specific to *completely* avoid interactions with β 2 receptors.

Consequently, these drugs should generally be **avoided in patients with asthma.**

Many patients with chronic obstructive pulmonary disease may tolerate these drugs & the benefits e.g. in patients with concomitant **ischemic heart disease**, may outweigh the risks.

Effects on the Eye

Reduce intraocular pressure in **glaucoma** by decreasing aqueous humor production.

Glaucoma is treated by:

1- reduction of aqueous humor secretion.

2- enhancement of aqueous out-flow.

Drugs useful in reducing intraocular pressure:

Cholinomimetics, α agonists, β blockers

prostaglandin F2 analogs., diuretics

Prostaglandin analogs & β blockers are the most popular.

Metabolic and Endocrine Effects

- Beta-receptor antagonists increases LDL, triglycerides, ↓ HDL by inhibiting **lipolysis**.
- **Glycogenolysis** in the liver is inhibited after β 2-receptor blockade.
- β –blockers should be used with caution in **insulin-dependent diabetic patients**.
 β blockers delay recovery from hypoglycemia due to insulin and oral anti diabetics and mask early symptoms of hypoglycemia (tremors, sweating & tachycardia).

Specific Agents

Propranolol

- Prototype of β -blocking drug. High lipid solubility.
- Has low and dose-dependent bioavailability (first-pass metabolism).
- First-pass effect varies among individuals,
- A long-acting form of propranolol is available; prolonged absorption of the drug may occur over a 24-hour period.
- No effect on α and M receptors but may block some serotonin receptors in the brain, though the clinical significance is unclear.
- It has no partial agonist action at β receptors.

Other non-selective beta blockers

Nadolol

Has a **very long duration of action.**

Timolol

no local anesthetic activity used topically to treat glaucoma.

Sotalol

Nonselective that also exhibits Class III antiarrhythmic properties.

Cardioselective β Blockers (β 1-selective antagonists)

less effects on bronchioles, carbohydrate metabolism, lipids.

Lower incidences of Cold hands and feet.

Less liable to impair exercise tolerance

Safer in patients who experience bronchoconstriction in response to propranolol, but their β 1 selectivity is modest, so they should be used with great caution in patients with **asthma**.

β 1-selective antagonists cont..

- However, the benefits may exceed the risks, e.g., in patients with myocardial infarction.
- Beta1-selective antagonists are preferred in patients with **diabetes or peripheral vascular disease** since β 2 receptors are important in liver (recovery from hypoglycemia) and blood vessels (vasodilation).