Alpha Adrenoceptor Antagonists
Beta Adrenoceptor Antagonists
Ganglion-Blocking Drugs

Alpha-Receptor Antagonist Drugs

- **Pharmacologic Effects**
- **Cardiovascular Effects**
- Decrease peripheral vascular resistance and blood pressure.
- Prevent the pressor effects of usual doses of α agonists
- Alpha-receptor antagonists often cause orthostatic hypotension and reflex tachycardia; nonselective (α 1 = α 2,) blockers usually cause significant tachycardia if blood pressure is lowered below normal, more marked with agents that block α 2-presynaptic receptors

- **Other Effects**
- **Miosis** (small pupils) and nasal stuffiness.
- decreases resistance to the flow of urine so used for the treatment of urinary retention due to prostatic hyperplasia .

Non selective alpha blockers

Phenoxybenzamine

irreversible blockade of long duration (14–48 h).

Blocks α1& to less extent α2 receptors.

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

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

Absorbed poorly but usually given orally.

Its major use is in the treatment of **pheochromocytoma**

Adverse effects

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

- **Phentolamine**
- Competitive α1 and α2 blocker.
- Reduces peripheral resistance (α1) and causes cardiac stimulation due to antagonism of presynaptic α 2 receptors (leading to enhanced release of NE and sympathetic activation from baroreflex).
- Minor inhibitory effects at serotonin receptors & agonist at muscarinic & histamine receptors.
- Adverse effects are severe tachycardia, arrhythmias, and myocardial ischemia.
- Used in the treatment of **pheochromocytoma.**

- **Selective alpha 1 blockers**
- **Prazosin**
- Relaxes **both arterial and venous vascular** smooth muscle & smooth muscle in the **prostate**, due to blockade of α 1 receptors with **no or little tachycardia**
- Bioavailability 50% & the half-life is **3** hours.
- **Terazosin**
- Effective in **hypertension** & in **benign prostatic hyperplasia (BPH).**
- High bioavailability. The half-life is 9–12 hours.
- **Doxazosin**
- Effective in of **hypertension** and BPH.
- Has a longer half-life of about 22 hours.

Their major adverse effect is orthostatic hypotension, which may be severe after the first few doses but is otherwise uncommon (First-Dose Phenomenon).

Tamsulosin

higher affinity for **α1A & α1D** than for the α1B subtype.

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

Has relatively greater potency in inhibiting contraction in *prostate* smooth muscle versus *vascular* smooth muscle compared with other α 1-selective antagonists.

used to treat **BPH.**

has less effect on standing blood pressure in patients.

Other Alpha- Adrenoceptor Antagonists

Labetalol

Has both α1 and β-antagonistic effects

Chlorpromazine and **haloperidol**

Neuroleptic drugs & also block α receptors.

Ergot derivatives, eg, **ergotamine** and **dihydroergotamine** are reversible α blockers.

- **Yohimbine**
- An indole alkaloid, is **α 2-selective antagonist**.
- It is sometimes used in the treatment of **orthostatic hypotension** because it promotes NErelease through blockade of presynaptic α 2 receptors.
- It was once widely used to improve male **erectile dysfunction** but has been superseded by phosphodiesterase-5 inhibitors like **sildenafil.**

Uses of the Alpha-Receptor–Blocking Drugs

1- Pheochromocytoma

Phenoxybenzamine (orally) preoperative & for the **chronic treatment of inoperable or metastatic pheochromocytoma, given with β blockers.**

Metyrosine (α -methyltyrosine), an inhibitor of tyrosine hydroxylase, useful in inoperable or metastatic pheochromocytoma.

2-Hypertensive Emergencies

Labetalol is used in **Hypertensive Emergencies**

3-Chronic Hypertension

α 1-selective antagonists in mild to moderate hypertension butNot recommended as monotherapy because other drugs are more effective in preventing heart failure.

4-Peripheral Vascular Disease

Raynaud's phenomenon (excessive reversible vasospasm in the peripheral circulation) **Prazosin** or **phenoxybenzamine** are used but **calcium channel blockers** may be preferable for most patients.

5-Urinary Obstruction

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

Improving urine flow involves partial reversal of smooth muscle contraction in the enlarged prostate and in the bladder base.

Prazosin, doxazosin, and terazosin are all effective.

Tamsulosin is **α 1A-receptor antagonists** effective in BPH and has relatively minor effects on blood pressure at a low dose.

β- Adrenoceptor Antagonist Drugs

Differ in their relative affinities for β 1 and β 2 receptors.

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

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

Absorption

Most of the drugs are well absorbed after oral administration; peak concentrations occur **1–3** hours after ingestion. **Propranolol** & **penbutolol** are lipophilic and readily cross the blood-brain barrier .

Most β antagonists have half-lives of 3–10 hours but effects of these drugs are well beyond the time predicted from half-life data.

	Selectivity	Partial Agonist	Local Anesthetic	t½
Acebutolol	β1	Yes	**Yes**	3–4hours
Atenolol	β1	No	No	6–9 hours
Bisoprolol	β1	No	No	9–12 hours
Esmolol	β1	No	No	10 minutes
Labetalol	None (α blocker)	Yes	**Yes**	5 hours
Metoprolol	β 1	No	**Yes**	3–4 hours
Nadolol	None	No	No	14–24 hours
Penbutolol	None	Yes	No	5 hours
Pindolol	None	Yes	**Yes**	3–4 hours
Propranolol	None	No	**Yes**	3.5–6 hours
Sotalol	None	No	No	12 hours
Timolol	None	No	No	4–5 hours

Pharmacodynamics

Effects on the Cardiovascular System

Chronic administration leads to a fall in peripheral resistance in patients with hypertension.

This may acutely lead to a **rise in peripheral resistance** from **unopposed α -receptor-mediated effects** as the sympathetic nervous system is activated in response to the fall in cardiac output.

Nonselective and β 1-blocking drugs antagonize the release of **renin** caused by the sympathetic nervous system.

Effects on the Respiratory Tract

Increase in airway resistance in patients with asthma.

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

Many patients 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.

The open-angle glaucoma is a chronic condition, and **treatment is largely pharmacologic**.

Glaucoma is treated by:

1- reduction of aqueous humor secretion.

2- enhancement of aqueous out-flow.

Drugs useful in reducing intraocular pressure:

1-cholinomimetics

2-α agonists

3- β blockers

4- prostaglandin F2 analogs.

5- diuretics

Prostaglandin analogs & β blockers are the most popular.

- **Metabolic and Endocrine Effects**
- Beta-receptor antagonists inhibit **lipolysis**.
- **Glycogenolysis** in the liver is inhibited after β 2-receptor blockade.
- β –blockers should be used with caution in **insulin-dependent diabetic patients**.

Effects Not Related to Beta-Blockade

Partial agonists **Pindolol** & **Penbutolol** are **useful** in patients who develop **bradycardia or bronchoconstriction.**

Local anesthetic action the concentration in plasma is **too low** for the anesthetic effects .

These membrane-stabilizing β- blockers are **not used topically on the eye,** where local anesthesia of the cornea would be undesirable.

Sotalol is a nonselective β blocker that has **marked class III antiarrhythmic** effects, reflecting **potassium channel blockade** (used to treat both ventricular & supraventricular arrhythmias).

Specific Agents

- **Propranolol**
- Prototype of β -blocking drug.
- Low and dose-dependent bioavailability &there is great individual variability in the plasma concentrations achieved after oral propranolol.
- No partial agonist action at β receptors.
- **Metoprolol, Atenolol.**
- **β1-selective** antagonists, **Safer in asthma**, but their β 1 selectivity is modest, so they should be used with great caution in patients with a **history of asthma.**
- However, the benefits may exceed the risks, eg, 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).

Nebivolol, the most highly selective β 1 blocker, causes vasodilation due to nitric oxide pathway.

Nadolol, has a **very long duration of action**.

Timolol, nonselective used topically to treat glaucoma.

Pindolol, acebutolol, and **celiprolol.**

Have **partial β -agonist activity.**

Effective in hypertension & angina and less likely to cause **bronchoconstriction, bradycardia and abnormalities in plasma lipids.**

Pindolol, non-selective **beta-adrenoceptor/5-HT1A** antagonist accelerates the antidepressant effect of selective serotonin reuptake inhibitors (SSRI).

Celiprolol, a β 1-selective antagonist with a **partial β2 -agonist activity** & may have less adverse bronchoconstrictor effect in asthma and may even promote bronchodilation.

Acebutolol is also a β 1-selective antagonist.

- **Labetalol**
- Racemic mixture of two pairs of isomers. The (*S,S*) & (*R,S*) isomers are inactive, **(*S,R*)- is a potent α1 blocker**, & the **(*R,R*)-isomer is a potent β blocker**.
- Causes Hypotension with less tachycardia.
- **Carvedilol**
- A nonselective beta blocker/alpha-1 blocker indicated in congestive heart failure (CHF) and hypertension.
- **Esmolol**
- β 1-selective blocker.
- An ester so esterases in red blood cells rapidly metabolize it. half-life 10 minutes. During continuous infusions of esmolol, **steady-state concentrations** are achieved quickly, and actions of the drug are terminated rapidly when its infusion is discontinued.
- Esmolol may be **safer** in critically ill patients who require a β -adrenoceptor antagonist.

Clinical uses

- **Hypertension**
- often used with either a diuretic or a vasodilator.
- **Ischemic Heart Disease**
- Reduce the frequency of anginal episodes and improve exercise tolerance in patients with angina.
- They decrease cardiac work, reduce oxygen demand & Slow heart rate which contribute to clinical benefits.
- The long-term use of **timolol, propranolol,** or **metoprolol** in patients who have had a myocardial infarction prolongs survival
- β -adrenoceptor antagonists are strongly indicated in the acute phase of a myocardial infarction.
- Contraindications include bradycardia, hypotension, moderate or severe left ventricular failure, shock, heart block, and active airways disease.
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- **Cardiac Arrhythmias**
- Effective in supraventricular & ventricular arrhythmias
- β antagonists slow ventricular response rates in atrial **flutter and fibrillation** & **reduce ventricular ectopic** beats, particularly if the ectopic activity has been precipitated by catecholamines.
- **Sotalo**l has a **marked class III antiarrhythmic** effects, due to **potassium channel blockade** (treats both ventricular & supraventricular arrhythmias).
- **Heart Failure**
- **Metoprolol, bisoprolol,** and **carvedilol** are effective in reducing mortality in selected patients with chronic heart failure.
- Cautious long-term use with gradual dose increments in patients who tolerate them may prolong life.
- Although mechanisms are uncertain, there appear to be beneficial effects on **myocardial remodeling** and in decreasing the risk of sudden death.

- **Glaucoma**
- **Timolol** and related β antagonists are suitable for local use in the eye because they lack local anesthetic properties.
- have efficacy comparable to that of **epinephrine** or **pilocarpine** in open-angle glaucoma and are far better tolerated. Sufficient timolol may be absorbed from the eye to cause serious adverse effects on the heart and airways in susceptible individuals.
- **Hyperthyroidism**
- The effects are due to **blockade of adrenoceptors** and perhaps in part to the **inhibition of peripheral conversion of thyroxine to triiodothyronine.**
- Propranolol has been used extensively in **thyroid storm** (severe hyperthyroidism) to control supraventricular tachycardias that often precipitate heart failure.

- **Neurologic Diseases**
- Propranolol reduces the frequency and intensity of **migraine** headache.
- Other β -receptor antagonists with preventive efficacy include **metoprolol** , **atenolol, timolol,** and **nadolol**.
- The mechanism is not known.
- β antagonists reduce certain **tremors.**
- The **somatic manifestations of anxiety** may respond dramatically to low doses of **propranolol**, particularly when taken prophylactically. Benefit has been found in musicians with **performance anxiety ("stage fright").**
- Propranolol may be used in symptomatic treatment of alcohol withdrawal in some patients.

- **Clinical Toxicity of the Beta Blockers**
- Bradycardia, cold hands & feet in winter. mild sedation, vivid dreams, and rarely, depression.
- worsening of preexisting **asthma.**
- Caution in patients with severe peripheral vascular disease and in patients with compensated heart failure. A very small dose of a β antagonist may provoke severe cardiac failure. interact with the calcium antagonist **verapamil** causing heart failure heart block.
- Stopping β blockers suddenly is dangerous due to **up-regulation** of **β receptors**.
- Insulin-dependent diabetic patients with frequent hypoglycemic reactions better use **β 1 antagonists.**

Ganglion-Blocking Drugs

Tetraethylammonium (TEA)

First ganglion blocker, very short duration of action.

Hexamethonium ("C6")

The first drug effective for hypertension. **Decamethonium**, the "C10" analog of hexamethonium, is a depolarizing neuromuscular blocking agent.

Mecamylamine

A secondary amine, was developed to improve absorption from the GIT because the quaternary amine were poorly absorbed after oral administration.

Trimethaphan

A short-acting ganglion blocker, is inactive orally and is given by intravenous infusion.

- **Organ System Effects**
- **Central Nervous System**
- **Mecamylamine** enters the CNS causing Sedation, tremor, choreiform movements, and mental abnormalities.
- **Eye**
- **Cycloplegia** with loss of accommodation & **moderate dilation of the pupil** because parasympathetic tone usually dominates this tissue.
- **Cardiovascular System**
- Marked decrease in arteriolar and venomotor tone.
- **BP** may fall because both peripheral vascular resistance and venous return are decreased
- **Orthostatic or postural hypotension**, **diminished contractility** and, because the sinoatrial node is usually dominated by the parasympathetic nervous system, a **moderate tachycardia**.

- **Other Effects:**
- Inhibit secretion & Motility & cause constipation,
- urinary retention in men with prostatic hyperplasia.
- **Sexual function** is impaired & **Sweating** is reduced.
- . **Clinical Applications & Toxicity**
- **Rarely used** because more selective agents are available.
- **Mecamylamine**
- Blocks central nicotinic receptors could be an adjunct with the transdermal nicotine patch to **reduce nicotine craving in patients attempting to quit smoking**.
- **Trimethaphan**
- Occasionally used in the treatment of hypertensive emergencies and in producing hypotension in neurosurgery to reduce bleeding in the operative field.
- The toxicity of the ganglion-blocking drugs is limited to the autonomic effects.
- These effects are intolerable except for acute use.