Alpha Adrenoceptor Antagonists

Beta Adrenoceptor Antagonists

Ganglion-Blocking Drugs
Pharmacologic Effects

Cardiovascular Effects

• Decrease peripheral vascular resistance and blood pressure.
• Prevent the pressor effects of usual doses of alpha agonists.
• Alpha-receptor antagonists often cause orthostatic hypotension and reflex tachycardia; nonselective ($\alpha_1 = \alpha_2$) blockers cause tachycardia if blood pressure is lowered below normal.
• **Orthostatic hypotension** is due to blockade of $\alpha_1$ receptors in vascular smooth muscle.

• Contraction of veins is an important component of the normal capacity to maintain blood pressure in the upright position since it decreases venous pooling in the periphery.

• Constriction of arterioles in the legs also contributes to the normal orthostatic response.

• **Tachycardia** is marked with agents that block $\alpha_2$-presynaptic receptors in the heart, since the augmented release of NE will further stimulate $\beta_1$ receptors in the heart.
Other Effects

• Blockade of $\alpha$ receptors in other tissues elicits **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.

• Alpha blockers are used for the **treatment of urinary retention due to prostatic hyperplasia**.
Effects of selective & Non selective alpha blockers on HR

- **Prazosin**
  - $\alpha_1$ selective
  - Decreases $\alpha_1$ tone + NE rise
  - NE + CV baroreceptor response
  - Loss of predominant tone + BP rise
  - $\alpha_2$ - presynaptic negative feedback intact
  - No tachycardia

- **Phentolamine**
  - $\alpha_1$ & $\alpha_2$ non-selective
  - Decreases both $\alpha_1$ & $\alpha_2$ tone + NE rise
  - NE + CV baroreceptor response
  - Loss of predominant tone + BP rise
  - $\alpha_2$ - presynaptic negative feedback BLOCKED
  - Reflex tachycardia!
Non selective alpha blockers

Phenoxybenzamine

Binds covalently to α receptors, causing 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.

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 α1 and α2 antagonist.
• Reduces peripheral resistance (α1) and causes **cardiac stimulation** (α2 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 NE, Dopamine.
• **Adverse effects:** severe tachycardia, arrhythmias, and myocardial ischemia.
Selective α 1 blockers

Prazosin

- Highly selective α1 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 α1 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 α1A/α1D blocker. α 1A are predominant in bladder base & prostate.
30 times high affinity for α1A
High bioavailability and a half-life of 9–15 hours.
Has greater potency in inhibiting contraction in prostate smooth muscle versus vascular smooth muscle.
It is used to treat BPH.
No effect on BP and heart rate.
Side Effects: Dizziness & retrograde ejaculation.
Other Alpha-Adrenoceptor Antagonists
Labetalol
- Has both $\alpha_1$ and $\beta$-antagonistic effects

Chlorpromazine and haloperidol
- Potent dopamine receptor antagonists (Neuroleptic drugs) but are also antagonists at $\alpha$ receptors. Their antagonism of $\alpha$ receptors causes hypotension.

Ergot alkaloids
- Ergotoxine, Ergotamine are partial agonist and antagonist at adrenergic $\alpha$, 5HT and DA receptors. Ergotoxine, dihydroergotoxine are more potent $\alpha$ blocker and less potent vasoconstrictor than ergotamine. USE: Ergotamine is used in Migraine
Yohimbine

- An indole alkaloid, is $\alpha_{2}$-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 $\alpha_{2}$ receptors.
- Was 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

Tumor of the adrenal medulla or sympathetic ganglion cells.

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 is used in Hypertensive Emergencies

3-Treatment of overdose of α1 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, which may be severe after the first few doses but is otherwise uncommon (First-Dose Phenomenon).

They may cause dizziness.

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. 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 & preferred in patients who have orthostatic hypotension with other α 1-receptor antagonists.
Beta Adrenoceptor Antagonists

More specific effect on β receptors due to similarity to isoproterenol structure.

All β blockers are competitive antagonists

• 1958 → Dichloroisoprenaline
  (low potency & partial agonist)
• 1963 → Propranolol
  blocks β1,β2 & weak activity on β3.

Also, an inverse agonist (↓ resting Heart Rate)
Differ in their relative affinities for $\beta_1$ and $\beta_2$ 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, propranolol) 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.
3 Generations of β-blockers

β-Adrenergic Receptor Antagonists

First-Generation Nonselective
- Nadolol
- Oxprenolol
- Penbutolol
- Pindolol
- Propranolol
- Sotalol
- Timolol

Second-Generation β₁-Selective
- Acebutolol
- Atenolol
- Bisoprolol
- Esmolol
- Metoprolol

Third-Generation Vasodilatory
- Nonselective
  - Carteolol
  - Carvedilol
  - Labetalol
- β₁-Selective
  - Betaxolol
  - Nebivolol

*Have additional α-blocking activity.

Distribution and Clearance

Rapidly distributed with large volumes of distribution.

Propranolol & penbutolol are lipophilic and readily cross the blood-brain barrier.

Most β antagonists have half-lives of 3–10 hours.

Esmolol is rapidly hydrolyzed & its half-life 10 minute.

Propranolol and metoprolol are extensively metabolized in the liver.

Atenolol & pindolol are less completely metabolized.

Nadolol is excreted unchanged in the urine and has the longest half-life (up to 24 hours).

The half-life of Nadolol is prolonged in renal failure.

The effects of these drugs are well beyond the time predicted from half-life data.
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.
In the vascular system, $\beta$-receptor blockade opposes $\beta_2$-mediated vasodilation. This may lead to a rise in peripheral resistance from unopposed $\alpha$-receptor-mediated effects as the sympathetic nervous system is activated in response to the fall in cardiac output, but chronic administration leads to a fall in peripheral resistance in patients with hypertension.

Nonselective and $\beta_1$-blocking drugs antagonize the release of renin caused by the sympathetic nervous system.
Effects on the Respiratory Tract

Increase in airway resistance, particularly in patients with asthma.

$\beta_1$ blockers are safer than nonselective $\beta$ blockers. $\beta_1$-selective blocker are not sufficiently specific to completely avoid interactions with $\beta_2$ 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).
Effects Not Related to Beta-Blockade

Partial agonists Pindolol, Celiprolol & Acebutolol
- Preferred in those prone to severe bradycardia
- Withdrawal less likely to exacerbate hypertension/angina
- Plasma lipid profile is not/less worsened.
- *useful* in patients who develop *bronchoconstriction*.

Sotalol is a nonselective β blocker that has *marked* class III antiarrhythmic effects, reflecting *potassium channel blockade* (used to treat both ventricular & supraventricular arrhythmias).
Local anesthetic action (membrane-stabilizing) is a prominent effect of several β blockers (Propranolol, Pindolol, Labetalol, Metoprolol, Acebutolol). However, the concentration in plasma is too low for the anesthetic effects to be evident. These membrane-stabilizing β-blockers are not used topically on the eye, where local anesthesia of the cornea would be undesirable.
Specific Agents
Propranolol

Prototype of $\beta$-blocking drug.

blocks $\beta_1$, $\beta_2$ & weak activity on $\beta_3$.

Also, an inverse agonist (↓ resting Heart Rate)

- Has low and dose-dependent bioavailability (first-pass metabolism).
- First-pass effect varies among individuals, so there is great individual variability in the plasma concentrations after oral propranolol.
- A long-acting form of propranolol is available; prolonged absorption of the drug may occur over a 24-hour period.
- No effect on $\alpha$ 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 $\beta$ receptors.
Other non-selective beta blockers

Nadolol

Has a very long duration of action.
Used in hypertension, acute MI, glaucoma & prevent migraine

Timolol

Nonselective with no local anesthetic activity
used to treat hypertension, acute MI, glaucoma & prevent migraine

Sotalol

Nonselective that also exhibits Class III antiarrhythmic properties.
Cardioselective β Blockers (β1-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.
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 \( \beta 2 \) receptors are important in liver (recovery from hypoglycemia) and blood vessels (vasodilation).
Metoprolol

• Cardioselective, Preferred in diabetics on insulin or oral hypoglycemics.
• Less likely to worsen asthma.
• used to treat **angina** and **hypertension** & also used to treat or prevent Myocardial Infarction (AMI) without bradycardia.

Atenolol

• Selective beta 1 blocker with low lipid solubility. Longer duration action. One dose/day.
• Side effects related to CNS are less prominent No effect on bronchus, carbohydrate metabolism, lipids
• Most commonly used in Hypertension & angina.
Nebivolol
The most highly selective $\beta_1$ blocker.

$\uparrow$ endothelial NO release (vasodilating effect)
Antioxidant properties that can protect the vascular wall from free radicals that damage blood vessels
Activates cardiac $\beta_3$-adrenergic receptors (protective mechanism against heart failure and myocardial ischemia)

Bisoprolol
Selective beta 1 blocker with low lipid solubility.
Longer duration action. One dose/day used to treat cardiovascular diseases such as hypertension, coronary heart disease, arrhythmias.
Esmolol

- Contains an ester linkage; esterases in red blood cells rapidly metabolize it.
- Has a short half-life (about 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.
- Esmolol is useful in controlling supraventricular arrhythmias, arrhythmias associated with thyrotoxicosis, perioperative hypertension, and myocardial ischemia in acutely ill patients.
**β Blockers with partial β-agonist activity.**

Effective in hypertension and angina & less likely to cause bronchoconstriction, bradycardia and abnormalities in plasma lipids than other β blockers.

**Pindolol** is a non-selective beta- adrenoceptor/5-HT1A antagonist accelerates the antidepressant effect of selective serotonin reuptake inhibitors.

**Celiprolol** is 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.

Used in the treatment of hypertension, angina pectoris and cardiac arrhythmias.
Drugs that block both alpha and beta receptors

Labetalol

- Racemic mixture of two pairs of isomers.
- The (S,S) & (R,S) isomers are inactive.
- (S,R)- is a potent α1 blocker
- (R,R)-isomer is a potent β blocker.
- Causes Hypotension with less tachycardia than occurs with phentolamine & similar α blockers.
- it is a **partial agonist** at beta2- receptors
- May cause postural hypotension.
- Used IV to treat severe hypertension emergency.
Carvedilol

- A nonselective beta blocker/alpha-1 blocker, calcium channel blocker.
- More potent at β than at α1 receptors
- Antioxidant property.

Inhibition of neutrophil release of O2

4. Antiapoptotic properties (prevent myocyte death and reduce infarct size in persons with myocardial ischemia and Systolic HF)

- Use: Hypertension, Angina, congestive heart failure
Clinical Uses of the Beta-Receptor–Blockers. Hypertension

- Although many hypertensive patients respond to a β blocker used alone, the drug is often used with either a diuretic or a vasodilator.
- In spite of the short half-life of many β antagonists, these drugs may be administered once or twice daily and still have an adequate therapeutic effect.
- Less effective in the elderly and in black patients.
- However, these differences are relatively small and may not apply to an individual patient.
Ischemic Heart Disease

- Reduce the frequency of anginal episodes and improve exercise tolerance in patients with angina.
- **Decrease cardiac work & reduce oxygen demand.**
- Slow heart rate may contribute to clinical benefits.
- The long-term use of **timolol, propranolol, or metoprolol** in patients who have had a myocardial infarction prolongs survival
- β blockers 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.
Cardiac Arrhythmias

• Effective in the treatment of both supraventricular and ventricular arrhythmias
• By increasing the AV nodal refractory period, β antagonists slow ventricular response rates in atrial flutter and fibrillation.
• They reduce ventricular ectopic beats, particularly if caused by catecholamines.

• Sotalol has a marked class III antiarrhythmic effects, due to potassium channel blockade (treats both ventricular & supraventricular arrhythmias).
Heart Failure

• Clinical trials have demonstrated that at least three β antagonists, metoprolol, bisoprolol, and carvedilol are effective in reducing mortality in selected patients with chronic heart failure.

• Although administration of these drugs may worsen acute congestive 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.
Hypertrophic Cardiomyopathy

- propranolol reduces the incidence of sudden death in patients with hypertrophic cardiomyopathy (HCM).
- The negative inotropic and chronotropic effects of beta-blockers attenuate adrenergic-induced tachycardia, ventricular contractility, and stiffness, thereby improving ventricular relaxation, increasing time for diastolic filling, and reducing excitability.
Glaucoma

Clinical Uses cont..

• Systemic administration of $\beta$-blocking drugs for other indications, reduced intraocular pressure in patients with glaucoma. Topical administration also reduces intraocular pressure.

• The mechanism involves reduced production of aqueous humor by the ciliary body.

• **Timolol** and related $\beta$ antagonists are suitable for local use in the eye because they lack local anesthetic properties.

• Beta antagonists have an 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

- Excessive CA action is important in the pathophysiology of hyperthyroidism, especially in relation to the heart.
- The β antagonists are beneficial in this condition due to blockade of adrenoceptors & in part to the inhibition of peripheral conversion of thyroxine to triiodothyronine.
- Propranolol has been used extensively in patients with thyroid storm (severe hyperthyroidism) to control supraventricular tachycardias that often precipitate heart failure.
- Propranolol has a direct antithyroid action, namely inhibition of iodide transport in the intact thyroid follicle.
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-Receptor Antagonist Drugs

- **Bradycardia** is the most common adverse effect. Coolness of hands and feet in winter.
- CNS effects include mild sedation, vivid dreams, and rarely, depression.
- Nonselective agents commonly causes worsening of preexisting **asthma**.
- Caution is required in patients with severe peripheral vascular disease and in patients with compensated heart failure even though long-term use may prolong life.
- A very small dose of a β antagonist may provoke severe cardiac failure in a susceptible individual.
• Beta blockers may interact with the calcium antagonist verapamil causing bradycardia, heart failure, and cardiac conduction abnormalities. These adverse effects may even arise in susceptible patients taking a topical β blocker and oral verapamil.

• Patients with ischemic heart disease or hypertension may be at increased risk if β blockade is suddenly interrupted.

• This might involve up-regulation of β receptors.

• It is inadvisable to use β antagonists in insulin-dependent diabetic patients who are subject to frequent hypoglycemic reactions. Beta1-selective antagonists are safer in these patients.
Ganglion-Blocking Drugs

Tetraethylammonium (TEA)
First ganglion blocker, very short duration of action.

Hexamethonium ("C6")
The first drug effective for hypertension.

Decamethonium, "C10" analog of hexamethonium, is a depolarizing neuromuscular blocker.

Mecamylamine
A secondary amine, 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 & is given by intravenous infusion.
Mechanism of Action

- Ganglionic nicotinic receptors are subject to both depolarizing and nondepolarizing blockade.
- Nicotine & acetylcholine (if amplified with a cholinesterase inhibitor) can produce depolarizing ganglion block.
- Drugs now used as ganglion blockers are classified as nondepolarizing competitive antagonists.
- However, hexamethonium actually produces most of its blockade by occupying sites in or on the nicotinic ion channel, not by occupying the cholinoceptor itself.
- Trimethaphan blocks the nicotinic receptor, not the channel pore.
- Blockade can be reversed by increasing the concentration of an agonist, e.g., acetylcholine.
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.
GIT

- Secretion & Motility are profoundly inhibited, and constipation can be marked.

Other Systems

- Hesitancy in urination and may precipitate urinary retention in men with prostatic hyperplasia.
- **Sexual function** is impaired in that both erection and ejaculation.
- **Sweating** is reduced by the ganglion-blocking drugs.
Response to Autonomic Drugs

- Patients receiving ganglion-blocking drugs are fully responsive to drugs acting on muscarinic, alpha, and beta adrenergic receptors.

- Responses may be exaggerated or even reversed (e.g., IV administered NE may cause tachycardia rather than bradycardia), because homeostatic reflexes are absent.
Clinical Applications & Toxicity

• Ganglion blockers are **used infrequently** because more selective agents are available.

**Mecamylamine**

• Blocks central nicotinic receptors and has been advocated as a possible 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.