Alpha Receptor Antagonists

1- Cardiovascular Effects:

- Stimulation of alpha receptors has an important role in maintaining blood pressure in the upright position through:

  a- Contraction of veins, since it decreases venous pooling in the periphery.

  b- Constriction of arterioles in the legs, contributing to the normal orthostatic response.

  → The blockade of alpha receptors with alpha antagonists, ↓ peripheral vascular resistance and blood pressure. It also prevents the pressor effects of usual doses of alpha agonists. Thus, causing orthostatic hypotension and reflex tachycardia; nonselective (α1 = α2) blockers cause tachycardia if blood pressure is lowered below normal.

- Tachycardia is marked with agents that block α2-presynaptic receptors in the heart, since the increased release of NE will further stimulate β1 receptors in the heart.

2- Other Effects:

- Blockade of α-receptors in other tissues elicits miosis and nasal stuffiness (vasodilation).

- α1-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

3- Effects of selective & Non-selective alpha blockers on HR:

- **α1 Selective (Prazosin):** Blockade of α1 receptors causes ↓ BP, little baroreceptor reflex is shown due to α2-presynaptic negative feedback causing no or slight Tachycardia.

- **Non-selective (Phentolamine):** BP ↓, α2-presynaptic negative feedback is blocked too, thus, increased release of NE stimulates β1 receptors in the heart causing reflex Tachycardia.

Drug	Notes	Uses & Adverse effects
Non-Selective α-Blockers (α1= α2) (PhPh)		
Phenoxybenzamine	- Binds covalently to α receptors, causing irreversible blockade of long duration (14–48 h). - Blocks α1 & to less extent α2 receptors. - Inhibits reuptake of NE and blocks histamine (H1), ACh, and serotonin receptors. - Reduces BP when sympathetic tone is high, e.g. because of upright posture, causing little fall in BP in normal supine individuals. - 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 t½ 19 min. - Competitive α1 and α 2 antagonist. - Reduces peripheral resistance (α1) 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 (↑ 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 α1-Blockers (TP TD)		
Prazosin	- Highly selective α1 blocker & less potent at α 2 receptors. - 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. -Extensively metabolized, only 50% is available after oral administration. -The half-life is 3 hours. Favorable effect on plasma lipids: ↑ HDL/LDL ratio.	- **Uses**: Antihypertensive, Benign prostatic hyperplasia (BPH) Blocks α1 in bladder trigone & prostate & ↓ 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 hrs.	-
Doxazosin	Has a longer half-life of about 22 hrs.	-
Tamsulosin	- Uroselective α1A/ α1D blocker. 30 times high affinity for α1A than α1D. - α1A are predominant in bladder base & prostate. - High bioavailability and a half-life of 9–15 hrs. - Has greater potency in inhibiting contraction in prostate smooth muscle versus vascular smooth muscle.	- **Uses**: to treat BPH. No effect on BP and heart rate. - **Side Effects**: Dizziness & retrograde Ejaculation (into the bladder).

Note: letters between brackets correspond to the drugs names. They help in memorizing, ignore them if u wish xp

Other Alpha adrenoceptors antagonists (LEYC)		
Labetalol	- Has both α1 and β-antagonistic effects	-
Chlorpromazine & Haloperidol	- Potent dopamine receptor antagonists (Neuroleptic drugs) but are also antagonists at α receptors. - Their antagonism of α receptors causes hypotension.	-
Ergot alkaloids	- Ergotoxine, Ergotamine are partial agonist and antagonist at adrenergic α, 5HT and DA receptors. - Ergotoxine, dihydroergotamine are more potent α blocker and less potent vasoconstrictor than ergotamine.	- **Uses**: Ergotamine is used in Migraine
Yohimbine	- An indole alkaloid, is α 2-selective antagonist. Blocks other receptors such as 5HT, DA. - ↑ ADH release. - Enhances sexual activity (aphrodisiac).	- **Uses**: 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.

Clinical Uses	Drug
Pheochromocytoma *Tumor of the adrenal medulla or sympathetic ganglion cells. Causes intermittent or sustained hypertension, headaches, palpitations & increased sweating.*	- **Phe**noxybenzamine (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 *(since they would increase the BP).* - Metyrosine. α -methyltyrosine, a competitive inhibitor of tyrosine hydroxylase. Used in inoperable or metastatic pheochromocytoma. Can cause extrapyramidal effects due to reduced dopamine levels
Hypertensive Emergencies	Labetalol
α1-agonis Overdose	Phentolamine
Chronic Hypertension	- α 1-selective antagonists are used 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.
Peripheral Vascular Disease (PrPh) *Raynaud's phenomenon (excessive reversible vasospasm in the peripheral circulation).*	- Prazosin or phenoxybenzamine are used but calcium channel blockers are preferable for most patients.
Urinary Obstruction (TP TD) *Benign prostatic hyperplasia (BPH) is common in elderly men. It causes urinary retention.* *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 α1A-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 α1-receptor antagonists.

Beta Receptor Antagonists

- All β blockers are competitive antagonists. They have more specific effect on β receptors due to similarity to isoproterenol in structure.

- In 1958 → Dichloroisoprenaline was found. It has a low potency & is a partial agonist.

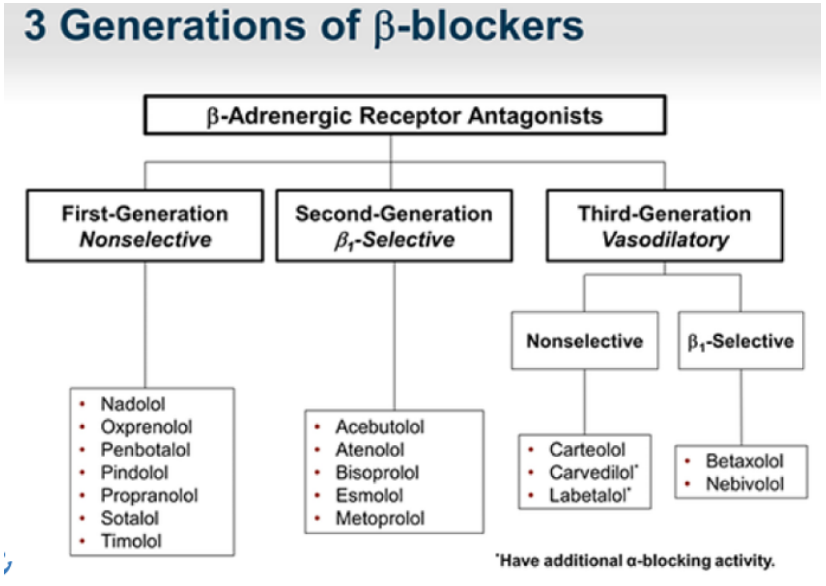
  In 1963 → Propranolol was found. It blocks β1, β2 & has weak activity on β3. Also, it is an inverse agonist (↓ resting Heart Rate).

- They differ in their relative affinities for β1 and β2 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.



Drug	Distribution & Clearance
Rapidly distributed with large volumes of distribution. The effects of these drugs are well beyond the time predicted from half-life data.	
Propranolol & penbutolol	- Lipophilic and readily cross the blood-brain barrier. - Most β antagonists have half-lives of 3–10 hours.
Propranolol and metoprolol	- Extensively metabolized in the liver.
Esmolol	- Rapidly hydrolyzed & its half-life 10 minutes.
Atenolol & pindolol	- Less completely metabolized
Nadolol	- 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.

System	Effects of Beta Receptors Blockade
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, β-receptor blockade opposes β2-mediated vasodilation. This may 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, but chronic administration leads to a fall in peripheral resistance in patients with hypertension. - Nonselective and β1-blocking drugs antagonize the release of renin caused by the sympathetic nervous system.
Respiratory Tract	- ↑ airway resistance, particularly in patients with asthma. - β1 blockers are safer than nonselective β blockers. - β1-selective blocker are not sufficiently specific to completely avoid interactions with β2 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 would outweigh the risks e.g. in patients with concomitant ischemic heart disease.
Eye	- ↓ Intraocular pressure by ↓ aqueous humor production. - Glaucoma is treated by: 1- ↓ of aqueous humor secretion (In-flow). 2- ↑ of aqueous drainage (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 & Endocrine	- Beta-receptor antagonists ↑ LDL, triglycerides, ↓ HDL by inhibiting lipolysis. → ↓ HDL/LDL - Glycogenolysis in the liver is inhibited after β 2receptor 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).

Drugs	Effects Not Related to Beta-Blockade
Pindolol, Celiprolol & Acebutolol	- Partial agonists. - 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	- Nonselective β blocker that has marked class III antiarrhythmic effects, reflecting potassium channel blockade (used to treat both ventricular & supraventricular arrhythmias).
Propranolol, Pindolol, Labetalol, Metoprolol, Acebutolol	- Local anesthetic action (membrane-stabilizing). 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.

Drug	Effect
Non-selective beta blockers (TNPS)	
Propranolol	- Prototype of β -blocking drug. Blocks β1, β2 & has a weak activity on β3. 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 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.
Nadolol	- 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 & prevents migraine.
Sotalol	- Nonselective that also exhibits Class III antiarrhythmic properties.
Cardio-selective β1 Blockers (BE MAN)	
	- 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 β 2 receptors are important in liver (recovery from hypoglycemia) and blood vessels (vasodilation).*
Metoprolol	- Cardio-selective, 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 β 1 blocker. ↑ endothelial NO release (vasodilating effect). - Antioxidant properties that can protect the vascular wall from free radicals that damage blood vessels. - Activates cardiac β3-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	- Ultra-short–acting β 1-selective blocker. - 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. - Safer in critically ill patients who require a β -adrenoceptor antagonist. - 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 (PAC)	
	Effective in hypertension and angina & less likely to cause bronchoconstriction, bradycardia and abnormalities in plasma lipids than other β blockers.
Pindolol	- Non-selective beta- adrenoceptor/5-HT1A antagonist accelerates the antidepressant effect of selective serotonin reuptake inhibitors.
Celiprolol	- β1-selective antagonist with a partial β2 agonist activity & may have less adverse bronchoconstrictor effect in asthma and may even promote bronchodilation.
Acebutolol	- β 1-selective antagonist. Used in the treatment of hypertension, angina pectoris and cardiac arrhythmias.

Drugs that block both alpha and beta receptors (CL)	
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): 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. - Antiapoptotic properties (prevent myocyte death and reduce infarct size in persons with myocardial ischemia and Systolic HF). - Used for hypertension, angina and congestive heart failure.

Clinical Uses	Drugs
Hypertension	- Although many hypertensive patients respond to a β blocker used alone, the drug is often used with either a diuretic or a vasodilator. - Despite the short half-life of many β antagonists, these drugs may be administered once or twice daily and still have an adequate therapeutic effect. They are Less effective in the elderly and in black patents. - However, these differences are relatively small and may not apply to an individual patient.
Ischemic Heart Disease **(TPM)**	- ↓ the frequency of anginal episodes and improve exercise tolerance in patients with angina. - ↓ cardiac work & ↓ 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 ↓ 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 **(MBC)**	- Clinical trials have demonstrated that at least three β antagonists, metoprolol, bisoprolol, and carvedilol (MBC) are effective in decreasing 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. - Mechanisms are uncertain, there appear to be beneficial effects on myocardial remodeling and in ↓ the risk of sudden death.
Hypertrophic Cardiomyopathy **(Prop)**	- Propranolol ↓ the incidence of sudden death in patients with hypertrophic cardiomyopathy (HCM). - The negative inotropic and chronotropic effects of betablockers attenuate adrenergic-induced tachycardia, ventricular contractility, and stiffness, thereby improving ventricular relaxation, increasing time for diastolic filling, and ↓ excitability.
Glaucoma **(Tim)**	- Systemic administration of β -blocking drugs for other indications, reduced intraocular pressure in patients with glaucoma. Topical administration also ↓ intraocular pressure. - The mechanism involves ↓ production of aqueous humor by the ciliary body. - Timolol and related β 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 **(Prop)**	- 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 **(TP MAN)**	- Propranolol ↓ 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

- 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 cause 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

1- 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 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.

2- 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.

3- Clinical Applications & Toxicity:

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

The toxicity of the ganglion-blocking drugs is limited to the autonomic effects. These effects are intolerable except for acute use.

Ganglion-Blocking Drugs	
Drugs	**Notes**
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. - 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	- A short-acting ganglion blocker, is inactive orally. - Occasionally used in the treatment of hypertensive emergencies and in producing hypotension in neurosurgery to reduce bleeding in the operative field.

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 ↓ 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.

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Best Wishes :)