Adrenergic Antagonists

The adrenergic antagonists (also called adrenergic blockers or sympatholytics) bind to adrenoceptors but do not trigger the usual receptor-mediated intracellular effects. These drugs act by either reversibly or irreversibly attaching to the adrenoceptors, thus preventing activation by endogenous catecholamines. Like the agonists, the adrenergic antagonists are classified according to their relative affinities for α or β receptors in the sympathetic nervous system. Numerous adrenergic antagonists have important roles in clinical medicine, primarily to treat diseases associated with the cardiovascular system. Adrenergic agonists drugs were classified into α and β- blockers as demonstrated in figure 1.

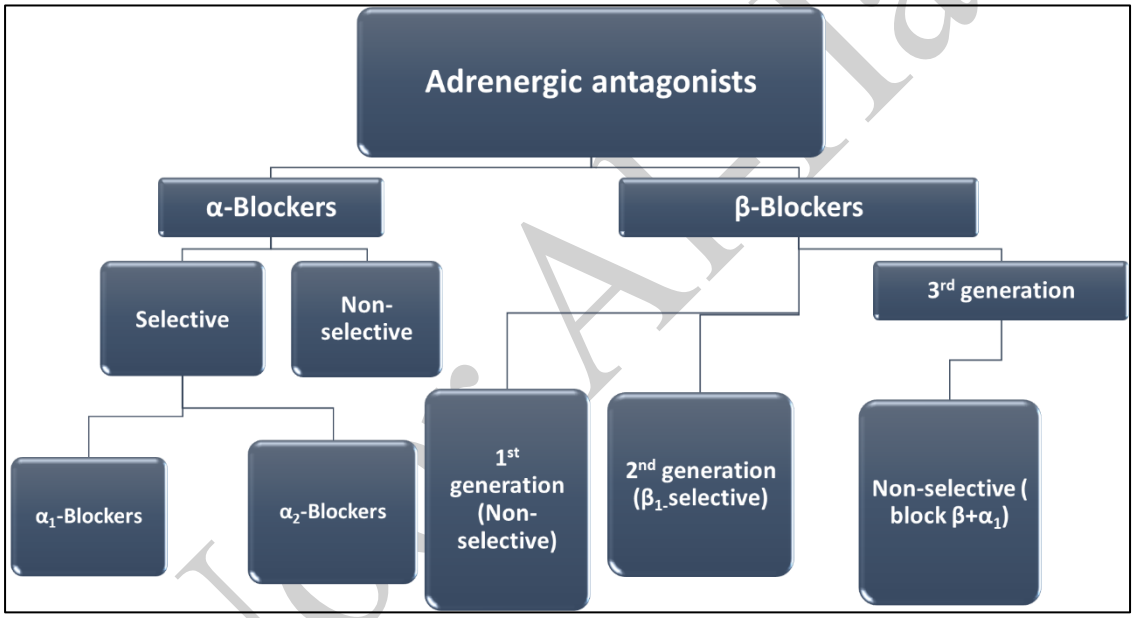

Figure 1: Adrenergic antagonists classification.

i. α-ADRENERGIC BLOCKING AGENTS

Drugs that block α adrenoceptors profoundly affect blood pressure. **(WHY)** Because normal sympathetic control of the vasculature occurs in large part through agonist actions on α-adrenergic receptors, blockade of these receptors reduces the sympathetic tone of the blood vessels, resulting in decreased peripheral vascular resistance. This induces a reflex tachycardia resulting from the lowered blood pressure.

a- Non-selective α-blocker drugs

One of the α-blocker drugs phenoxybenzamine is nonselective, linking covalently to both α1 and α2 receptors. The block is irreversible and the only way the body can overcome the block is to synthesise new adrenoceptors, which requires a day or

longer. Therefore, the actions of phenoxybenzamine last about 24 hours. The other α-blocker drug is the phentolamine produces a competitive block of α1 and α2 receptors that lasts for approximately 4 hours after a single injection.

A summary about **nonselective α- blockers'** mechanism of action (MOA), therapeutic uses and adverse effects is illustrated in table 1.

Table 1: A summary of mechanism of action (MOA), therapeutic uses and adverse effects of phenoxybenzamine and phentolamine.

α-blocker drug	Receptor selectivity	MOA	Therapeutic uses	Adverse effects
Phenoxybenz-amine	α_2 and α_1	**Cardiovascular system:** blocking α-receptors prevents vasoconstriction of peripheral blood vessels by endogenous catecholamines. ↓ ↓ Peripheral resistance ↓ Provokes a reflex tachycardia. *The ability to block presynaptic inhibitory α_2 receptors in the heart can contribute to an increased cardiac output **(HOW).**	*Mainly for the treatment of pheochromocytoma.	***Postural hypotension** *Nasal stuffiness *Nausea *Vomiting. *May inhibit ejaculation. *Tachycardia, (which is mediated by the baroreceptor reflex). *Should be used with caution in patients with **cerebrovascular** or **cardiovascular disease.**
		***Epinephrine (EP) reversal:** All α-adrenergic blockers reverse the α agonist actions of epinephrine. E.g. the vasoconstrictive action of EP is interrupted, but vasodilation of other vascular beds caused by stimulation of β_2 receptors is not blocked. Therefore, in the presence of phenoxybenzamine, the systemic blood pressure decreases in response to EP.		
Phentolamine	α_2 and α_1	Produces a competitive block of α_1 and α_2 receptors that lasts for about 4 hours after a single injection.	*Short-term management of pheochromocytoma. *Used locally to prevent dermal necrosis following extravasation of norepinephrine (NE).	*Postural hypotension and causes EP reversal. *Tachycardia (WHY)

b- α Selective blockers

1- α_1 Selective blockers

Prazosin, terazosin, doxazosin, tamsulosin, and alfuzosin are acting as selective competitive blockers of α_1 receptor; however, the first 3 drugs are useful in hypertension treatment whilst the others are indicated for the treatment of benign prostatic hyperplasia (BPH). A summary of α_1- selective blockers' mode of action, therapeutic uses and adverse effect is illustrated in table 2.

Table 2: A summary of the mechanism of action (MOA), the therapeutic uses and the adverse effects of α_1-blocker drugs

α1-blocker drugs	MOA	Therapeutic uses	Adverse effects
Prazosin, terazosin, doxazosin, tamsulosin, and alfuzosin	Decrease peripheral vascular resistance ↓ ↓ Blood pressure by causing relaxation of both arterial and venous smooth muscle.	*For elevated blood pressure treated with no tolerant effect can be recognised. * FIRST-DOSE effect causing syncope. *First-dose effect minimised by adjusting the first dose to one-third or one-fourth of the normal dose and by giving the drug at bedtime. * Used as an alternative to surgery in patients with symptomatic BPH.	*Dizziness * Lack of energy *Nasal congestion *Headache *Drowsiness *Orthostatic hypotension

2- α_2-blocker

Yohimbine is a selective competitive α_2-blocker. It is found as a component of the bark of the yohimbe tree and has been used as a sexual stimulant and in the treatment of erectile dysfunction. Its use in the treatment of these disorders is not recommended, due to lack of demonstrated efficacy.

ii. β-ADRENERGIC BLOCKING AGENTS

All of the clinically available β-blockers are competitive antagonists. Nonselective β-blockers act at both β_1 and β_2 receptors, whereas cardioselective β antagonists primarily block β_1 receptors. (Note: There are no clinically useful β_2 antagonists). Although all β-blockers lower blood pressure, they do not induce postural hypotension, because the α adrenoceptors remain functional. Therefore, normal sympathetic control of the vasculature is maintained. β-Blockers are effective in treating

hypertension, angina, cardiac arrhythmias, myocardial infarction, heart failure, hyperthyroidism, and glaucoma. They are also used for the prophylaxis of migraine headaches (Note: The names of all β-blockers end in "-olol" except for labetalol and carvedilol.).

First generation (Nonselective β antagonists)

A nonselective β-adrenergic antagonist **blocks both β_1 and β_2 receptors with equal affinity**. Propranolol is considered the prototype of a nonselective β-adrenergic antagonist. Sustained release preparations for once-a-day dosing are available.

A summary of propanol's mode of actions, therapeutic uses and side effects is illustrated in table 3.

Table 3: A summary of the mechanism of action (MOA), the therapeutic uses and the adverse effects of propranolol.

A nonselective β-adrenergic antagonist	MOA	Therapeutic uses	Adverse effects
Propranolol	* **Cardiovascular system** -Diminishes cardiac output (having both negative inotropic and chronotropic effects) -Cardiac output, workload and oxygen consumption are decreased by blockade of β_1 receptors, and these effects are useful in the treatment of angina. ***Peripheral vasoconstriction** *Preventing β_2-mediated vasodilation in skeletal muscles ⇒ ↑ peripheral vascular resistance. The reduction in cardiac output produced by all β-blockers leads to decreased blood pressure, which triggers a reflex peripheral vasoconstriction.	***Hypertension** -Lowers blood pressure in hypertension by several different mechanisms of action which are: -Decreasing cardiac output (which is the primary mechanism). - Inhibition of renin release from the kidney leads to decrease in total peripheral resistance with long-term use. ***Angina pectoris** - ↓ O_2 demand by heart muscles ⇒ ↓ chest pain. So, it is used in chronic management of stable angina. ***Myocardial infarction (MI):** -Prophylactic use of β-blockers can prevent a second attack of MI. Immediate administration following a MI reduces infarct size and hastens recovery. ***Migraine** *reduces migraine episodes when used prophylactically due to its hydrophobic property. ***Hyperthyroidism** Prevent cardiac arrhythmias.	***Bronchoconstriction** ***Arrhythmias** ***Sexual impairment** ***Metabolic disturbances** ***CNS effects** (as depression, dizziness, lethargy, fatigue, weakness and visual disturbances). **Why all of the above side effects CNS side effects) can be recorded when propranolol is used??**
	***Bronchoconstriction** - β blockade leads to ↓ Glycogenolysis and ↓ Glucagon secretion. (Causes hypoglycaemia).		

Nadolol and timolol (Nonselective β antagonists)

Nadolol and timolol also block β_1- and β_2-adrenoceptors and are more potent than propranolol. Nadolol has a very long duration of action. Timolol reduces the production of aqueous humor in the eye. It is used topically in the treatment of chronic open-angle glaucoma and, occasionally, for systemic treatment of hypertension.

****Treatment of glaucoma:** β-blockers, such as topically applied timolol, betaxolol, or carteolol, are effective in diminishing intraocular pressure in glaucoma. Unlike the cholinergic drugs, these agents neither affect the ability of the eye to focus for near vision nor change pupil size. When administered intraocularly, the onset is about 30 minutes, and the effects last for 12 to 24 hours. The β-blockers are only used for chronic management of glaucoma. **In an acute attack of glaucoma, pilocarpine is still the drug of choice for emergency lowering of intraocular pressure.**

Second generation (Selective β_1 antagonist)

Acebutolol, atenolol, betaxolol, bisoprolol, esmolol, metoprolol, and nebivolol are selective β_1 antagonist drugs that preferentially block the β_1 receptors and minimise the unwanted bronchoconstriction (β_2 effect) seen with propranolol so it can be used in asthma patients. Cardioselective β-blockers, such as acebutolol, atenolol, and metoprolol, antagonise β_1 receptors at doses 50- to 100-fold less than those required to block β_2 receptors. This cardioselectivity is most pronounced at low doses and is lost at high doses. (Note: Since β_1 selectivity of these agents is lost at high doses, they may antagonise β_2 receptors).

1- **Actions:** These drugs lower blood pressure in hypertension and increase exercise tolerance in angina. Esmolol has a very short half-life due to metabolism of an ester linkage. It is only available intravenously and is used to control blood pressure or heart rhythm during surgery or diagnostic procedures. **In contrast to propranolol, the cardioselective β-blockers have fewer effects on pulmonary function, peripheral resistance, and carbohydrate metabolism**. Nevertheless, asthma patients treated with these agents must be carefully monitored to make certain that respiratory activity is not compromised. In addition to its cardioselective β blockade, **nebivolol releases nitric oxide from endothelial cells and causes vasodilation.**
2- **Therapeutic uses:** The cardioselective β-blockers are useful in hypertensive patients with impaired pulmonary function. These agents are also first-line therapy for chronic stable angina. Bisoprolol and the extended-release formulation of metoprolol are indicated for the management of chronic heart failure. Because these drugs have less effect on peripheral vascular β_2 receptors, coldness of extremities

(Raynaud phenomenon), a common side effect of β-blockers, is less frequent.

Third generation (Antagonists of both α and β adrenoceptors):

This group is represented by the **Labetalol and carvedilol.** These are nonselective β-blockers with concurrent α_1-blocking actions that produce peripheral vasodilation, thereby reducing blood pressure. They contrast with the other β-blockers that produce initial peripheral vasoconstriction, and these agents are, therefore, useful in treating hypertensive patients for whom increased peripheral vascular resistance is undesirable. Carvedilol also decreases lipid peroxidation and vascular wall thickening, effects that have benefit in heart failure.

Therapeutic use in hypertension and heart failure:

1- Labetalol is employed as an alternative to methyldopa in the treatment of pregnancy- induced hypertension. Intravenous labetalol is also used to treat hypertensive emergencies, because it can rapidly lower blood pressure.

2- β-blockers should not be given to patients with an acute exacerbation of heart failure, as they can worsen the condition. However, carvedilol as well as metoprolol and bisoprolol are beneficial in patients with stable chronic heart failure. These agents work by blocking the effects of sympathetic stimulation on the heart, which causes worsening heart failure over time.

The main adverse effect is the orthostatic hypotension and dizziness, which are associated with α_1 blockade.

There is another group of adrenergic antagonist drugs, which is the **antagonists with partial agonist activity.** This means that these drugs are not pure antagonists because they have the ability to weakly stimulate both β_1 and β_2 receptors and are said to have intrinsic sympathomimetic activity (ISA).

Accordingly, these partial agonists can stimulate the β receptor to which they are bound, **yet they inhibit stimulation by the more potent endogenous catecholamines, epinephrine and norepinephrine**. The result of these opposing actions is a diminished effect on cardiac rate and cardiac output compared to that of β-blockers without ISA.

β-blockers with ISA has an important advantage, which is minimising the disturbances of lipid and carbohydrate metabolism that are seen with other β-blockers. For example, these agents do not decrease plasma HDL levels.

According to the above mentioned features of this group, it can be used therapeutically to treat the hypertensive patients with moderate bradycardia, because a further decrease in heart rate is less pronounced with these drugs. [Note: β-blockers with ISA are not used for stable angina or arrhythmias due to their partial agonist effect].

The β-adrenergic antagonists and their therapeutic uses with the affected receptors were summarised in table 4.

Table 4: Summary of β-adrenergic antagonists. NO = nitric oxide. [1]Acebutolol and pindolol are partial agonists, as well. [2]Bisoprolol, metoprolol, and carvedilol are also used for the treatment of heart failure.

DRUG	RECEPTOR SPECIFICITY	THERAPEUTIC USES
Propranolol	β_1, β_2	Hypertension Migraine Hyperthyroidism Angina pectoris Myocardial infarction
Nadolol *Pindolol*[1]	β_1, β_2	Hypertension
Timolol	β_1, β_2	Glaucoma, hypertension
Atenolol *Bisoprolol*[2] *Esmolol* *Metoprolol*[2]	β_1	Hypertension Angina Myocardial infarction
Acebutolol[1]	β_1	Hypertension
Nebivolol	β_1, NO ↑	Hypertension
Carvedilol[2] *Labetalol*	$\alpha_1, \beta_1, \beta_2$	Hypertension