Pharmacology

Adrenergic Antagonists

Sympatholytic drugs

Lecturer

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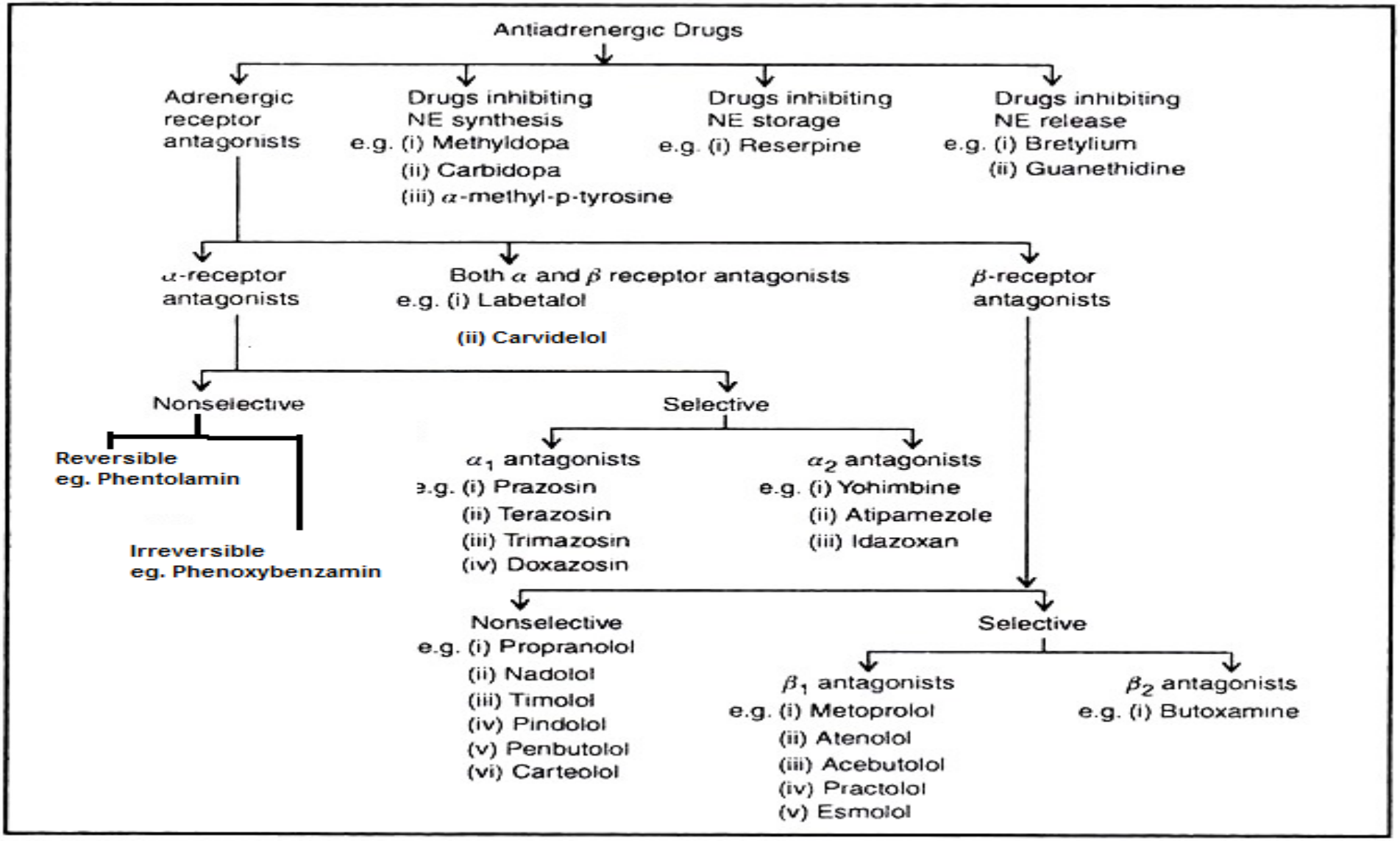
Adrenergic Antagonists

The adrenergic antagonists (also called blockers or sympatholytic agents) bind to adrenoceptors but do not trigger the usual receptor-mediated intracellular effects. These drugs act by either reversibly or irreversibly attaching to the receptor, thus preventing its activation by endogenous catecholamines. Like the agonists, the adrenergic antagonists are classified according to their relative affinities for α or β receptors in the peripheral nervous system.

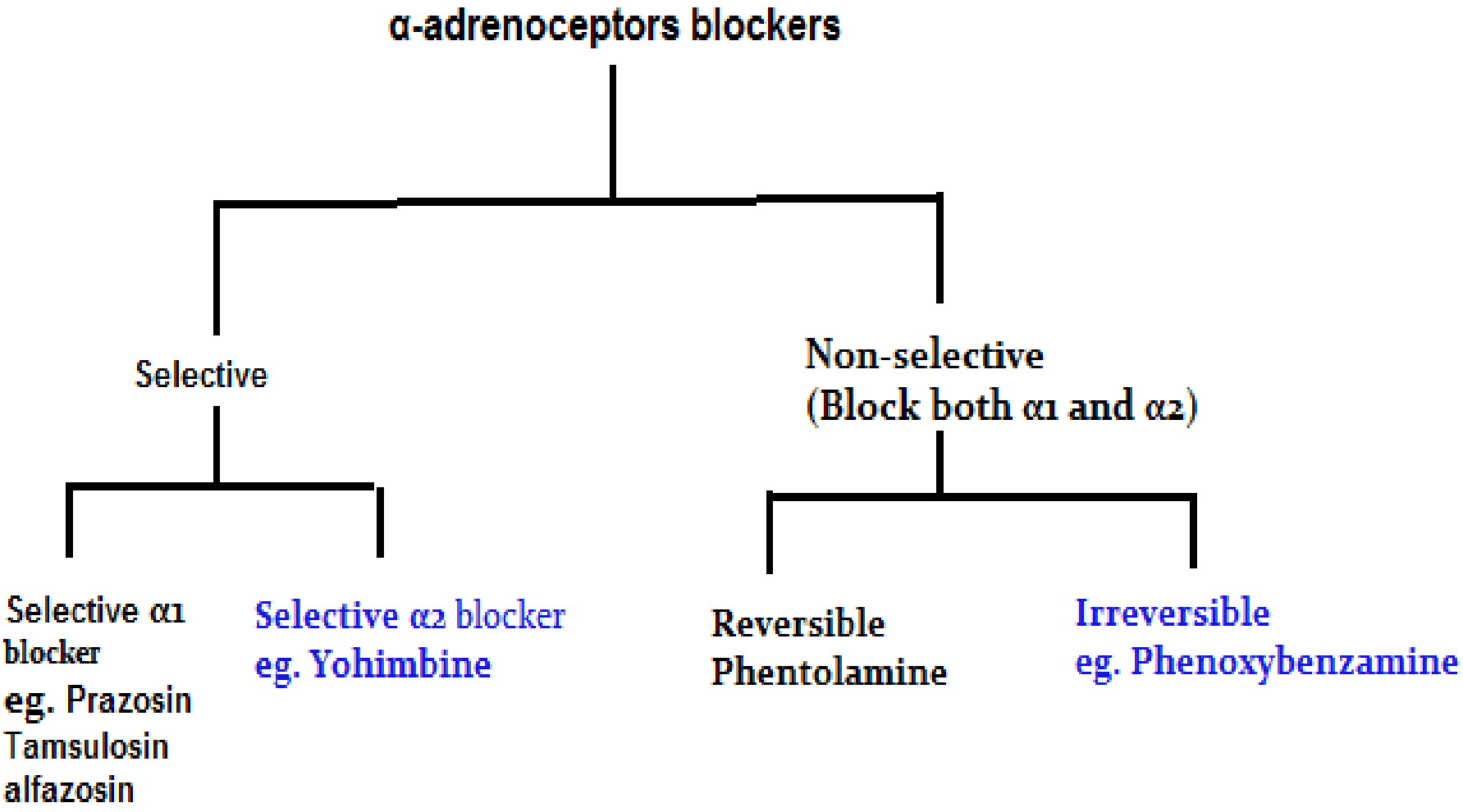
Classification of anti-adrenergic drugs



α-Adrenergic Blocking Agents

Drugs that block α-adrenoceptors profoundly affect blood pressure. 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. They are divided into:

Classification of α-Adrenergic Blocking Agents



General properties of α-blockers

- Effect on blood pressure
- Caused vasodilation (decreased peripheral vascular resistance)
- Induce reflex tachycardia
- They are not effect on β receptors

Phenoxybenzamine

Phenoxybenzamine is nonselective, linking covalently to both α1-postsynaptic and α2-presynaptic receptors . The block is irreversible and noncompetitive, and the only mechanism the body has for overcoming the block is to synthesize new adrenoceptors, which requires a day or more. Therefore, the actions of phenoxybenzamine last about 24 hours after a single administration.

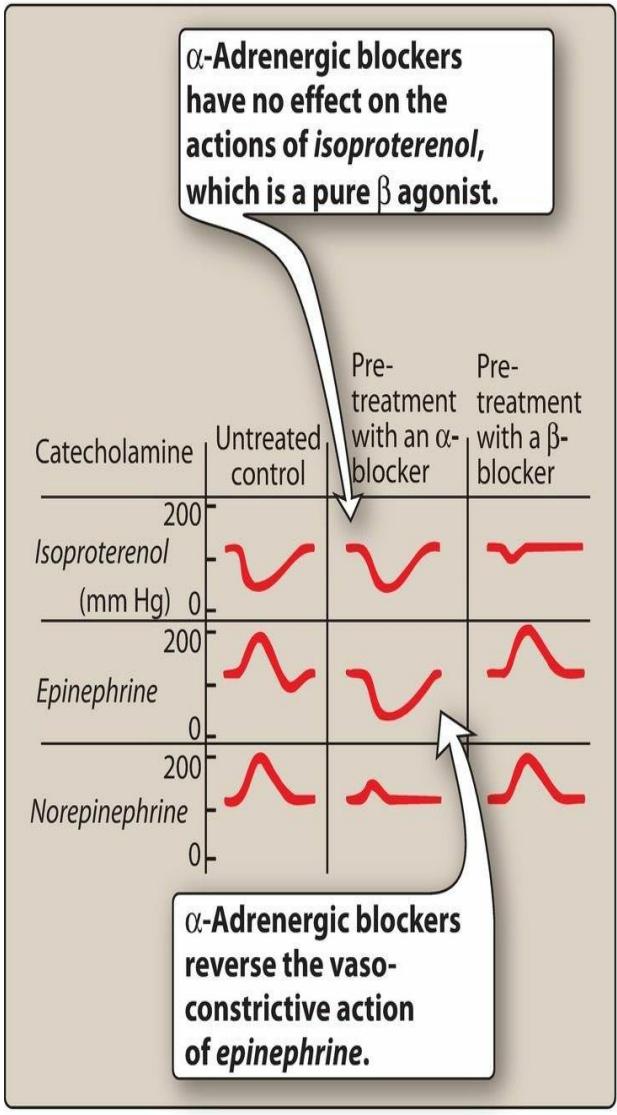
Cardiovascular effects of phenoxybenzamine

- The drug prevents α_1 receptor vasoconstriction of peripheral blood vessels caused by endogenous catecholamines, which leads to decreased peripheral resistance and resultant reflex tachycardia. However, by blocking presynaptic α_2 receptors on the sympathetic nerve terminals in the heart, *phenoxybenzamine* causes an increase in the release of norepinephrine, which in turn increases heart rate and cardiac output (mediated by β_1 receptors). This may also lead to cardiac arrhythmias and anginal pain. Thus, the drug has been unsuccessful in maintaining lowered blood pressure in hypertension, and it is no longer used for this purpose.

- Epinephrine reversal: All α-adrenergic blockers reverse the α-agonist actions of epinephrine.

Epinephrine reversal:

All **α**-adrenergic blockers reverse the α agonist actions of *epinephrine*. For example, the vasoconstrictive action of *epinephrine* 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 *epinephrine*. [Note: The actions of *norepinephrine* are not reversed but are diminished because *norepinephrine* lacks significant β agonist action on the vasculature.] *Phenoxybenzamine* has no effect on the actions of *isoproterenol*, which is a pure β agonist.



Therapeutic uses of phenoxybenzamine:

1. Used in the treatment of sweating and hypertension associated with pheochromocytoma (tumor of adrenal gland).
2. Raynaoud's disease and frostbite

Side effects of phenoxybenzamine

- Postural hypotension
- Nasal stuffiness
- Nausea and vomiting
- Inhibit ejaculation
- Reflex tachycardia (mediated by the baroreceptor reflex)

Phentolamine

In contrast to phenoxybenzamine, phentolamine produces a competitive block of α1 and α2 receptors and thus produce reversible effect. The drug's action lasts for approximately 4 hours after a single administration. Like phenoxybenzamine, causes epinephrine reversal.

Uses:

1. Diagnosis and short-term management of pheochromocytoma.
2. Used locally to prevent dermal necrosis following extravasation of norepinephrine.
3. Phentolamine is useful to treat hypertensive crisis due to abrupt withdrawal of clonidine or ingestion of tyramine-containing foods in patients taking monoamine oxidase inhibitors.

Selective α 1 blockers

- Prazosin, terazosin, doxazosin , alfuzosin and tamsulosin are selective competitive blockers of the α_1 receptor.
- The first three drugs are useful in the treatment of hypertension (Prazosin, terazosin, doxazosin) .
- Tamsulosin and alfuzosin are indicated for the treatment of benign prostatic hyperplasia (BPH).
- Doxazosin is the longest acting of these drugs.
- All are metabolize by the liver and excreted in the urine except doxazosin its metabolites excreted in the feces.

Mechanism of action

- These agents decrease peripheral vascular resistance and lower blood pressure by causing relaxation of both arterial and venous smooth muscle.
- Unlike *phenoxybenzamine* and *phentolamine*, these drugs cause minimal changes in cardiac output, renal blood flow, and glomerular filtration rate.
- *Tamsulosin*, *alfuzosin*, and *silodosin* have less pronounced effects on blood pressure because they are less selective for α_{1B} receptors found in the blood vessels and more selective for α_{1A} receptors in the prostate and bladder.
- Blockade of the α_{1A} receptors decreases tone in the smooth muscle of the bladder neck and prostate and improves urine flow.

Therapeutic uses of selective α_1 antagonists

1. Used in treatment of hypertension (but not as monotherapy).
2. When used in treatment of hypertension these drugs may cause modest improvement in lipid profiles and glucose metabolism. In addition to that it not induced tolerance.
3. Also can be used in treatment of benghing prostatic hyperplasia. (*Tamsulosin*, *alfuzosin*, and *silodosin*)

Adverse effects:

1. First dose of these drugs produces an exaggerated orthostatic hypotensive response that can result in syncope (fainting). This action, termed a ((first-dose)) effect, may be minimized by adjusting the first dose to one-third or one-fourth of the normal dose and by giving the drug at bedtime.
2. Dizziness, headache, drowsiness,
3. a lack of energy,
4. nasal congestion,
5. orthostatic hypotension
6. An additive antihypertensive effect occurs when a1 antagonists are given with vasodilators such as nitrates or PDE-5 inhibitors (for example, sildenafil), so it is necessary to do dose titration and use at the lowest possible doses.
7. These agents may cause "floppy iris syndrome," a condition in which the iris billows in response to intraoperative eye surgery.

Yohimbine
(selective competitive α2 blocker)

Yohimbine is a selective competitive α_2 blocker. It is sometimes used as a sexual stimulant.

Mechanism of action: Yohimbine works at the level of the CNS to increase sympathetic outflow to the periphery. It directly blocks α_2 receptors that found in the postsynaptic membrane of the vascular smooth muscle and has been used to relieve vasoconstriction associated with Raynaud's disease.

Yohimbine is contraindicated in CNS and cardiovascular conditions because it is a CNS and cardiovascular stimulant.

β-Adrenergic Blocking Agents

- All the clinically available β-blockers are competitive antagonists.
- Nonselective β-blockers act at both β1 and β2 receptors, whereas cardioselective β antagonists primarily block β1 receptors [Note: There are no clinically useful β2 antagonists].
- They act by occupy β receptors and competitively reduce receptor occupancy by catecholamines and other agonists.
- Although all β-blockers lower blood pressure in hypertension, they do not induce postural hypotension, because the α-adrenoceptors remain functional.
- They are mainly used in treatment of hypertension. However, They are also effective in treating angina, cardiac arrhythmias, myocardial infarction, congestive heart failure, hyperthyroidism, and glaucoma, as well as serving in the prophylaxis of migraine headaches.

What are the major differences among the many - receptor-blocking drugs?

1. Differ in their selectivity and affinity to β1 and β2 receptors.
2. Some of them are pure β receptor antagonist while other show partial agonist.
3. Differ in their pharmacokinetic properties (like half-life, bioavailability, and rout of administration).
4. These drugs also differ in intrinsic sympathomimetic activity (ISA), CNS effects, blockade of sympathetic receptors, vasodilation, and pharmacokinetics

Propranolol: A nonselective β antagonist

Propranolol is the prototype β-adrenergic antagonist and blocks both β1 and β2 receptors.

Propranolol action with (isoproterenol, epinephrine and norepinephrine)

- Nonselective β-blockers, including propranolol, have the ability to block the actions of isoproterenol (β1, β2 agonist) on the cardiovascular system. Thus, in the presence of a β-blocker, isoproterenol does not produce cardiac stimulation (β1 mediated) or reductions in mean arterial pressure and diastolic pressure (β2 mediated)
- In the presence of a nonselective β-blocker, epinephrine no longer lowers diastolic blood pressure or stimulates the heart, but its vasoconstrictive action (mediated by a receptors) remains unimpaired.
- The actions of norepinephrine on the cardiovascular system are mediated primarily by a receptors and are, therefore, mostly unaffected.

Cardiovascular action

Cardiovascular action: Propranolol diminishes cardiac output and oxygen consumption by myocrdiam (block $\beta_{1)}$, having both negative inotropic and chronotropic effects . These effects are useful in the treatment of angina.

Peripheral vasoconstriction: by blocking of β 1 receptors prevents β_2-mediated vasodilation .The reduction in cardiac output leads to decreased blood pressure. This hypotension triggers a reflex peripheral vasoconstriction that is reflected in reduced blood flow to the periphery.

Bronchoconstriction by blocking β_2 receptors in the lungs thus propranolol is contraindicated in patients with COPD or asthma.

Increased Na+ retention: by reducing blood pressure propranolol causes a decrease in renal perfusion, resulting in an increase in Na+ retention and plasma volume .

Disturbances in glucose metabolism by decreased glycogenolysis and decreased glucagon secretion. In addition to that, β -Blockers also attenuate the normal physiologic response to hypoglycemia.

Block the action of isoproterenol on cardiovascular system.

Therapeutic effects:

1. **Hypertension:** Decreased cardiac output is the primary mechanism, but inhibition of renin release from the kidney and decreased sympathetic outflow from the CNS also contribute to propranolol's antihypertensive effects.
2. **Angina pectoris:** Propranolol decreases the oxygen requirement of heart muscle and, therefore, is effective in reducing chest pain on exertion that is common in angina. Propranolol is therefore useful in the management of chronic stable angina.
3. **Myocardial infarction:** propranolol and other β-blockers have a protective effect on the myocardium ,administration of a β-blocker immediately following a MI reduces infarct size and early mortality. The mechanism for these effects may be a reduction in the actions of circulating catecholamines that increase the oxygen demand in an already ischemic heart muscle. Propranolol also reduces the incidence of sudden arrhythmic death after myocardial infarction.
4. Glaucoma
5. **Migraine: Propranalol mainly used due** to its lipophilic nature that allows it to penetrate the CNS.
6. **Hyperthyroidism:** *Propranolol* and other β-blockers are effective in blunting the widespread sympathetic stimulation that occurs in hyperthyroidism. In acute hyperthyroidism (thyroid storm), β-blockers may be lifesaving in protecting against serious cardiac arrhythmias.

Adverse effects:

1) Bronchoconstriction: that is why propranolol is contraindicated in patients with COPD or asthma.

2) Arrhythmias: Treatment with β-blockers must never be stopped abruptly because of the risk arrhythmias. The β-blockers must be tapered off gradually over a period of at least a few weeks. Long-term treatment with a β antagonist leads to up-regulation of the β receptor. On suspension of therapy, the increased receptors can precipitate worsened angina or hypertension through action of endogenous catecholamines on the upregulated β receptors.

3) Sexual impairment: unknown reason

Adverse effects:

4- Disturbances in metabolism: β-Blocker leads to decreased glycogenolysis and decreased glucagon secretion. Fasting hypoglycemia may occur. In addition, β-blockers can prevent the counter regulatory effects of catecholamines during hypoglycemia. Thus, the perception of symptoms of hypoglycemia such as tremor, tachycardia, and nervousness are blunted by β-blockers. A major role of β receptors is to mobilize energy molecules such as free fatty acids. [Note: Lipases in fat cells are activated mainly by β receptor stimulation, leading to the metabolism of triglycerides into free fatty acids.] Patients administered nonselective β-blockers may have increased triglycerides and reduced high-density lipoprotein ("good" cholesterol) through β-blockade. These effects on the serum lipid profile may be less pronounced with the use of β1 selective antagonists such as metoprolol.

Drug interaction with propranolol

1. Drugs that interfere with, or inhibit, the metabolism of *propranolol*, such as *cimetidine*, *fluoxetine*, *paroxetine*, and *ritonavir*, may potentiate its antihypertensive effects.
2. Conversely, those that stimulate or induce its metabolism, such as barbiturates, *phenytoin*, and *rifampin*, can decrease its effects.
3. Nonselective β-blockers such as *propranolol* may prevent the rescue effects of *epinephrine* in anaphylaxis.

Timolol and nadolol: Nonselective β antagonists

Timolol and nadolol also block β1- and β2- 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. This occurs by decreasing the secretion of aqueous humor by the ciliary body. It is used topically in the treatment of chronic (not acute) open-angle glaucoma and, occasionally, for systemic treatment of hypertension.

Note: 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.

Acebutolol, atenolol, metoprolol, Bisoprolol Nebiand esmolol

Selective β1 antagonists

- Drugs that preferentially block the β1 receptors have been developed to eliminate the unwanted bronchoconstrictor effect (β2 effect) of propranolol seen among asthmatic patients. Also it is not effect on glucose metabolism.
- Cardioselective β-blockers, such as acebutolol , atenolol , and metoprolol , antagonize β1 receptors at doses 50- to 100-fold less than those required to block β2 receptors. This cardioselectivity is thus most pronounced at low doses and is lost at high doses. [Note: Acebutolol has some intrinsic agonist activity].
- Nebivolol releases nitric oxide from endothelial cells and causes vasodilation.

Therapeutic use in hypertension:

- 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.

Pindolol and acebutolol
Antagonists with partial agonist activity

Cardiovascular action: Acebutolol and pindolol are not pure antagonists; instead, they have the ability to weakly stimulate both β1 and β2 receptors and are said to have intrinsic sympathomimetic activity (ISA). These partial agonists 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 much diminished effect on cardiac rate and cardiac output compared to that of β-blockers without ISA.

Note: **ISA = partial agonist.**

Therapeutic use:

β-Blockers with ISA are effective in hypertensive patients with moderate bradycardia, because a further decrease in heart rate is less pronounced with these drugs. Carbohydrate and lipid metabolism is less affected with acebutolol and pindolol than it is with propranolol, making them valuable in the treatment of diabetics. [Note: The b blockers with ISA are not used as antiarrhythmic agents due to their partial agonist effect.]

Labetalol and carvedilol: Antagonists of both α- and β- adrenoceptors

Actions: Labetalol and carvedilol are reversible β-blockers with concurrent α1-blocking actions that produce peripheral vasodilation, thereby reducing blood pressure. They contrast with the other β-blockers that produce peripheral vasoconstriction, and they are therefore useful in treating hypertensive patients for whom increased peripheral vascular resistance is undesirable. They do not alter serum lipid or blood glucose levels. Carvedilol also decreases lipid peroxidation and vascular wall thickening, effects that have benefit in heart failure.

Therapeutic use of Labetolol in hypertension:

1. H.T in the elderly or black hypertensive patient.
2. As an alternative to methyldopa in the treatment of pregnancy-induced hypertension.
3. Intravenous labetalol is also used to treat hypertensive emergencies, because it can rapidly lower blood pressure.

Adverse effects:

Orthostatic hypotension and dizziness are associated with α1 blockade.

Drugs Affecting Neurotransmitter synthesis, storage and Release :

1- Those drugs that inhibit norepinephrine synthesis include methyldopa.

2- Those drugs that inhibit norepinephrine storage include reserpine

3- Those drugs that inhibit norepinephrine release include Bretylium.

Reserpine

Reserpine, a plant alkaloid, blocks the Mg^{2+}/adenosine triphosphate-dependent transport of biogenic amines (norepinephrine, dopamine, and serotonin) from the cytoplasm into storage vesicles in the adrenergic nerve terminals in all body tissues. This causes the ultimate depletion of biogenic amines. Sympathetic function, in general, is impaired because of decreased release of norepinephrine. *Reserpine* has a slow onset, a long duration of action, and effects that persist for many days after discontinuation. It has been used for the management of hypertension but has largely been replaced with newer agents with better side effect profiles and fewer drug interactions. It is also indicated in agitated psychotic states such as schizophrenia to relieve symptoms.


THANKYOU