Adrenergic Antagonists (Adrenergic Blockers)

- 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.**

A-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. The magnitude of the response depends on the **sympathetic tone of the individual when the agent is given.**

- [Note: β receptors, including β1 adrenoceptors on the heart, are not affected by α blockade.].
- The α-adrenergic blocking agents, **phenoxybenzamine and phentolamine, have limited clinical applications.**

A. **Phenoxybenzamine:**

- Is nonselective, linking **covalently** to both α1 and α2 receptors.
- The block is **irreversible** and **noncompetitive**, and the only way the body can overcome the block is to **synthesize new adrenoceptors**, which **requires a day or longer**. Therefore, the actions of phenoxybenzamine last about 24 hours.
- After the drug **is injected**, a **delay of a few hours occurs before a blockade develops.**

❑ Actions of Phenoxybenzamine:

- a. **Cardiovascular effects**: By **blocking α1 receptors**, phenoxybenzamine prevents **vasoconstriction of peripheral blood vessels by endogenous catecholamines**.

- The decreased peripheral resistance(↓ PVR) **provokes a reflex tachycardia**. Furthermore, the **ability to block presynaptic inhibitory α2 receptors in the heart can contribute to an increased cardiac output*****.

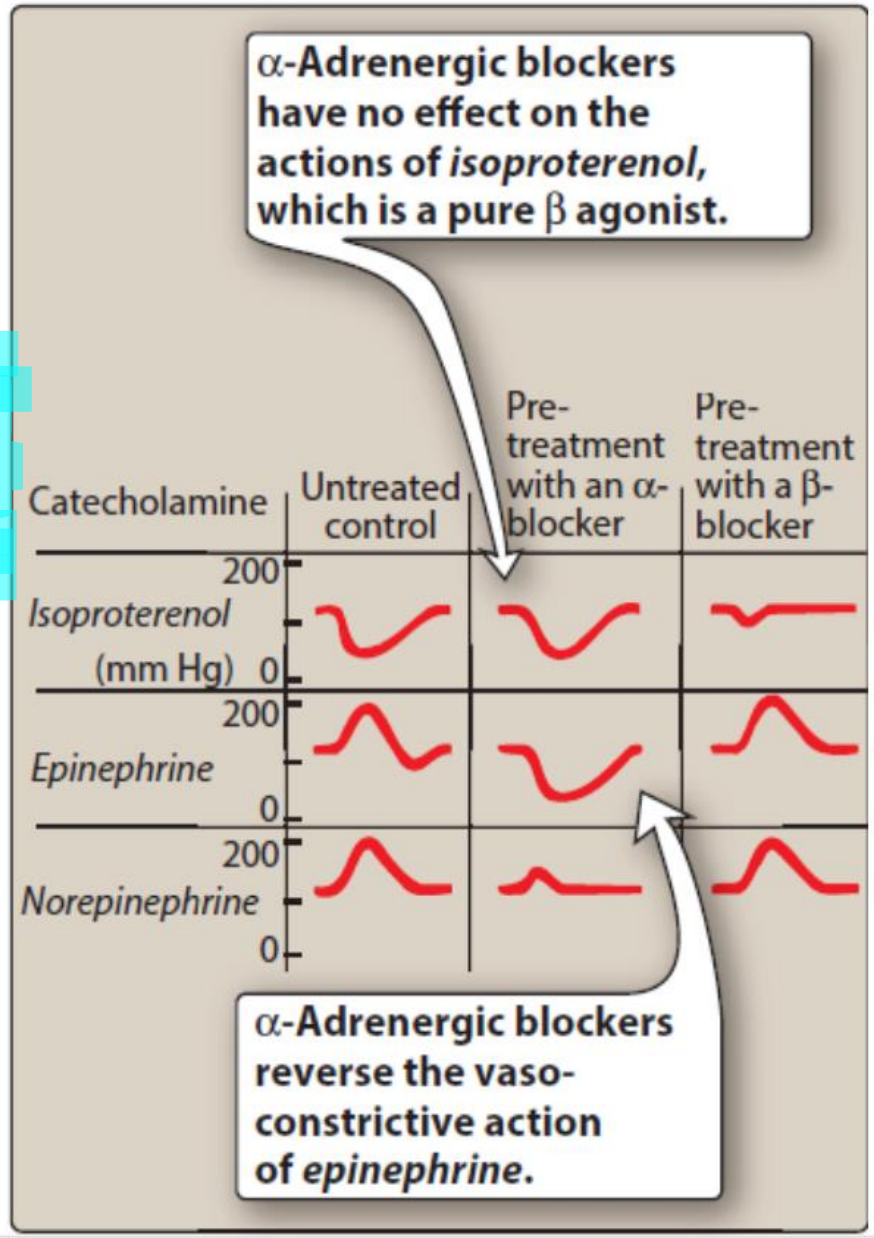
- **[Note: Blocking these receptors results in more norepinephrine release, which stimulates β1 receptors on the heart, increasing cardiac output.].**

- **Thus, the drug has been unsuccessful in maintaining lowered blood pressure in hypertension, and it is no longer used for this purpose**.

❑ Actions of Phenoxybenzamine:

- ❖ b. **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 β2 receptors is not blocked**.
- ❖ Therefore, in the presence of phenoxybenzamine, the systemic blood pressure decreases in response to epinephrine (Figure 1).
- ❖ [**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** (Figure 1).

Figure 1: Summary of effects of adrenergic blockers on the changes in blood pressure induced by *isoproterenol*, *epinephrine*, and *norepinephrine*.



2. Therapeutic uses of Phenoxybenzamine:

- Phenoxybenzamine is used in the treatment of sweating and hypertension associated with pheochromocytoma, a catecholamine-secreting tumor of

- cells derived from the adrenal medulla. Phenoxybenzamine is sometimes effective in treating Raynaud disease and frostbite.

- Figure 1: Summary of effects of adrenergic blockers on the changes in blood pressure induced by isoproterenol, epinephrine, and norepinephrine.

❑ 3. Adverse effects:

- ❖ Phenoxybenzamine can cause **postural hypotens**ion, nasal stuffiness, **nausea, and vomiting.**
- ❖ It may **inhibit ejaculation**. It may also **induce reflex tachycardia**, which is mediated by the baroreceptor reflex.
- ❖ Phenoxybenzamine should be used with **caution in patients with cerebrovascular or cardiovascular disease.**

B. Phentolamine

In contrast to phenoxybenzamine, phentolamine produces a competitive block of α1 and α2 receptors. Effects last for approximately 4 hours after a single injection. Pharmacological effects of phentolamine are very similar to those of phenoxybenzamine. It is used for the diagnosis and short-term management of pheochromocytoma.

It is also used locally to prevent dermal necrosis following extravasation of norepinephrine. 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.

C. Prazosin, terazosin, doxazosin, tamsulosin, and alfuzosin

Prazosin, *terazosin*, and *doxazosin* are selective competitive blockers of the α1 receptor.

In contrast to *phenoxybenzamine* and *phentolamine*, they are useful in the treatment of hypertension. *Tamsulosin* and *alfuzosin* are examples of other selective α1 antagonists indicated for the treatment of benign prostatic hyperplasia (BPH). Metabolism leads to inactive products that are excreted in urine except for those of *doxazosin*, which appear in feces. *Doxazosin* is the longest acting of these drugs.

1. Mechanism of action: All of these agents decrease peripheral vascular resistance and lower blood pressure by causing relaxation of both arterial and venous smooth muscle. These drugs, unlike *phenoxybenzamine* and *phentolamine*, cause minimal changes in cardiac output, renal blood flow, and glomerular filtration rate.

Tamsulosin has the least effect on blood pressure because it is 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 a decrease tone in the smooth muscle of the bladder neck and prostate and improves urine flow.

2. Therapeutic uses: Individuals with elevated blood pressure treated with one of these drugs do not become tolerant to its action. However, the first dose of these drugs may produce 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. These drugs may cause modest improvement in lipid profiles and glucose metabolism in hypertensive patients. Because of inferior cardiovascular outcomes as compared to other antihypertensives, α1 antagonists are not used as monotherapy for the treatment of hypertension.

The α1 receptor antagonists have been used as an alternative to surgery in patients with symptomatic BPH.

- 3. Adverse effects:
- α1-Blockers such as prazosin and doxazosin may cause dizziness, a lack of energy, nasal congestion, headache, drowsiness,
- and orthostatic hypotension (although to a lesser degree than that observed with phenoxybenzamine and phentolamine)

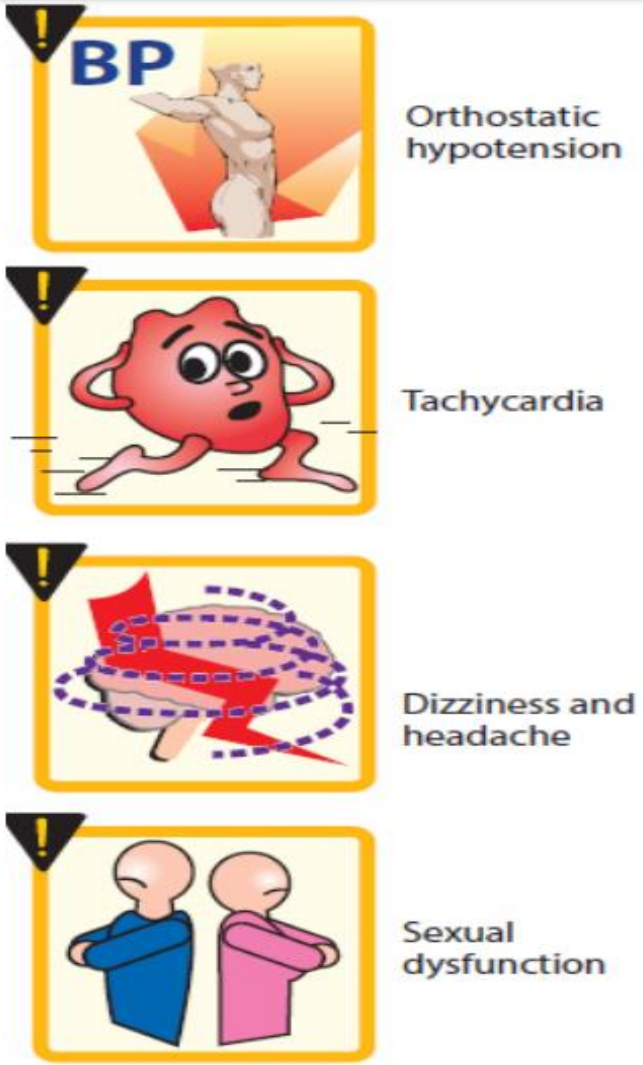


Figure 2: Some adverse effects commonly observed with nonselective α-adrenergic blocking agents.

D. Yohimbine:

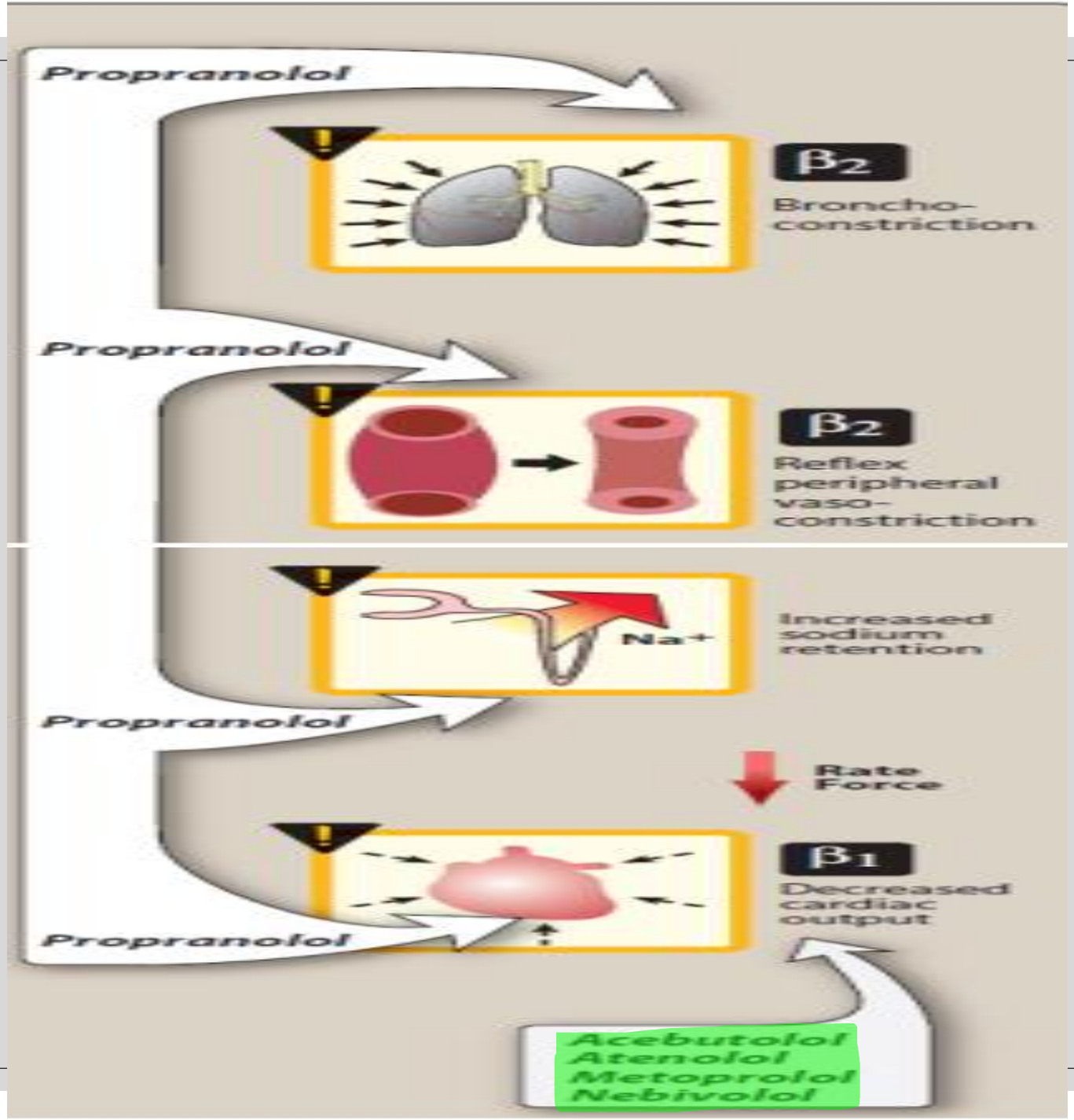
- Is a selective competitive α2-blocker that works at the **level of the CNS to increase sympathetic outflow to the periphery**.
- It is found as a **component of the bark of the yohimbe** tree (Pausinystalia yohimbe) and has been used as a **sexual stimulant** and **in the treatment of erectile dysfunction**.
- Its use in the treatment of these disorders is not recommended due to lack of demonstrated efficacy.

III. β-ADRENERGIC BLOCKING AGENTS

All of 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.]

These drugs also differ in intrinsic sympathomimetics activity, CNS effects, blockade of sympathetic receptors, vasodilation, and pharmacokinetics

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. B 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*.]


Propranolol
β2
Broncho-constriction
Propranolol
β2
Reflex peripheral vaso-constriction
Na+
Increased sodium retention
Propranolol
Rate
Force
Propranolol
β1
Decreased cardiac output
Acebutolol
Atenolol
Metoprolol
Nebivolol

A. Propranolol: A nonselective β antagonist

Propranolol is the prototype β-adrenergic antagonist and blocks both β1 and β2 receptors with equal affinity. Sustainedrelease preparations for once-a-day dosing are available.

1. Actions:

a. Cardiovascular: *Propranolol* diminishes cardiac output, having both negative inotropic and chronotropic effects (Figure 3). It directly depresses sinoatrial and atrioventricular nodal activity.

The resulting bradycardia usually limits the dose of the drug. During exercise or stress, when the sympathetic nervous system is activated, β-blockers attenuate the expected increase in heart rate. Cardiac output, workload, and oxygen consumption are decreased by blockade of β1 receptors, and these effects are useful in the treatment of angina. The β-blockers are effective in attenuating supraventricular cardiac arrhythmias, but generally are not effective against ventricular arrhythmias (except those induced by exercise).

b. Peripheral vasoconstriction: Nonselective blockade of β receptors prevents β2-mediated vasodilation in skeletal muscles, increasing peripheral vascular resistance (Figure 3). The reduction in cardiac output produced by all β-blockers leads to decreased blood pressure, which triggers a reflex peripheral vasoconstriction that is reflected in reduced blood flow to the periphery. In patients with hypertension, total peripheral resistance returns to normal or decreases with long term use of *propranolol*. There is a gradual reduction of both systolic and diastolic blood pressures in hypertensive patients.

c. Bronchoconstriction: Blocking β2 receptors in the lungs of susceptible patients causes contraction of the bronchiolar smooth muscle (Figure 3). This can precipitate an exacerbation in patients with chronic obstructive pulmonary disease (COPD) or asthma. Therefore, β-blockers, particularly, nonselective ones, are contraindicated in patients with COPD or asthma.

d. Disturbances in glucose metabolism:

- β blockade leads to decreased glycogenolysis and decreased glucagon secretion.
- Therefore, if propranolol is given to a diabetic patient receiving insulin, careful monitoring of blood glucose is essential, because pronounced hypoglycemia may occur after insulin injection.
- β-blockers also attenuate the normal physiologic response to hypoglycemia.

e. Blocked action of isoproterenol: 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).

[Note: 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 α receptors) remains unimpaired. The actions of *norepinephrine* on the cardiovascular system are mediated primarily by α receptors and are, therefore, unaffected.]

2. Therapeutic uses:

a. Hypertension: *Propranolol* does not reduce blood pressure in people with normal blood pressure. *Propranolol* lowers blood pressure in hypertension by several different mechanisms of action. Decreased cardiac output is the primary mechanism, but inhibition of renin release from the kidney, decrease in total peripheral resistance with long-term use, and decreased sympathetic outflow from the CNS also contribute to the antihypertensive effects.

b. 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, thus, useful in the chronic management of stable angina.

c. Myocardial infarction: *Propranolol* and other β-blockers have a protective effect on the myocardium. Thus, patients who have had one myocardial infarction appear to be protected against a second heart attack by prophylactic use of β-blockers. In addition, administration of a β-blocker immediately following a myocardial infarction reduces infarct size and hastens recovery.

The mechanism for these effects may be a blocking of the actions of circulating catecholamines, which would increase the oxygen demand in an already ischemic heart muscle. *Propranolol* also reduces the incidence of sudden arrhythmic death after myocardial infarction.

d. Migraine: *Propranolol* is effective in reducing migraine episodes when used prophylactically. It is one of the more useful β-blockers for this indication, due to its lipophilic nature that allows it to penetrate the CNS. [Note: For the acute management of migraine, serotonin agonists such as *sumatriptan* are used, as well as other drugs.]

e. 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.

3. Pharmacokinetics: After oral administration, *propranolol* is almost completely absorbed. It is subject to first-pass effect, and only about 25% of an administered dose reaches the circulation.

The volume of distribution of *propranolol* is quite large (4 L/kg), and the drug readily crosses the blood–brain barrier due to its high lipophilicity.

Propranolol is extensively metabolized, and most metabolites are excreted in the urine.

4. Adverse effects:

a. Bronchoconstriction: *Propranolol* has the potential to cause significant bronchoconstriction due to blockade of β2 receptors (Figure 4). Death by asphyxiation has been reported for patients with asthma whom were inadvertently administered the drug. Therefore, *propranolol* is contraindicated in patients with COPD or asthma.

b. Arrhythmias: Treatment with β-blockers must never be stopped abruptly because of the risk of precipitating cardiac arrhythmias, which may be severe. 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 worsen angina or hypertension.

c. Sexual impairment: Because ejaculation in the male is mediated through α-adrenergic activation, β-blockers do not affect ejaculation or internal bladder sphincter function. On the other hand, some men do complain of impaired sexual activity. The reasons for this are not clear and may be independent of β receptor blockade.

- **d. Metabolic disturbances**:
- β Blockade 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 β2 and β3 receptor stimulation, leading to the metabolism of triglycerides into free fatty acids.] Patients administered nonselective β-blockers have increased low density lipoprotein ("bad" cholesterol), increased triglycerides, and reduced high-density lipoprotein ("good" cholesterol). These effects on the serum lipid profile may be less pronounced with the use of β1-selective antagonists such as *metoprolol*.

e. CNS effects: *Propranolol* has numerous CNS-mediated effects, including depression, dizziness, lethargy, fatigue, weakness, visual disturbances, hallucinations, short-term memory loss, emotional lability, vivid dreams (including nightmares), and depression. Fewer CNS effects may be seen with more hydrophilic β-blockers (for example, *atenolol*), since they do not cross the blood–brain barrier as readily.

B. Nadolol and timolol: Nonselective β antagonists

Nadolol and *timolol* 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. It is used topically in the treatment of chronic open-angle glaucoma.

1. Treatment of glaucoma: β-blockers, such as topically applied *timolol*, *betaxolol*, or *carteolol*, are effective in diminishing intraocular pressure in glaucoma. This occurs by decreasing the secretion of aqueous humor by the ciliary body. 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.

CLASS OF DRUG	DRUG NAMES	MECHANISM OF ACTION	SIDE EFFECTS
β-Adrenergic antagonists (topical)	*Betaxolol, carteolol, levobunolol, metipranolol, timolol*	Decrease of aqueous humor production	Ocular irritation; contraindicated in patients with asthma, obstructive airway disease, bradycardia, and congestive heart failure.
α-Adrenergic agonists (topical)	*Apraclonidine, brimonidine*	Decrease of aqueous humor production and increase of aqueous outflow	Red eye and ocular irritation, allergic reactions, malaise, and headache.
Cholinergic agonists (topical)	*Pilocarpine, carbachol*	Increase of aqueous outflow	Eye or brow pain, increased myopia, and decreased vision.
Prostaglandin-like analogues (topical)	*Latanoprost, travoprost, bimatoprost*	Increase of aqueous humor outflow	Red eye and ocular irritation, increased iris pigmentation, and excessive hair growth of eye lashes.
Carbonic anhydrase inhibitors (topical and systemic)	*Dorzolamide* and *brinzolamide* (topical), *acetazolamide*, and *methazolamide* (oral)	Decrease of aqueous humor production	Transient myopia, nausea, diarrhea, loss of appetite and taste, and renal stones (oral drugs).

C. Acebutolol, atenolol, betaxolol, bisoprolol, esmolol, metoprolol, and nebivolol: Selective β1 antagonists

Drugs that preferentially block the β1 receptors minimize the unwanted bronchoconstriction (β2 effect) seen with *propranolol* use in asthma patients. 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 most pronounced at low doses and is lost at high doses. [Note: Since β1 selectivity of these agents is lost at high doses, they may antagonize β2 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 in critically ill patients and those undergoing surgery or diagnostic procedures. In addition to its cardioselective β -blockade, nebivolol releases nitric oxide from endothelial cells and causes vasodilation. 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. 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.

2. Therapeutic uses: The cardioselective B-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.

D. Acebutolol and pindolol: Antagonists with partial agonist activity

1. Actions:

a. Cardiovascular: *Acebutolol* (β1-selective antagonist) and *pindolol* (nonselective β-blocker) are not pure antagonists. These drugs also have the ability to weakly stimulate both β1 and β2 receptors (Figure 5) 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 diminished effect on cardiac rate and cardiac output compared to that of β-blockers without ISA.

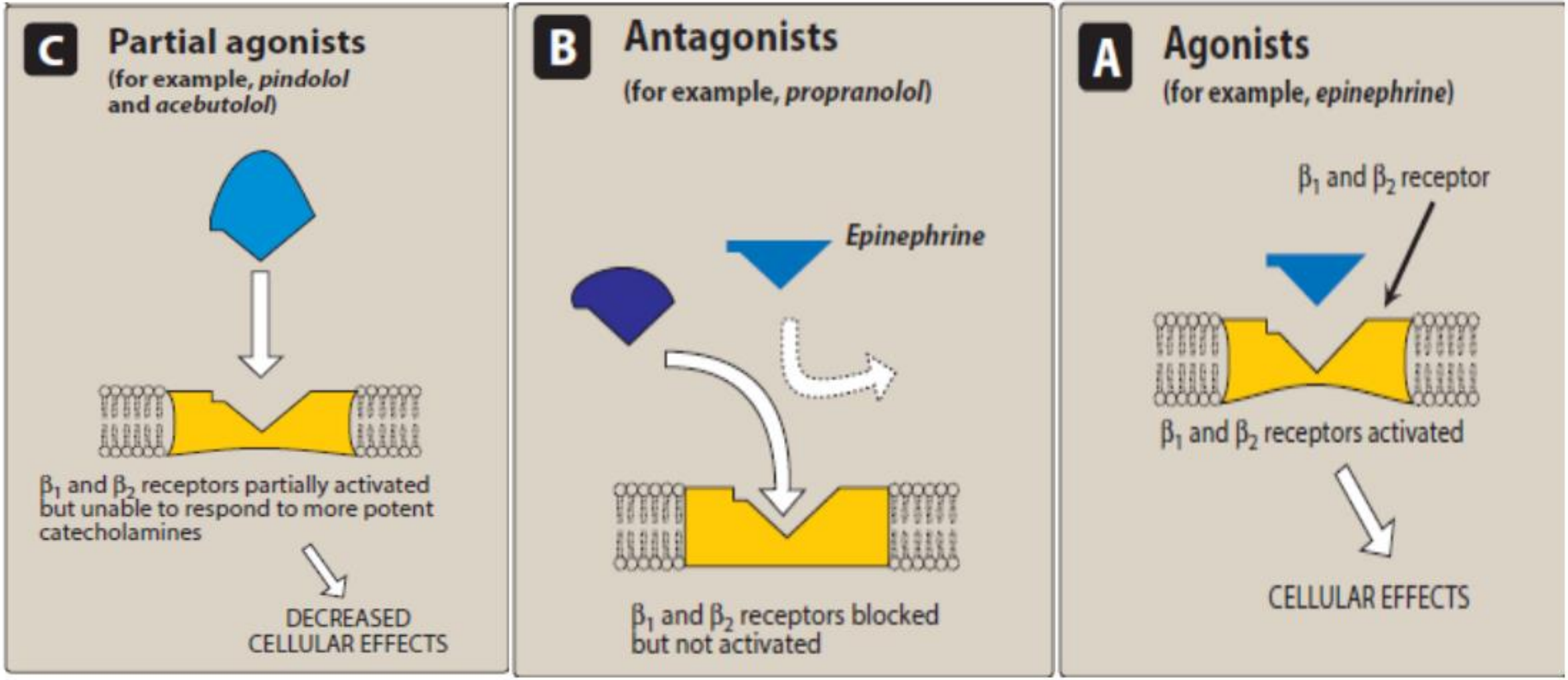


Figure 5: Comparison of agonists, antagonists, and partial agonists of β adrenoceptors.

b. Decreased metabolic effects: β-blockers with ISA minimize the disturbances of lipid and carbohydrate metabolism that are seen with other β-blockers. For example, these agents do not decrease plasma HDL levels.

2. Therapeutic use in hypertension: 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. [Note: β-blockers with ISA are not used for stable angina or arrhythmias due to their partial agonist effect.].

E. Labetalol and carvedilol: Antagonists of both α and β adrenoceptors

1. Actions: *Labetalol* and *carvedilol* are nonselective β-blockers with concurrent α1-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.

DRUG	RECEPTOR SPECIFICITY	THERAPEUTIC USES
Propranolol[1]	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

DRUGS AFFECTING NEUROTRANSMITTER RELEASE OR UPTAKE

Some agents act on the adrenergic neuron, either to interfere with neurotransmitter release from storage vesicles or to alter the uptake of the neurotransmitter into the adrenergic neuron. However, due to the advent of newer and more effective agents with fewer side effects, these agents are seldom used therapeutically. Reserpine is one of the remaining agents in this category.

Reserpine, a plant alkaloid, blocks the Mg^{2+}/adenosine triphosphatedependent 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.

Thanks for Listening