Pharmacology I

Adrenergic Antagonists

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Lecture No. : 6

مستقبل له تاريخ

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 Antagonists

❑ 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.

α BLOCKERS

Alfuzosin UROXATRAL
Doxazosin CARDURA
Phenoxybenzamine
Phentolamine GENERIC
Prazosin MINIPRESS
Silodosin RAPAFLO
Tamsulosin FLOMAX
Terazosin GENERIC ONLY
Yohimbine YOCON

Adrenergic Antagonists

❑α-Adrenergic Blocking Agents

(Phenoxybenzamine and Phentolamine)

- 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**.].
- ***Phenoxybenzamine*** and ***phentolamine***, have **limited** clinical applications.

α-Adrenergic Blocking Agents

❑ A. Phenoxybenzamine (nonselective *α1 and α2 irreversible blocker)*

- ***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**.

α-Adrenergic Blocking Agents

❑ A. Phenoxybenzamine (nonselective *α1 and α2 irreversible blocker)*

- **Actions:**

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

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

α-Adrenergic Blocking Agents

❑ A. Phenoxybenzamine (nonselective *α1 and α2 irreversible blocker)*

- **Actions:**

- [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.

α-Adrenergic Blocking Agents

A. Phenoxybenzamine (nonselective *α1 and α2 irreversible blocker)*

- **Actions:**

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** .

α-Adrenergic Blocking Agents

A. Phenoxybenzamine (nonselective *α1 and α2 irreversible blocker)*

- **Actions:**

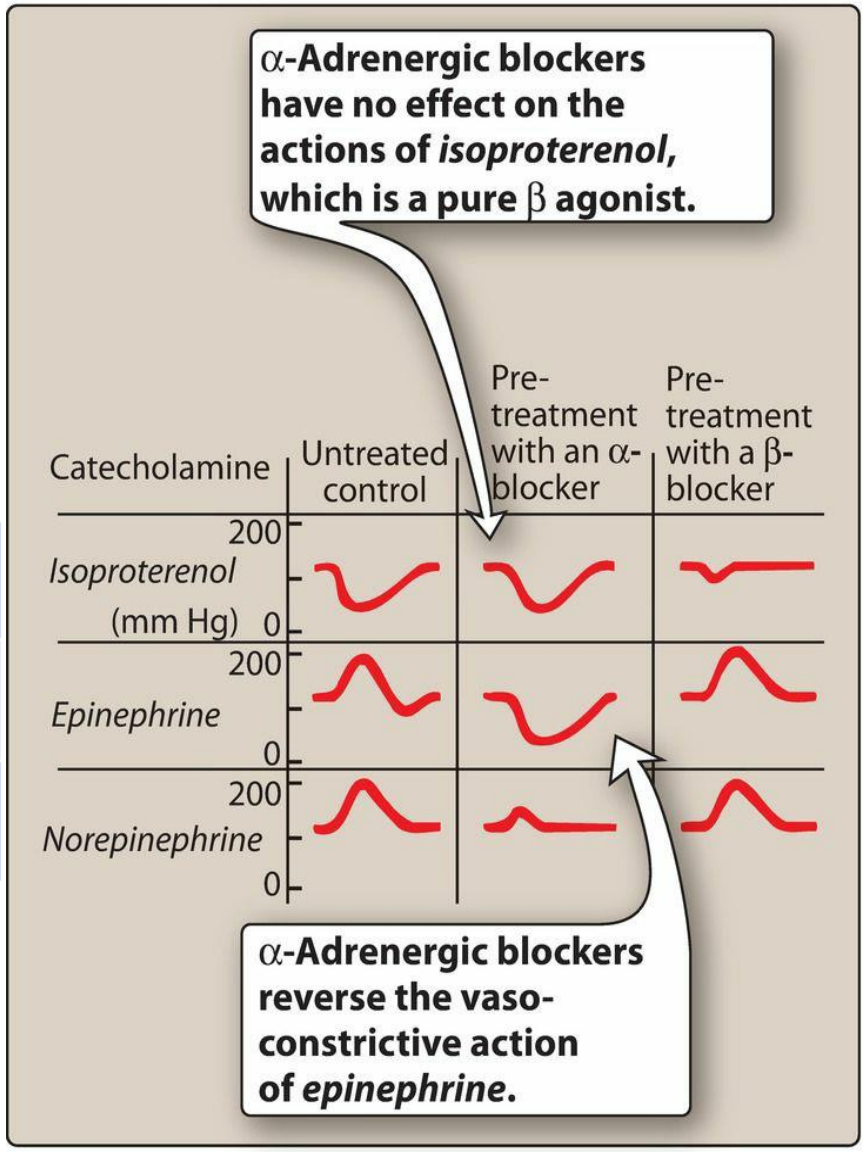
- [Note: The actions of **norepinephrine** are **not reversed but are diminished** because norepinephrine **lacks significant β agonist action on the vasculature**.]

- Phenoxybenzamine has **no effect** on the actions of **isoproterenol**, which is **a pure β agonist** .

β

α β

α



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

α-Adrenergic Blocking Agents

A. Phenoxybenzamine (nonselective *α1 and α2 irreversible blocker)*

2. Therapeutic uses:

i. Phenoxybenzamine is used in the **treatment of sweating and hypertension associated with pheochromocytoma**, a catecholamine-secreting tumor of cells derived from the adrenal medulla.

ii. Phenoxybenzamine is sometimes effective in trea **r disease and frostbite**.

Frostbite of fingers

α-Adrenergic Blocking Agents

A. Phenoxybenzamine (nonselective *α1 and α2 irreversible blocker)*

3. Adverse effects:

- Phenoxybenzamine can cause **postural hypotension**, **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**.

α-Adrenergic Blocking Agents

B. Phentolamine (nonselective *α1 and α2 reversible blocker)*

- 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.

α-Adrenergic Blocking Agents

B. Phentolamine

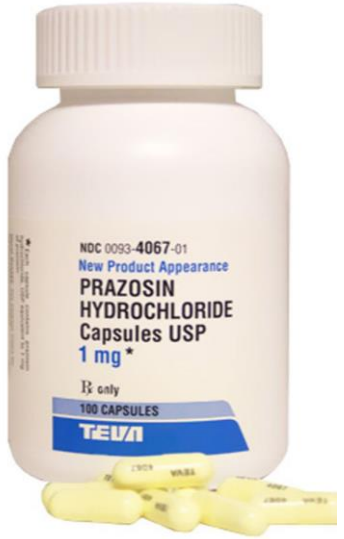
- **It is used for the**

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

α-Adrenergic Blocking Agents

C. Prazosin, terazosin, doxazosin, tamsulosin, and alfuzosin (selective competitive α1-blocker).

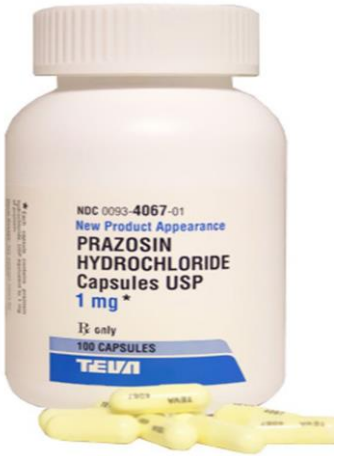
- **Prazosin, terazosin, and doxazosin** are **selective competitive blockers of the α1 receptor**.
- In contrast to *phenoxybenzamine* and *phentolamine*, they are **useful** in the **treatment of hypertension**.



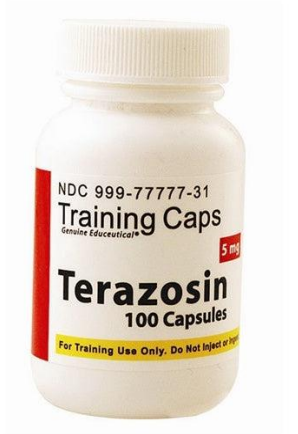
α-Adrenergic Blocking Agents

C. Prazosin, terazosin, doxazosin, tamsulosin, and alfuzosin (selective competitive α1-blocker) .

- **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.



α-Adrenergic Blocking Agents

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

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**.

α-Adrenergic Blocking Agents

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

1. Mechanism of action:

- **Tamsulosin** has **the least effect** on blood pressure because it is **less selective** for **α1B receptors** found in the **blood vessels** and more **selective** for **α1A receptors** in the **prostate and bladder**.
- **Blockade** of the **α1A receptors** a **decrease tone** in the smooth muscle of the **bladder neck** and **prostate** and **improves** urine flow.

α-Adrenergic Blocking Agents

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

2. Therapeutic uses:

A. 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

I. By adjusting the first **dose to one-third or one fourth of the normal dose**

II. By **giving the drug at bedtime**.

α-Adrenergic Blocking Agents

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

2. Therapeutic uses:

- 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**.

α-Adrenergic Blocking Agents

C. Prazosin, terazosin, doxazosin, tamsulosin, alfuzosin

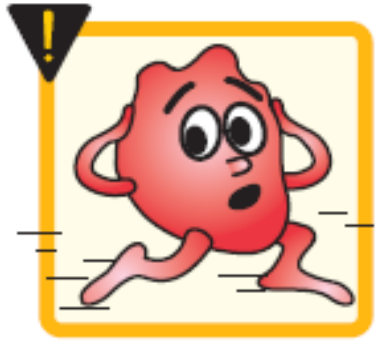
3. Adverse effects:

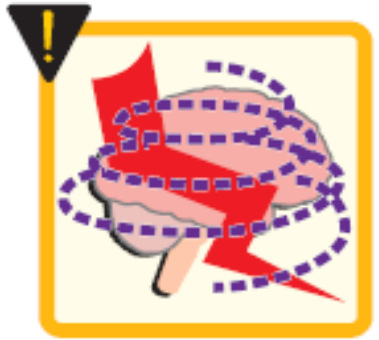
- α1-Blockers such as prazosin and doxazosin may cause

1. **Dizziness,**
2. **A lack of energy,**
3. **Nasal congestion,**
4. **Headache,**
5. **Drowsiness,**
6. **Orthostatic hypotension**

- (although to a lesser degree than that observed with phenoxybenzamine and phentolamine)

Orthostatic hypotension


Tachycardia


Dizziness and headache


Sexual dysfunction

II. α-Adrenergic Blocking Agents

D. Yohimbine (selective competitive α2-blocker)

- **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**.]

III. β-Adrenergic Blocking Agents

- **These drugs also differ in**

1. **Intrinsic sympathomimetics activity,**
2. **CNS effects,**
3. **Blockade of sympathetic receptors**
4. **Vasodilation**
5. **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.

III. β-Adrenergic Blocking Agents

- **β-Blockers are effective in treating :**

1. **Hypertension,**
2. **Angina,**
3. **Cardiac arrhythmias,**
4. **Myocardial infarction,**
5. **Heart failure,**
6. **Hyperthyroidism, and**
7. **Glaucoma.**
8. 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*.]

III. β-Adrenergic Blocking Agents

A. Propranolol: A nonselective β antagonist

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

III. β-Adrenergic Blocking Agents A. Propranolol: A nonselective β antagonist

1. Actions:

a. Cardiovascular:

- *Propranolol* **diminishes** cardiac output, having both **negative** inotropic and chronotropic effects.
- 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**.

III. β-Adrenergic Blocking Agents A. Propranolol: A nonselective β antagonist

1. Actions:

a. Cardiovascular:

- **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).

III. β-Adrenergic Blocking Agents A. Propranolol: A nonselective β antagonist

1. Actions:

b. Peripheral vasoconstriction:

- Nonselective blockade of β receptors **prevents** **β2-mediated vasodilation** in skeletal muscles, increasing peripheral vascular resistance.
- 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.

III. β-Adrenergic Blocking Agents A. Propranolol: A nonselective β antagonist

1. Actions:

b. Peripheral vasoconstriction:

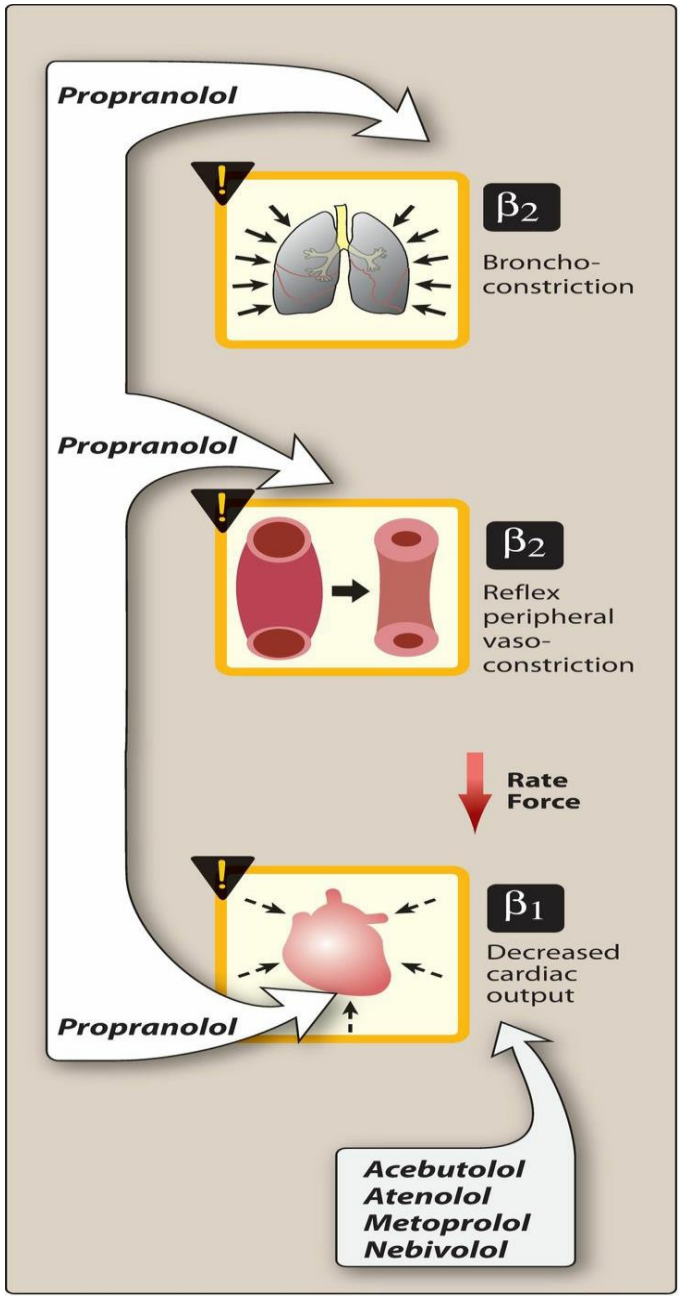
- In patients with hypertension, **total peripheral resistance returns to normal or decreases** with **long term** use of *propranolol*.
- There is a **gradual reduction of both systolic and diastolic blood pressures in hypertensive patients**.

III. β-Adrenergic Blocking Agents A. Propranolol: A nonselective β antagonist

1. Actions:

c. Bronchoconstriction:

- **Blocking β2 receptors** in the lungs of susceptible patients causes **contraction of the bronchiolar smooth muscle**.
- 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**.



III. β-Adrenergic Blocking Agents A. Propranolol: A nonselective β antagonist

1. Actions:

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**.

III. β-Adrenergic Blocking Agents A. Propranolol: A nonselective β antagonist

1. Actions:

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).

III. β-Adrenergic Blocking Agents A. Propranolol: A nonselective β antagonist

1. Actions:

e. Blocked action of isoproterenol:

- [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 :

1. **Decreased cardiac output** is the **primary** mechanism,
2. But **inhibition** of **renin** release from the kidney,
3. **Decrease** in **total peripheral resistance** with long-term use, and
4. **Decreased sympathetic outflow** from the CNS also contribute to the antihypertensive effects.

2. Therapeutic uses:

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**.

2. Therapeutic uses:

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 **fastens 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

2. Therapeutic uses:

d. Migraine:

- *Propranolol* is effective in **reducing migraine episodes** when used prophylactically. It is one of the most 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.]

2. Therapeutic uses:

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**.
- **Death** by **asphyxiation** has been reported for patients with asthma whom were **carelessly** administered the drug.

❑ **Therefore, *propranolol* is contraindicated in patients with COPD or asthma.**

4. Adverse effects:

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**.

4. Adverse effects:

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**.

4. Adverse effects:

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.

4. Adverse effects:

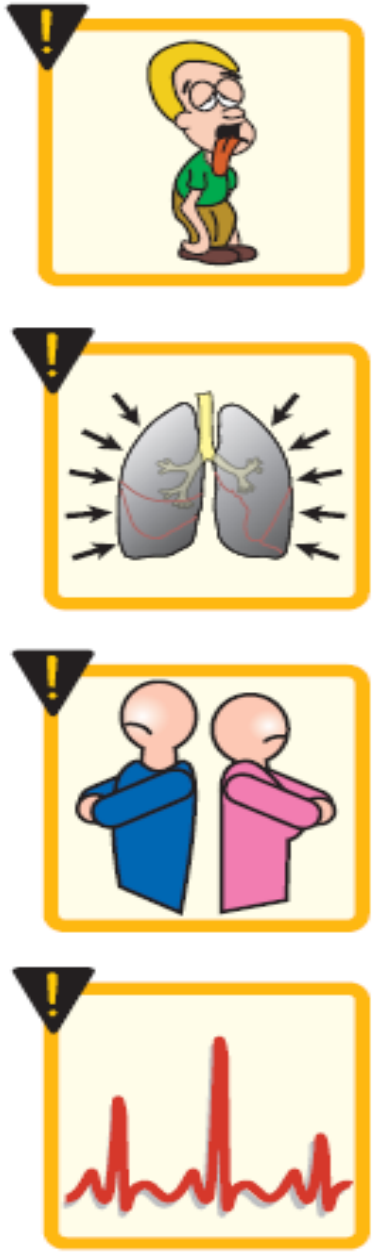
d. Metabolic disturbances:

- 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.

4. Adverse effects:

e. CNS effects:

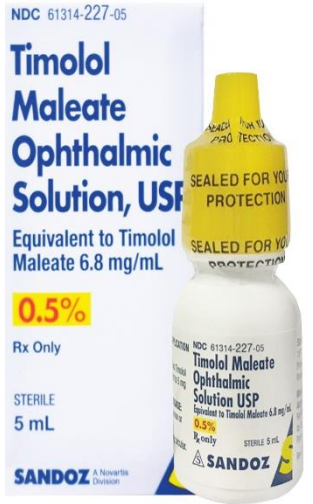
- *Propranolol* has numerous **CNS-mediated effects**, including depression, dizziness, lethargy, fatigue, weakness, visual disturbances, hallucinations, short-term memory loss, emotional lability, vivid dreams (including nightmares), and depression.
- Fewer CNS effects may be seen with more **hydrophilic**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



III. β-Adrenergic Blocking Agents

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**.



III. β-Adrenergic Blocking Agents

B. Nadolol and timolol: Nonselective β antagonists

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.

III. β-Adrenergic Blocking Agents

B. Nadolol and timolol: Nonselective β antagonists

1. Treatment of glaucoma:

- 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**.

III. β-Adrenergic Blocking Agents

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).

III. β-Adrenergic Blocking Agents

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.]**

III. β-Adrenergic Blocking Agents

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

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.**
- It is **used** to: **1)** control **blood pressure or 2) heart rhythm** in critically ill patients and those undergoing surgery or diagnostic procedures.

III. β-Adrenergic Blocking Agents

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

1. Actions:

- 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

1. Pulmonary function,
2. Peripheral resistance, and
3. Carbohydrate metabolism.

III. β-Adrenergic Blocking Agents

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

1. Actions:

- 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 β2 receptors**, **coldness of extremities** (**Raynaud's phenomenon**), a common side effect of β -blockers, is **less frequent**.

III. β-Adrenergic Blocking Agents

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

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**.

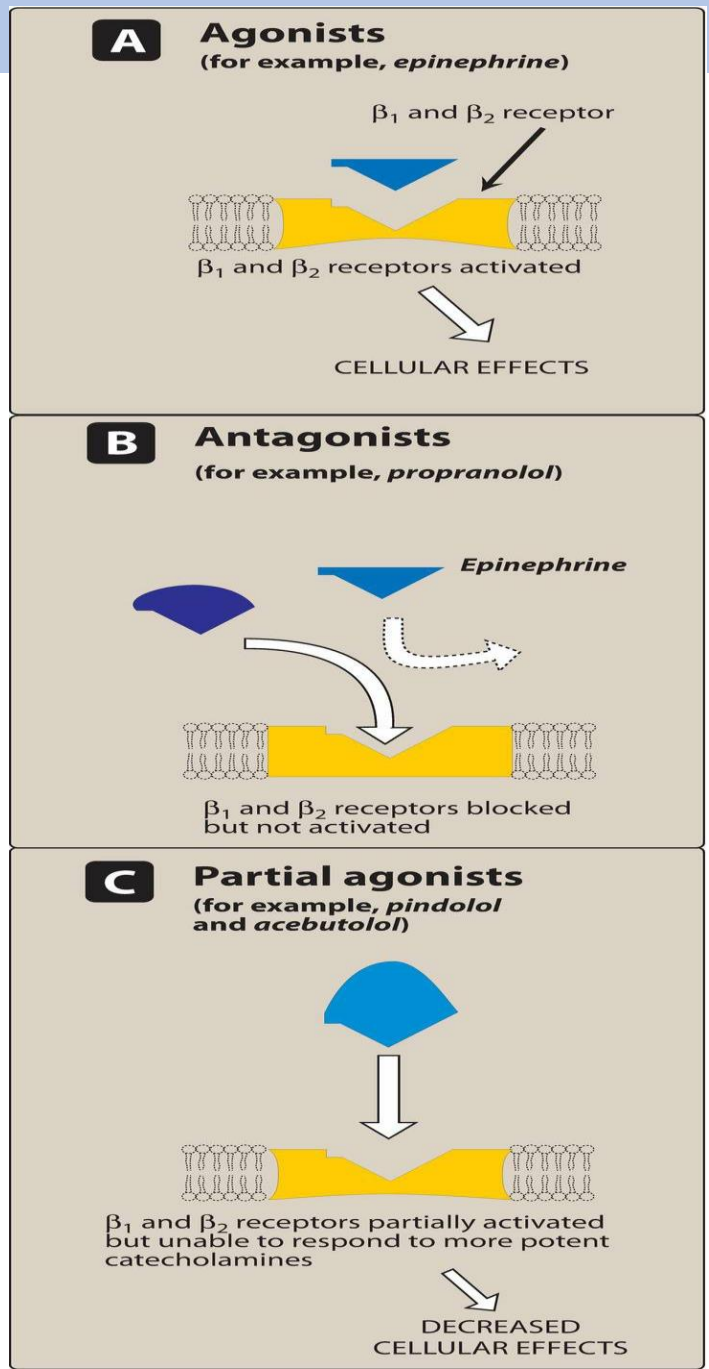
III. β-Adrenergic Blocking Agents

D. Acebutolol and pindolol: Antagonists with partial agonist activity

1. Actions:

a.Cardiovascular:

- ***Acebutolol*** **(β1-selective antagonist)**
- ***Pindolol*** **(nonselective β-blocker)**
- **They not pure antagonists.**
- These drugs also have the **ability** to **weakly** **stimulate** both **β1 and β2 receptors** and are said to have **intrinsic sympathomimetic activity** (ISA).



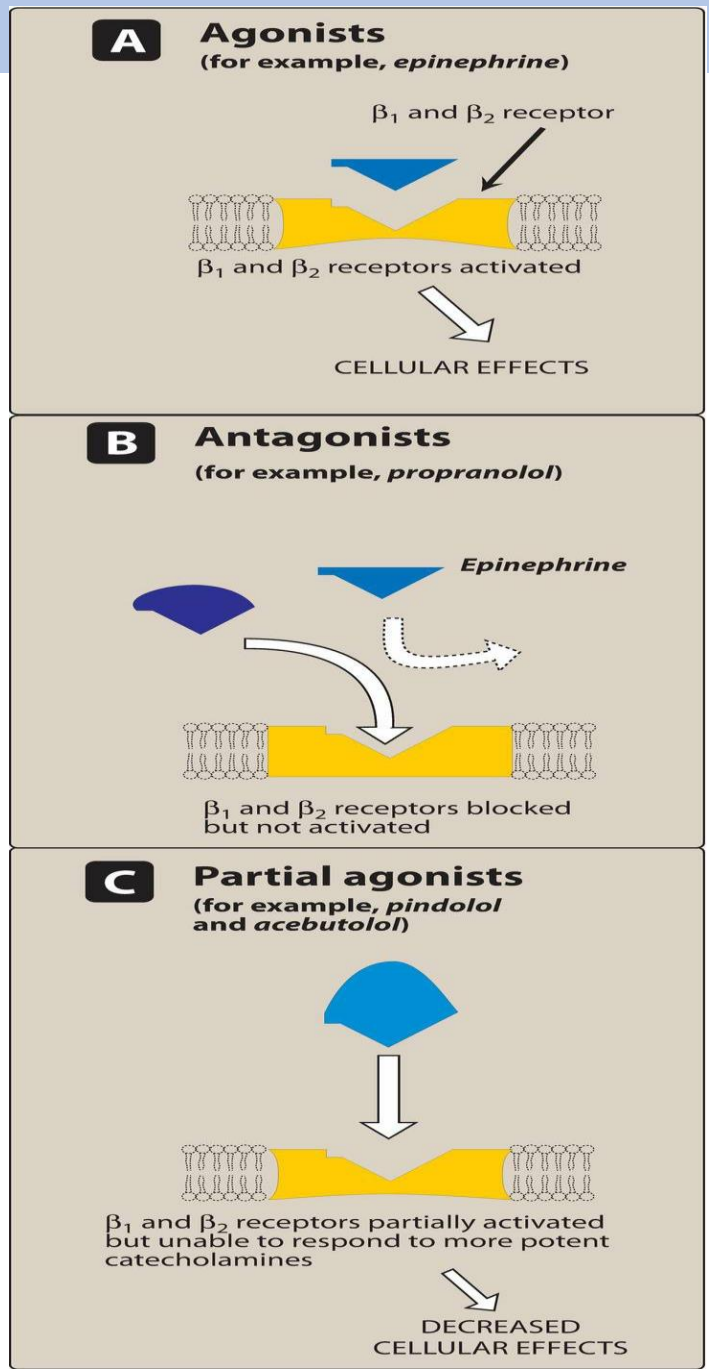
III. β-Adrenergic Blocking Agents

D. Acebutolol and pindolol: Antagonists with partial agonist activity

1. Actions:

a.Cardiovascular:

- 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.



III. β-Adrenergic Blocking Agents

D. Acebutolol and pindolol: Antagonists with partial agonist activity

1. Actions:

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.

III. β-Adrenergic Blocking Agents

D. Acebutolol and pindolol: Antagonists with partial agonist activity

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**.].

III. β-Adrenergic Blocking Agents

E. Labetalol and carvedilol: Antagonists α and β

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**.

III. β-Adrenergic Blocking Agents

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

2. Therapeutic use in hypertension and heart failure:

- ***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.
- β-blockers **should not be given** to patients with an **acute exacerbation of heart failure,** as they can worsen the condition.

III. β-Adrenergic Blocking Agents

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

2. Therapeutic use in hypertension and heart failure:

- 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.

III. β-Adrenergic Blocking Agents

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

3. Adverse effects:

- **Orthostatic hypotension** and **dizziness** are associated with α1 blockade. Below Figure summarizes the receptor specificities and uses of the β- adrenergic antagonists.

III. β-Adrenergic Blocking Agents

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*	α_1, β_1, β_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.

Drugs Affecting Neurotransmitter Release Or Uptake

- **Reserpine**, a plant alkaloid, **blocks the Mg2+/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.

Drugs Affecting Neurotransmitter Release Or Uptake

❑ Reserpine

- 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.