Class 2: Alpha and Beta Blockers – Antiarrhythmic Drugs

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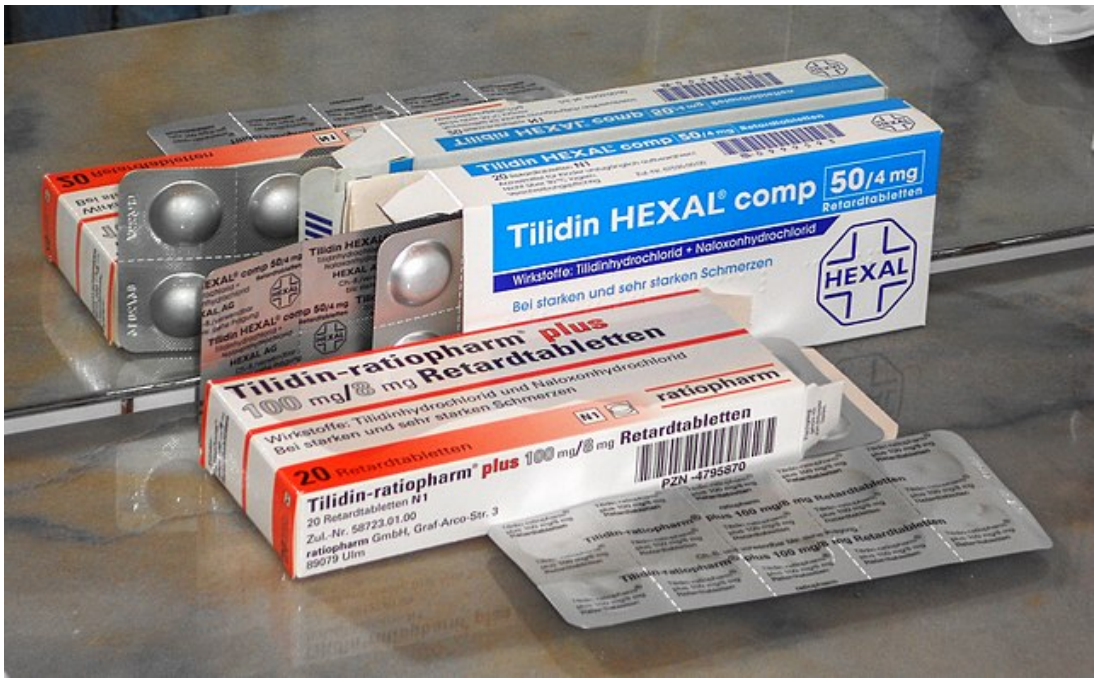
This article examines the important pharmacological aspects of alpha and beta blockers including their classification, pharmacokinetics, mechanism of action, important actions on various organ systems, clinical uses, and toxicity.



Definition of Alpha and Beta Blockers

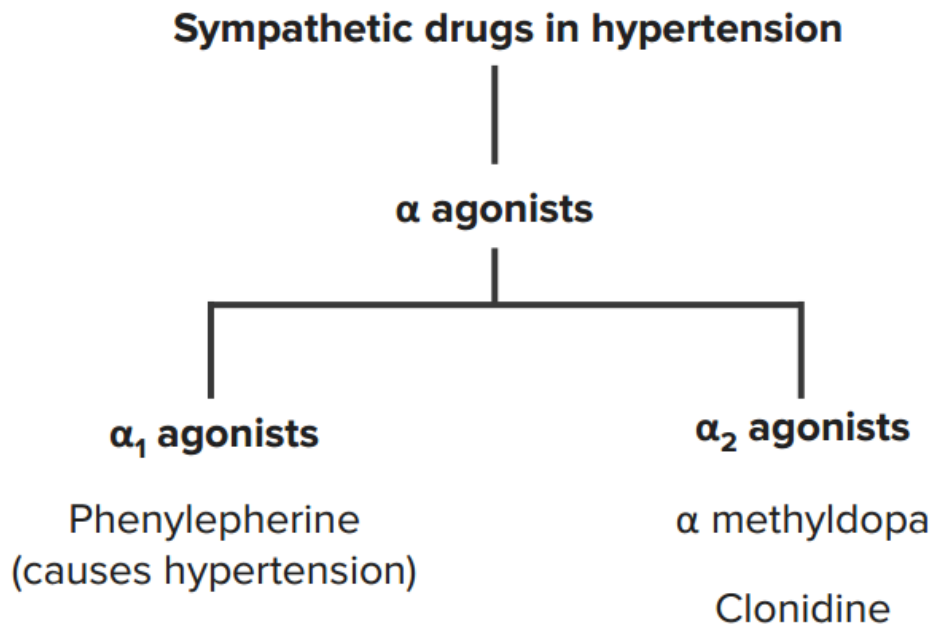
Alpha blockers generally help relax the muscles, which in turn can lead to the opening of blood vessels for smooth circulation. Alpha blockers work by keeping the hormones of norepinephrine or noradrenaline at bay, leading to smoother blood flow through open veins.

Beta blockers work by blocking the hormone called epinephrine (better known as adrenaline). This hormone often causes increased heart rate, which can lead to increased blood pressure levels. Beta blockers prevent this from happening by reducing the heart rate, thereby reducing blood flow. Blood pressure is decreased because of the dilation of the blood vessels.

Classification of Alpha and Beta Blockers

Adrenoceptor blockers are classified based upon their selectivity toward adrenoreceptors.

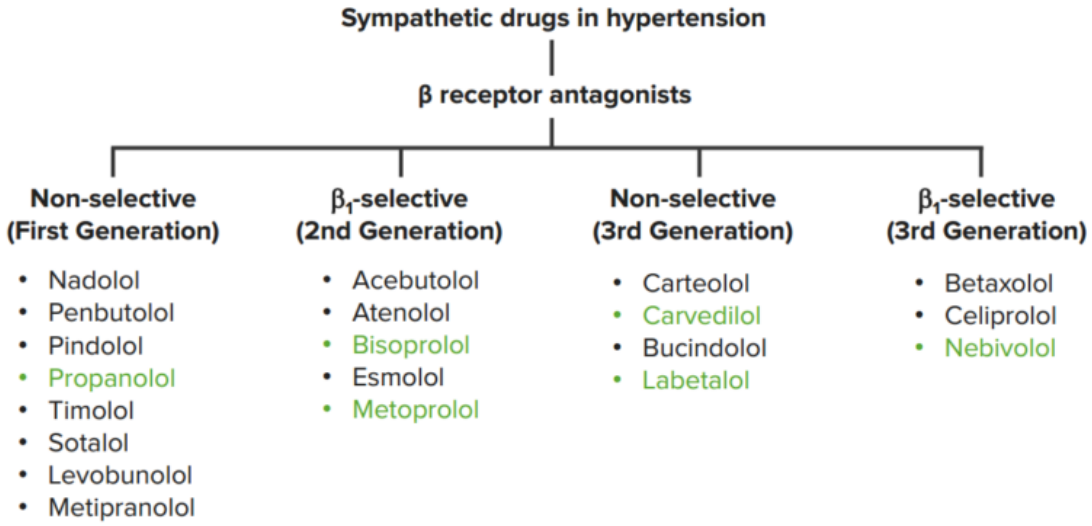
Alpha blockers



- **Non-selective:** phenoxybenzamine, phentolamine
- **α1-selective:** prazosin, terazosin, doxazosin, alfuzosin, indoramin, urapidil, bunazosin, tamsulosin
- **α2-selective:** yohimbine

α-Methyldopa (Aldomet^{R})	**Clonidine**
Decrease central sympathetic outflow	Decrease central sympathetic outflow
Prodrug; metabolized to methylnorepinephrine	
Decreases central sympathetic outflow, cardiac output, and vascular resistance	Decreases central sympathetic outflow, cardiac output, and vascular resistance
Compensatory reaction: salt retention	Compensatory reaction: salt retention
Idiosyncratic reaction: • Hematologic immunotoxicity (positive Coombs test) → hemolytic anemia • Sedation	**Idiosyncratic reaction:** • Rebound hypertension if discontinued (restart it, or use phentolamine, an alpha blocker) • Sedation
Previously used extensively for pregnancy; second most common	**Not** used in pregnancy

Beta Blockers



- **Non-selective:** nadolol, penbutolol, pindolol, propranolol, timolol, sotalol, metoprolol, carteolol, carvedilol*, labetalol*
- **β1- selective:** acebutolol, atenolol, bisoprolol, esmolol, metoprolol, betaxolol, nebivolol
- **β2- selective:** butoxamine

Notable β-Blocker	
Propranol • Prototypical β-blocker • Short-acting, poor BP control • Used in anxiety and stage fright also • Can be used to fool a lie detector test!	**Metoprolol** • Prototypical cardiac β-blocker • Used twice daily • Most commonly used in MI period • More β1 selective, less BP control
Labetalol • Nonselective third generation • Wide therapeutic margin (200—2400 mg/day) • Excellent BP control • Most used BP med in pregnancy	**Bisoprolol** • Once daily β-blocker • More β1 selective, used post-MI • Good BP control
β-Blockers with additional activity	
Nebivolol • 'Novel' third generation selective β-blocker • β1 selective • Also, has nitric oxide activity — direct vasodilator • Excellent BP control • Caution: Endothelial dysfunction	**Carvedilol** • Nonselective third generation β-blocker • Also, has alpha activity • Used in heart failure • Poor BP control

Note:

- The names of α-blockers generally end with **-in, while those of** β-blockers generally end with –**olol**.
- Phenoxybenzamine is a long-acting irreversible α-blocker.
- Phentolamine is a short-acting reversible α-blocker.
- In the sympathetic nervous system, the transmitter in effector organs is **norepinephrine,** while, in the parasympathetic nervous system, the transmitter in effector organs is **acetylcholine (Ach)**. Alpha and beta blockers have an antagonistic action on the **sympathetic nervous system.**

Adrenoceptors – Alpha and Beta Receptors

α1 Receptors

- Location: at the gastrointestinal tract and bladder sphincter, vascular smooth muscles of skin and splanchnic regions, and radial muscle of iris
- Function: generally produce **smooth muscle constriction**
- Mechanism of action: act via **stimulation of IP3/Ca3+**

α2 Receptors

- Present in presynaptic nerve terminals, platelets, fat cells, and the wall of the gastrointestinal tract.
- Function: generally produce **relaxation/dilation**.
- Mechanism of action: act via **inhibition** of adenylate cyclase and decreasing the concentration of **cAMP (cyclic adenosine monophosphate)**.

β1 Receptors

- Location: sinoatrial node, atrioventricular node, atrial and ventricular muscle, His-Purkinje system, and kidney.
- Mechanism of action: act via **stimulation** of adenylate cyclase and decreasing the concentration of cAMP (cyclic adenosine monophosphate).

β2 Receptors

- Location: smooth vessels of skeletal muscle, blood vessels, gastrointestinal tract, uterus, liver, and urinary tract
- **Mechanism of action: act via stimulation of adenylate cyclase and decreasing the concentration of cAMP**

Effect of Adrenoceptors on Organ Systems

Understanding the action of **alpha and beta receptors** on various organ systems will aid in remembering the effect of alpha and beta blockers on those organ systems because they have opposite actions to the alpha/beta-agonists.

Receptor/organ system	Actions
α1 receptors	
Eyes	Contraction (mydriasis) of the iris dilator muscle.
Bladder	Constriction of bladder sphincter, Control of micturition and urine flow. Note: α-blockers increase the urine flow by promoting the relaxation of the bladder muscles.
Prostate	Cause ejaculation by prostate contraction. α-blockers are used to treat benign prostatic hyperplasia (BPH) induced urinary obstructions because it causes the relaxation of the bladder muscles (the opposite actions to the alpha agonists). α-blockers also produce impaired ejaculation due to their α-receptor antagonism.
Kidney	Decrease renin secretion.
Veins and arterioles (skin)	Contraction of smooth muscles of the peripheral blood vessels.
α2 receptors	
Platelets	Increase the platelet aggregability.

β1 receptors	
Heart	Increase heart rate, conduction velocity, contractibility, and AV node conduction.
β2 receptors	
Veins and arterioles	Promote dilation of arterioles and veins. Consequently a decrease in TPR, BP, afterload. Beta blockers are used in the treatment of hypertension.
Bladder	In contrast to the receptors, these stimulate bladder relaxation. No effect on the ejaculation.
Bronchioles	Bronchiolar smooth muscle relaxation
Kidney	Increase the renin secretion
Liver	Increased glycogenolysis

Alpha Adrenergic Blocking Agents

These drugs block the action of alpha-adrenoceptors. They are commonly used in the treatment and management of **hypertension** and **benign prostatic hyperplasia** (BPH).

- **Phenoxybenzamine** and **phentolamine** are two nonselective alpha-adrenergic blocking agents. Thus, they act as both α1 and α2 receptors**.**
- **Phenoxybenzamine** binds covalently with the adrenergic receptors (irreversible and non-competitive). Due to irreversible binding, phenoxybenzamine has a longer duration of action. It decreases blood pressure by preventing **constriction of the peripheral blood vessels**. However, due to increased cardiac output, phenoxybenzamine does not cause a prolonged drop in blood pressure, so it is not widely used for this purpose.
- **Phentolamine** is a reversible and competitive type of alpha-adrenergic blocking agents. It has a shorter duration of action and it is used in the treatment of **pheochromocytoma**.
- **Prazosin, terazosin, doxazosin,** and **tamsulosin** have selective antagonistic action on **α1 receptors.**
- **Prazosin** has 1,000 times more selectivity action on α1 receptors. Due to selectivity in action, marked **orthostatic hypotension** and **tachycardia** are generally observed with nonselective alpha-adrenergic blocking agents such as phenoxybenzamine and phentolamine.
- Prazosin is an important drug in the **treatment of hypertension** and BPH. Terazosin and doxazosin have similar actions. Terazosin has a **higher bioavailability** (80%) than prazosin (50%).
- Postural hypotension is not observed with **tamsulosin**.
- Before the discovery of phosphodiesterase-5-inhibitors such as sildenafil, **yohimbine** was used to treat impotence (erectile dysfunction) in men, but safer and effective alternatives are now available.

Alpha-blockers (both selective and non-selective) are not recommended as monotherapy in hypertension due to the availability of other effective antihypertensives.

Adverse Effects of Alpha Adrenergic Blocking Agents

Adverse effects of alpha blockers are mainly due to their antagonistic action/blocking effects on alpha receptors.

- **Orthostatic hypotension:** This results from the pooling of blood in the veins of the legs. Fainting can also result due to the reduced supply of blood to the brain. This is the most common side effect of alpha-blockers. It is more common with the use of nonselective than -selective alpha blockers.
- **Dizziness and headache**.
- **Reflex tachycardia**: Increased heart rate due to the stimulation of baroreceptors.
- **Nasal stiffness:** Occurs due to alpha-receptor blockage.
- Since alpha receptors have a role in the contraction of smooth muscle of the prostate, which induces ejaculation in males, blockage of alpha receptors inhibits the **ejaculation process** in males.

Beta-Adrenergic Blocking Agents

All beta blockers or beta-adrenoceptor blockers antagonize the action of beta receptors.

Understanding the action of **beta blockers** on various organ systems will aid in remembering the effect of beta-agonists on those organ systems because they have opposite actions to the beta agonists.

Note:

- **Cardioselective β blockers** (atenolol, metoprolol, acebutolol, esmolol, bisoprolol, betaxolol) have a selective action on **β1 receptors.**
- **Cardioselective β blockers** are safer to use in patients with asthma (as they don't cause bronchoconstriction), diabetes, and peripheral vascular disease.
- Beta blockers do not cause postural hypotension as they do not have any action on alpha receptors.
- Beta blockers act by reducing **cardiac output** (volume of blood pumped by the heart per minute), thereby reducing blood pressure.

Effects of Beta-Adrenergic Blocking Agents

Effect on Cardiovascular System

- Decreases **cardiac output**
- Decreases heart rate (produce **bradycardia**)
- Decreases force of contraction
- Decreases **total peripheral resistance**
- Negative chronotropic and inotropic actions
- **Decreases renin release** from the kidneys, which is thought to be their mechanism of action in reducing blood pressure

Always remember:

Note:

- Action by beta blockers on β2 receptors is considered to be undesired because nonselective beta blockers cause bronchoconstriction and decrease insulin secretion and glycogenolysis.
- **Cardioselective beta-blockers** always act on β1 receptors.

Effect on Pulmonary System

Nonselective beta-blockers such as propranolol can produce **bronchoconstriction** or

exacerbate **asthma** in asthmatics. Due to this, propranolol should be avoided in **asthmatics** and patients suffering from **COPD**.

- Beta-blockers always show effects opposite to beta agonists.
- β1 agonists such as salmeterol and salbutamol have a **bronchodilatory effect** on the **lungs**.

Effects on the Eyes

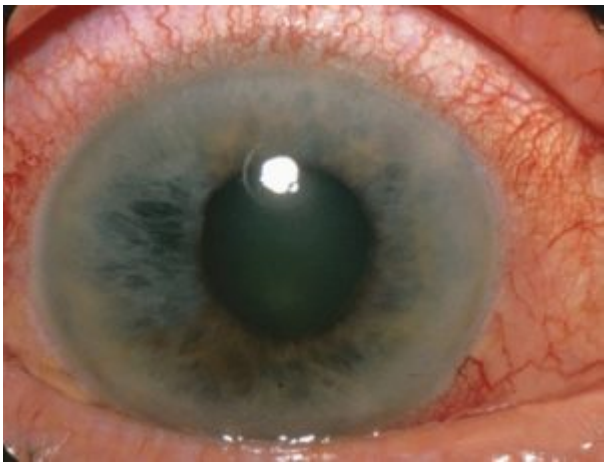


Image: "Photograph showing acute angle-closure glaucoma which is a sudden elevation in intraocular pressure that occurs when the iris blocks the eye's drainage channel—the trabecular meshwork." by Jonathan Trobe, M.D. – The Eyes Have It. License: CC-BY 3.0

Beta-blockers reduce **intraocular pressure**. Thus, they are used to treat glaucoma. They also reduce the production of aqueous humor in the eyes (timolol).

Metabolic effects

Beta-blockers increase the levels of insulin in the body, so if given to a diabetic patient who is on insulin therapy, drastic hypotension may result. Thus, beta blockers are **contraindicated in diabetes**.

Beta-blockers also block **glycogenolysis** and **gluconeogenesis.**

Clinical uses of beta-adrenergic blocking agents

- Hypertension (carvedilol, labetalol, propranolol)
- Angina pectoris (propranolol)
- Myocardial infarction (propranolol and esmolol)
- Glaucoma (timolol, betaxolol, carteolol – applied topically)
- Migraine (propranolol)
- Performance anxiety (propranolol)
- Hyperthyroidism (propranolol)

Adverse effects and toxicity of beta blockers

- **Bradycardia**
- **AV blockage**
- Severe asthma attacks (propranolol)
- **Hypoglycemia**
- **Arrhythmias** (upon abrupt stoppage of therapy with beta blockers)

- Sexual dysfunction (propranolol)
- Fatigue
- Vivid dreams (propranolol)

The Renin-Angiotensin-Aldosterone System

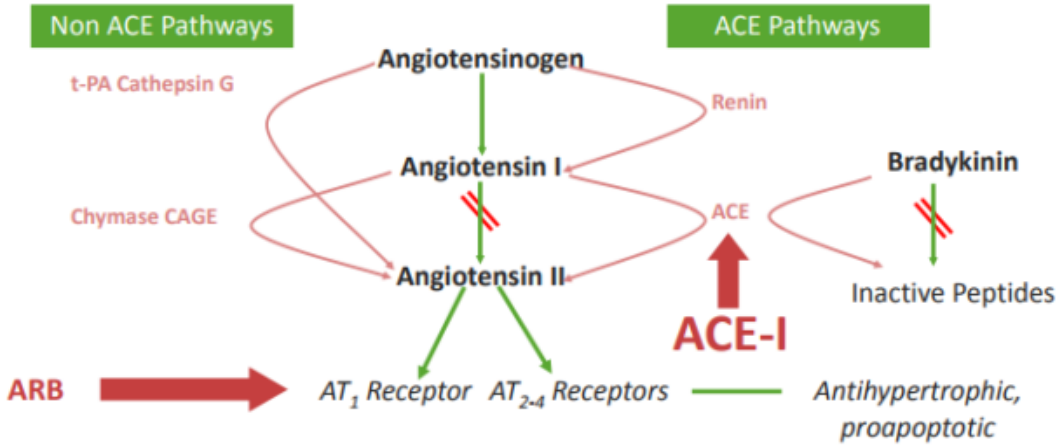
Blockers of the renin-angiotensin-aldosterone system

Beta-blockers control and regulate blood pressure. The kidney and the central nervous system are the critical components of this action. Peripheral baroreceptors and the autonomic nervous system also play important roles.

Medical therapy for MI patients: ACE inhibitors (ACEI) and angiotensin receptor blockers (ARBs)

ACE inhibitors and ARBs decrease blood pressure and decrease the work of the heart by dilating arteries. Side effects include cough, dizziness, and low blood pressure. Pregnancy is contraindicated.

The kidney is crucial to blood pressure regulation via the juxtaglomerular apparatus and renin release. Renin initiates a biochemical sequence that eventually converts angiotensinogen, which is produced in the liver, into angiotensin, a strong vasoconstrictor. Angiotensin stimulates the release of aldosterone from the adrenal gland, which causes the kidney to retain salt (NaCl) and water. Angiotensin stimulates the release of antidiuretic hormone from the pituitary gland, which causes the kidney to retain water.

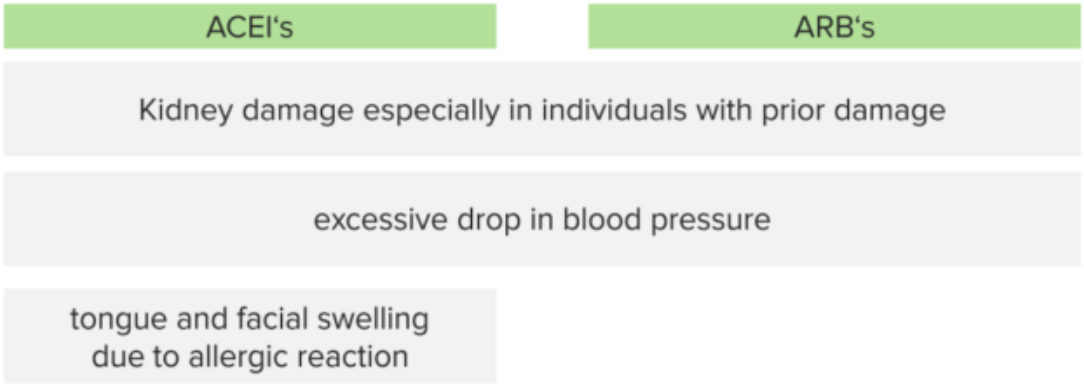


CE inhibitors may lower blood pressure too much and cause allergic reactions. This system is part of the body´s defense against dehydration and/or blood loss. Blood volume should be restored to normal as quickly as possible.

Commonly used ACEI and AII blockers	Initial daily dose(s)	Target dose
**Captopril	6.25 mg tid	50 mg tid
**Enalapril	2.5 mg bid	10—20 mg bid
Fosinopril	5—10 mg daily	40 mg daily
**Lisinopril	2.5—5 mg daily	20—40 mg daily
Perindopril	2 mg daily	8—16 mg daily
Quinapril	5 mg bid	20 mg bid

**Ramipril	1.25—2.5 mg daily	10 mg daily
Trandolapril	1 mg daily	4 mg daily
**Candesartan	4—8 mg daily	32 mg daily
**Losartan	25—50 mg daily	50—100 mg daily
**Valsartan	20—40 mg bid	160 mg bid

AE´s with ACEI and ARB — first-line Rx



Summary

1. Alpha blockers work on the blood muscles to open up the blood vessels, while the beta blockers work on the heart to ease the flow of blood.
2. Alpha blockers work on norepinephrine or noradrenaline, while beta blockers work on epinephrine or adrenaline.
3. Alpha blockers affect only blood pressure levels, while beta blockers affect both the heart and blood pressure.
4. Beta blockers can cause weight gain, while alpha blockers do not.

Review Questions on Alpha and Beta Blockers

The correct answers can be found below the references.

1. Which of the following alpha blockers was once used for the treatment of erectile dysfunction?

A. Prazosin
B. Doxazosin
C. Yohimbine
D. Propranolol
E. Nadolol

2. Which of the following drug causes orthostatic hypotension as a side effect?

A. Prazosin
B. Propranolol
C. Nadolol
D. Atenolol
E. Metoprolol

3. Which of the following beta-blocker is not a cardioselective in its action?

A. Propranolol

B. Atenolol
C. Bisoprolol
D. Esmolol
E. Acebutolol

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Correct answers: 1C, 2A, 3A

Notes