β-Adrenergic Receptor Antagonists (β-Blockers)

Tuesday, October 28, 2025 10:09 AM

🔍 Overview

β-Adrenergic receptor antagonists (commonly called β-blockers) are drugs that competitively block β-adrenergic receptors, thereby inhibiting the actions of catecholamines (epinephrine and norepinephrine).

They are used in multiple cardiovascular, endocrine, and neurological conditions.

⚙️ Mechanism of Action

🧩 Receptor Subtypes

- β_1 receptors: Heart, juxtaglomerular cells
- β_2 receptors: Bronchi, vascular smooth muscle, uterus, liver, skeletal muscle
- β_3 receptors: Adipose tissue (lipolysis and

thermogenesis)

🔬 Pharmacological Antagonism

All β-blockers act as reversible, competitive antagonists of β-receptors.

🧭 Flowchart: Mechanism of Action

Catecholamines (Epinephrine / Norepinephrine) → Bind β-receptors → ↑ cAMP → ↑ Heart rate, contractility, renin release, bronchodilation, lipolysis

β-Blocker administration → Competitive blockade of β-receptors → ↓ cAMP formation → ↓ Heart rate, ↓ contractility, ↓ renin release, bronchoconstriction

♡ Blockade Sites

1. Postsynaptic blockade (β_1):

- ↓ Heart rate (negative chronotropy)
- ↓ Contractility (negative inotropy)
- ↓ AV conduction (negative dromotropy)

2. Presynaptic blockade:

- ↓ NE release (negative feedback regulation)

3. Blockade of β_2 and β_3 receptors:

- May cause bronchoconstriction and ↓ glycogenolysis
- β_3 blockade inhibits lipolysis

⚖️ Receptor Affinity & Selectivity

- β_1-selective (cardioselective): Prefer β_1 over β_2 receptors — safer in asthma or diabetes (e.g., Metoprolol, Betaxolol).
- Non-selective: Block both β_1 and β_2 receptors (e.g., Propranolol, Timolol).

🔁 Inverse Agonism

Some β-blockers act as inverse agonists, decreasing basal receptor activity even in the absence of agonists.

🧪 *Example:* Metoprolol, Betaxolol.

⚡ Additional Mechanisms

◈ Intrinsic Sympathomimetic Activity (ISA)

- These drugs act as partial agonists at β-receptors.
- Produce mild activation when sympathetic tone is low, but block strong stimulation.
    - Advantage: Useful in patients with low cardiac reserve.
    - Disadvantage: Counterproductive in angina or post-MI patients.
    - 🧪 *Examples:* Pindolol, Acebutolol, Carteolol.

◈ Membrane Stabilizing Activity (MSA)

- Local anesthetic-like effect by blocking Na^+ channels.
- At high doses → Cardiodepression 💔
- *Clinical note:* Betaxolol (in eye drops) helps preserve protective corneal sensation.

◈ Other Additional Effects

Effect	Mechanism	Example Drugs
α-Blockade	Vasodilation	Carvedilol, Labetalol
↑ NO Production	Endothelial activation	Nebivolol, Celiprolol
↓ Ca^{2+} entry	Calcium channel inhibition	Carvedilol
β_2 activation	Bronchodilation	Carteolol, Celiprolol
K^+ channel opening	Vasodilation	Tilisolol
Antioxidant effect	Free radical scavenging	Carvedilol
↑ Insulin sensitivity	Metabolic modulation	Celiprolol, Carteolol, Carvedilol

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✿ Classification of β-Blockers

1 Based on Receptor Selectivity & Mechanism

A. Non-selective β-blockers (β_1 + β_2)

Subtype	Examples
Pure antagonists	Nadolol, Timolol, Sotalol

With MSA	Propranolol
With ISA	Carteolol, Penbutolol, Pindolol (±MSA)
With Both MSA & ISA	Oxprenolol

B. Selective β_1 (Cardioselective)

Subtype	Examples
Pure antagonists	Atenolol, Bisoprolol, Esmolol, Nebivolol
With MSA	Metoprolol, Betaxolol
With ISA	Celiprolol
With Both MSA & ISA	Acebutolol

C. Selective β_2 Blocker

- Butoxamine (mainly experimental)

D. β-Blockers with Additional Actions

Additional Action	Example Drugs
α-blockade	Carvedilol, Labetalol

Nitric oxide release	Nebivolol, Celiprolol, Carteolol
Ca^{2+} entry blockade	Carvedilol
β_2 agonism	Carteolol, Celiprolol
Antioxidant property	Carvedilol
K^+ channel opening	Tilisolol
↑ Insulin sensitivity	Celiprolol, Carteolol, Carvedilol

2 Based on Pharmacokinetic Pattern / Solubility

Solubility	Drugs	Characteristics
Highly lipid soluble	Propranolol, Penbutolol	Cross BBB, more CNS side effects
Moderately lipid soluble	Metoprolol, Carvedilol, Pindolol	Balanced hepatic and renal elimination
Poorly lipid soluble (water-soluble)	Nadolol, Atenolol, Bisoprolol, Acebutolol, Esmolol, Nebivolol, Carteolol, Celiprolol, Sotalol	Longer half-life, less CNS effect

3 Based on Duration of Action

Duration	Drugs	Duration (hrs)
Ultra-short acting	Esmolol	0.2–0.3 hr (10–15 min)
Intermediate acting	Propranolol, Metoprolol, Timolol, Pindolol	3–6 hrs
Long acting	Nadolol, Atenolol, Bisoprolol	6–24 hrs

4 Newer Classification (Generational)

Generation	Type	Description	Examples
1st Gen	Non-selective	β_1 + β_2 blockade	Propranolol, Timolol
2nd Gen	β_1-selective	Cardioselective	Metoprolol, Atenolol
3rd Gen	Additional effects	α-blockade / NO release / Antioxidant	Carvedilol, Nebivolol

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📚 Feedback Mechanism

↓ Cardiac Output → ↓ BP → Reflex ↑ Sympathetic activity

↓

β-Blocker blocks this compensatory sympathetic effect
→ Stabilizes BP and heart rate

✅ Net Effect: Balanced control of cardiac workload and oxygen demand.

🩺 Key Takeaways

💊 β-blockers = Reversible competitive antagonists at β-receptors

🫀 β_1-selective = Safer for asthma/diabetes

🧩 MSA = Na^+ channel blockade (local anesthetic effect)

⚡ ISA = Partial agonism (mild stimulation when tone is low)

🌿 Newer drugs (e.g., Nebivolol, Carvedilol) add vasodilation, antioxidant, and metabolic benefits

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Pharmacokinetics

Routes of Administration (ROA)

β-blockers can be administered through multiple routes depending on drug solubility and clinical purpose:

- Oral – most common (e.g., Propranolol, Atenolol)
- Sustained Release (SR) – for prolonged effect (e.g., Metoprolol SR)
- Parenteral (IV) – for emergency use (e.g., Esmolol in arrhythmias)
- Topical – mainly ophthalmic (e.g., Timolol in glaucoma)

Lipid-Soluble β-Blockers

Property	Description	Example
Absorption	Rapidly absorbed orally, food enhances absorption	Propranolol
First-pass metabolism	Extensive, thus low bioavailability	
Half-life (t½)	Moderate (3–6 hours)	

CNS penetration	Yes → can cross BBB 🧠 → CNS side effects possible

Flowchart: Lipid-Soluble β-Blockers

Oral Intake ➜ Rapid Absorption ➜ Extensive First-Pass Metabolism ➜ ↓ Bioavailability ➜ Cross BBB ➜ CNS Effects (fatigue, sleep disturbances)

💧 Water-Soluble β-Blockers

Property	Description	Example
Absorption	Best absorbed on an empty stomach	Atenolol
First-pass metabolism	Minimal, thus higher bioavailability	
Half-life (t½)	Usually longer	
CNS penetration	❌ Cannot cross BBB → minimal CNS effects	

Summary:

💡 *Lipid-soluble drugs act faster but cause more CNS effects; water-soluble drugs act longer with fewer side effects.*

Metabolism & Excretion

- Lipid-soluble drugs: Hepatic metabolism → Metabolites excreted in urine
- Water-soluble drugs: Excreted largely unchanged in urine
- Dose adjustment required in renal impairment (esp. for Atenolol)

Pharmacological Actions

♡ 1. Cardiovascular System

Effects on Heart (β_1 Blockade):

Parameter	Effect	Mechanism
Contractility (Inotropy)	↓	Blocks β_1 → ↓ cAMP → ↓ Ca^{2+} influx
Heart Rate (Chronotropy)	↓	Suppresses SA node activity
Conduction (Dromotropy)	↓	Prolongs AV conduction time (↑ PR interval)

Refractory period	↑	Stabilizes cardiac rhythm
Cardiac output (CO)	↓	Due to ↓ HR & contractility

Special Note: Sotalol is both a β-blocker and a K^+ channel blocker, giving it antiarrhythmic (Class III) activity.

💧 Effects on Blood Vessels

Receptor Type: β_2 receptors in vascular smooth muscle

- Normal BP: β-blockers have little effect initially
- In Hypertension (HTN):
    - Short-term: ↓ Cardiac output → transient reflex ↑ in peripheral resistance
    - Chronic use: ↓ Peripheral resistance due to ↓ renin and central sympathetic inhibition

Flowchart: Antihypertensive Action of β-Blockers

↓ β_1 stimulation → ↓ HR & contractility → ↓ CO

↓ Renin release (JGA) → ↓ Angiotensin II → ↓ Peripheral resistance

Central inhibition → ↓ Sympathetic tone

✅ Net Effect: Sustained ↓ BP

🧠 Feedback Mechanism

↓ Cardiac output → ↓ BP → Reflex ↑ sympathetic tone

↓

β-blocker blocks β_1-receptors → prevents reflex tachycardia

✅ Stable BP without overactivation of the heart

💡 Additional Cardiovascular Effects

Effect	Mechanism	Example
α_1-blockade	Vasodilation	Carvedilol, Labetalol
NO production	Endothelial vasodilation	Nebivolol
Ca^{2+} entry blockade	↓ Vascular tone	Carvedilol
β_2 receptor activation	Bronchodilation	Celiprolol

K^+ channel opening	Vasodilation	Tilisolol
Central action	↓ Sympathetic outflow	Propranolol

2. Respiratory System

- β_2 receptors mediate bronchodilation
- Non-selective β-blockers block β_2 → bronchoconstriction (dangerous in asthma/COPD).
- Selective β_1-blockers (e.g., Atenolol, Metoprolol) are safer for such patients.

3. Eye

- Mechanism: ↓ Aqueous humor (AH) production by blocking β-receptors in the ciliary body.
- Result: ↓ Intraocular pressure (IOP)
- Used in: Glaucoma (e.g., Timolol).

4. Kidney

- Site: Juxtaglomerular cells

- Mechanism: Block β_1-receptor → ↓ Renin release → ↓ Angiotensin II → ↓ BP

This mechanism is central to the antihypertensive action of β-blockers.

🔍 5. Metabolic and Endocrine Effects

Parameter	Effect	Explanation
Glucose	↓ response to hypoglycemia	Catecholamine-mediated glycogenolysis blocked
Hypoglycemia recovery	Delayed	Blunts tremor and tachycardia (warning signs)
Insulin sensitivity	May ↑ (with 3rd gen drugs)	Via vasodilation and NO production
Lipolysis	↓	Inhibits β_3-mediated fat breakdown
VLDL/HDL ratio	↑ VLDL, ↓ HDL	Seen with non-selective β-blockers

Flowchart: β-Blocker Effect on Glucose Regulation

↓ β_2 stimulation ➔ ↓ Glycogenolysis ➔ ↓ Glucose

release → Delayed recovery from hypoglycemia

💡 *Cardioselective β_1-blockers* (e.g., Atenolol) are safer in diabetic patients.

🧠 6. Central Nervous System (CNS)

- Lipid-soluble β-blockers (e.g., Propranolol) cross BBB → cause
    - Fatigue 😴
    - Depression
    - Vivid dreams / nightmares
    - Anti-hypertensive central effects
- Water-soluble ones (Atenolol) → minimal CNS side effects.

💪 7. Skeletal Muscle

- Effect: ↓ Tremors and ↓ muscle spindle discharge
- Mechanism: Block β_2 receptors → ↓ K^+ uptake during exercise → stabilize excitability

- *Clinical relevance:* Used in essential tremor and performance anxiety.

8. Miscellaneous Effects

- Block inhibition of mast cell degranulation by catecholamines → may slightly increase allergic susceptibility.

Summary Table: Pharmacological Actions

System	Main Effect	Mechanism / Note
Heart	↓ HR, ↓ contractility, ↓ AV conduction	β_1 blockade
Vessels	↓ BP (chronic use)	↓ Renin, ↓ sympathetic tone
Lungs	Bronchoconstriction (non-selective)	β_2 blockade
Eye	↓ IOP	↓ AH production
Kidney	↓ Renin	β_1 blockade
Metabolism	↓ Glycogenolysis, ↓ Lipolysis	β_2 & β_3 blockade
CNS	Sedation, fatigue	Lipid-soluble agents
Muscle	↓ Tremor	β_2 blockade

Therapeutic Uses

I. Cardiovascular Uses

1. Hypertension (HTN)

Mechanism:

- ↓ Cardiac Output (CO) → ↓ Blood Pressure
- ↓ Renin release (β_1 blockade on juxtaglomerular cells) → ↓ Angiotensin II
- Central ↓ in sympathetic outflow
- Long-term: ↓ Peripheral resistance

Flowchart: Mechanism of Antihypertensive Effect

↓ β_1 stimulation → ↓ CO → ↓ BP

↓ Renin release → ↓ Ang II → ↓ Peripheral resistance

↓ Central sympathetic tone → Sustained ↓ BP

Cardioprotective Role:

- Prevents cardiac remodeling and hypertrophy
- ↓ Risk of myocardial infarction and stroke

Combination Therapy:

- Often combined with Diuretics or Vasodilators to enhance BP control.

Advantages:

✅ Good tolerance
✅ Protection from cardiac complications

2. Ischemic Heart Disease (IHD)

Used in: *Chronic stable angina, exertional angina, post-MI prevention*

Mechanism:

↓ Heart rate & contractility → ↓ Myocardial O_2 demand

↑ Diastolic filling time → ↑ O_2 supply

Effects:

❤ ↓ Frequency of anginal attacks
❤ ↑ Exercise tolerance
❤ ↓ Mortality in ischemic patients

3. Myocardial Infarction (MI)

Phases of Use:

A. Primary Prevention:

- In high-risk patients (HTN, IHD) → β-blockers are cardioprotective.

B. Acute Phase:

- I/V β-blocker (e.g., Esmolol) given under strict monitoring

- ↓ O_2 demand → limits size of infarct

- Esmolol preferred for short t½ and quick reversal if needed

C. Secondary Prevention:

- ↓ Recurrent attacks, ↓ arrhythmias, ↓ mortality
- Common drugs: Metoprolol, Propranolol, Timolol

4. Cardiac Arrhythmias (Class II Antiarrhythmics)

Mechanism:

↓ SA node excitability → ↓ AV conduction → Prolonged refractory period

Effective in:

- Sinus arrhythmias
- Supraventricular tachycardia
- Ventricular arrhythmias
- Premature ventricular contractions (PVCs)

Examples:

- Esmolol (short-acting, I/V)
- Sotalol (β-blocker + K^+ channel blocker)

5. Cardiac Failure (Chronic Stable / Compensated CCF)

Pathophysiology:

Chronic sympathetic stimulation → cardiac remodeling → worsens failure

Mechanism of β-Blockers:

↓ HR → ↑ diastolic filling

↓ Remodeling → ↓ morbidity & mortality

Drugs of Choice:

- Metoprolol
- Bisoprolol
- Carvedilol (also α-blocker)

⚠ *Avoid in acute decompensated failure.*

6. Obstructive Cardiomyopathies

Used in:

- Hypertrophic Subaortic Stenosis (↓ LV outflow)
- Tetralogy of Fallot (↓ RV outflow)

Mechanism:

↓ Contractility → ↓ Outflow obstruction → ↓ Symptoms

7. Dissecting Aortic Aneurysm

- Seen in Marfan's syndrome or severe hypertension
- ↓ Shear stress on aortic wall
- Drugs: Propranolol + Nitroprusside

8. Portal Hypertension

Mechanism:

↓ Cardiac output + splanchnic vasoconstriction → ↓ Portal pressure

Clinical Use:

- Prevents variceal bleeding in cirrhosis
- Combined with Isosorbide mononitrate
- Drugs: Propranolol, Nadolol
- Also used with Variceal band ligation

9. Subarachnoid Hemorrhage

- β-blockers ↓ sympathetic surge → ↓ risk of rebleeding

10. Infantile Hemangiomas

- Propranolol causes vasoconstriction and inhibition of angiogenic factors
- Now preferred therapy for these benign vascular

tumors in infants 👶

🌿 II. Non-Cardiovascular Uses

A. Conditions Associated with Sympathetic Overactivity

Condition	Mechanism / Benefit	Common Drugs
Hyperthyroidism (Thyrotoxicosis)	↓ Tremor, anxiety, palpitations; also ↓ peripheral conversion of $T_4 \rightarrow T_3$	Propranolol
Anxiety States	↓ Somatic symptoms (tremor, palpitations)	Propranolol
Withdrawal Syndrome (Alcohol)	Symptomatic relief from sympathetic overactivity	Propranolol
Acute Porphyria	Inhibits enzyme induction that worsens attack	Propranolol
Pheochromocytoma	Used after α-blocker to control tachycardia	Propranolol, Labetalol

B. Miscellaneous Uses

Condition	Mechanism	Drugs

Glaucoma	↓ Aqueous humor production	Timolol, Betaxolol, Carteolol
Migraine (Prophylaxis)	↓ Frequency & intensity (↓ vascular pulsations)	Propranolol
Familial (Essential) Tremor	↓ Tremor amplitude	Propranolol
Torticollis	↓ Spasm of sternocleidomastoid	Propranolol

⚠ Adverse Effects

1. Cardiovascular Effects

- Bradycardia / Heart block (due to ↓ AV conduction)
- Worsening of Heart Failure (if given in acute phase)
- Cold extremities, worsening of Peripheral Vascular Disease

2. Pulmonary Effects

- Bronchoconstriction (β_2 blockade → asthma/COPD worsening)

- Safer: Selective β_1-blockers like Atenolol, Metoprolol

3. Central Nervous System Effects

- Fatigue 😴
- Lethargy
- Dizziness
- Nightmares / Insomnia
- Depression or hallucinations (esp. lipid-soluble drugs)

4. Metabolic & Endocrine Effects

- Hypoglycemia (↓ glycogenolysis and gluconeogenesis)
- Masking of hypoglycemia symptoms (important for diabetics)
- Dyslipidemia (↑ VLDL, ↓ HDL)
- ↓ Insulin sensitivity (older agents)
- Male sexual dysfunction

5. Hypersensitivity Reactions

- Mild rashes or drug fever (rare)

6. Drug Withdrawal

Mechanism:

Chronic blockade → Upregulation of β-receptors → Sudden withdrawal → Rebound tachycardia, angina, or MI

Prevention:

→ Gradual tapering of dose

7. Overdose

Manifestations: Severe bradycardia, hypotension, heart block

Management:

Atropine → Sympathomimetic agents (Isoprenaline, Dopamine, Dobutamine) → Glucagon (↑ cAMP → positive inotropic & chronotropic effect)

Drug Interactions

Interacting Agent	Interaction	Result
Verapamil (CCB)	Additive depressant effect on AV node	Heart block risk
Enzyme inducers / inhibitors	Alter β-blocker metabolism	Toxicity or inefficacy
Other antihypertensives	Additive hypotension	Monitor BP
Sympathomimetic agents (nasal decongestants)	Oppose β-blocker effect	BP fluctuation
NSAIDs (Indomethacin)	↓ Prostaglandin synthesis → ↓ antihypertensive effect	Reduced efficacy

Choice of β-Adrenergic Receptor Antagonist

Clinical Condition	Preferred Drug	Reason
Hypertension	Atenolol, Bisoprolol	Long-acting, cardioselective

Angina / MI	Metoprolol, Propranolol	↓ O_2 demand, cardio-protective
Arrhythmias	Esmolol, Sotalol	Class II / III antiarrhythmic
Heart Failure	Bisoprolol, Metoprolol, Carvedilol	↓ Remodeling & mortality
Asthma / COPD (caution)	Selective β_1-blockers (Atenolol)	Less bronchospasm
Portal HTN	Propranolol, Nadolol	↓ Portal pressure
Glaucoma	Timolol	↓ AH production
Migraine	Propranolol	↓ Frequency
Anxiety	Propranolol	↓ Tremor, palpitations

Mnemonic Sheet

β-Adrenergic Receptor Antagonists

Classification

Mnemonic: "BLEND"

B – Based on receptor selectivity & mechanism of action

L – Lipid solubility / pharmacokinetic pattern

E – Extended (duration) of action

N – Newer classification

D – Drugs with additional actions

♡ Therapeutic Uses

Mnemonic: "HIM CARD"

H – Hypertension

I – Ischemic heart disease (angina)

M – Myocardial infarction (acute & secondary prevention)

C – Cardiac arrhythmias

A – Cardiac failure / cardiomyopathies / aortic aneurysm

R – Reduction of portal pressure (portal hypertension)

D – Disorders with sympathetic overactivity (e.g. hyperthyroidism, anxiety, withdrawal, pheochromocytoma)

🧍 Non-Cardiovascular Uses

Mnemonic: "GAMT" 🎯

G – Glaucoma

A – Anxiety / hyperthyroidism / acute porphyria

M – Migraine prophylaxis

T – Tremors / Torticollis

⚠ Adverse Effects

Mnemonic: "BREATHE" 😮💨

(β-blockers can make you lose your "BREATHE")

B – Bradycardia / heart block

R – Reduced cardiac output → worsening heart failure

E – Extremities cold (PVD aggravation)

A – Asthma & airway obstruction

T – Tiredness / CNS effects (fatigue, depression)

H – Hypoglycemia risk

E – Erectile dysfunction / hypersensitivity