

DRUGS THAT ACT IN THE ANS

Indirect-Acting Adrenergic Agonists and Adrenergic Antagonists

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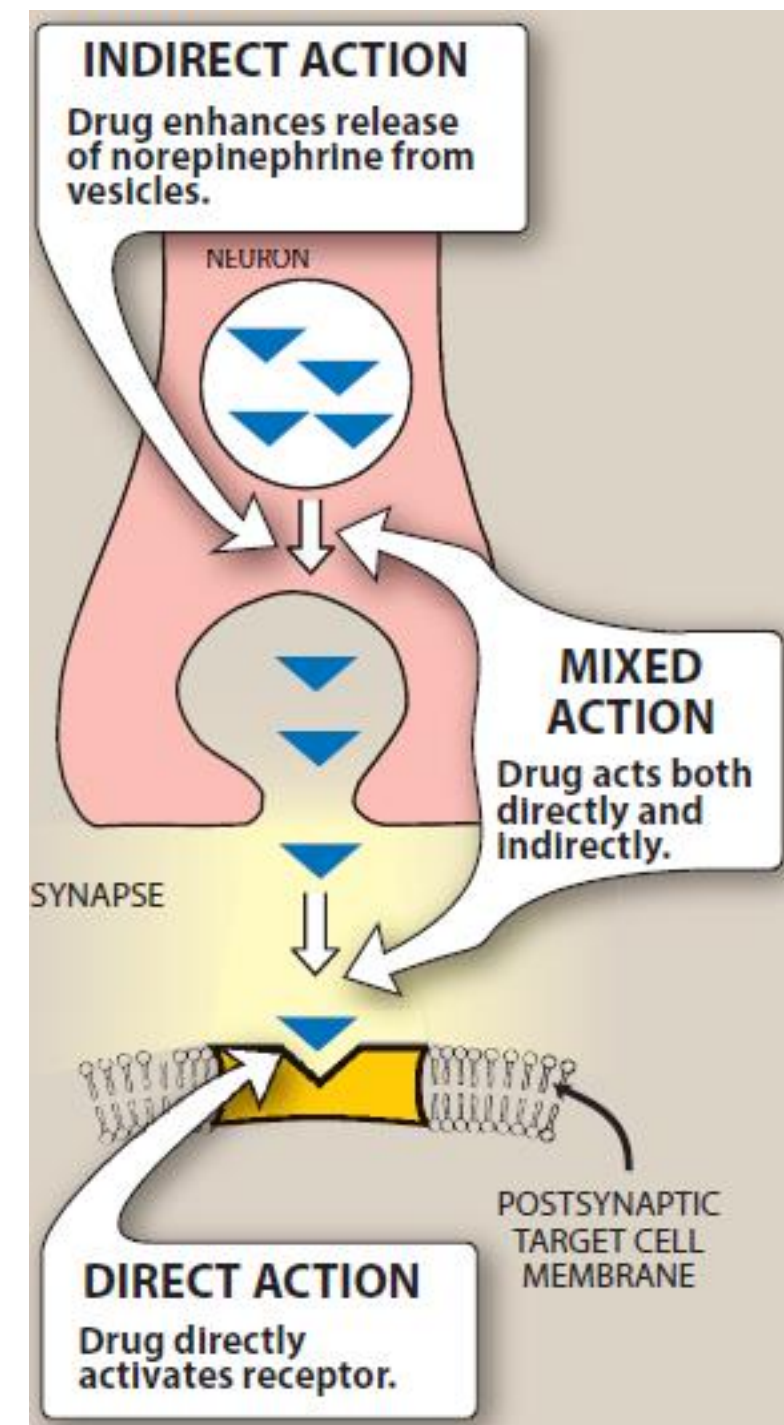
PhD Clinical Pharmacology



INDIRECT-ACTING ADRENERGIC AGONISTS

Indirect-acting adrenergic agonists **cause the release, inhibit the reuptake, or inhibit the degradation** of epinephrine or norepinephrine.

They potentiate the effects of epinephrine or norepinephrine produced endogenously, but do not directly affect postsynaptic receptors.



INDIRECT-ACTING ADRENERGIC AGONISTS/ A. Amphetamine

The marked **central stimulatory** action of amphetamine is often mistaken by **drug abusers** as its only action.

However, the drug can also **increase blood pressure** significantly by **α 1** agonist action on the vasculature, as well as **β 1**-stimulatory effects on the heart.

Its actions are mediated primarily through an increase in **release of catecholamines** such as dopamine and norepinephrine from nerve terminals.

INDIRECT-ACTING ADRENERGIC AGONISTS/ B. Tyramine

Tyramine is **not a clinically useful drug**, but it is important because it is found in fermented **foods**, such as aged cheese and Chianti wine.

It is a normal by-product of tyrosine metabolism.

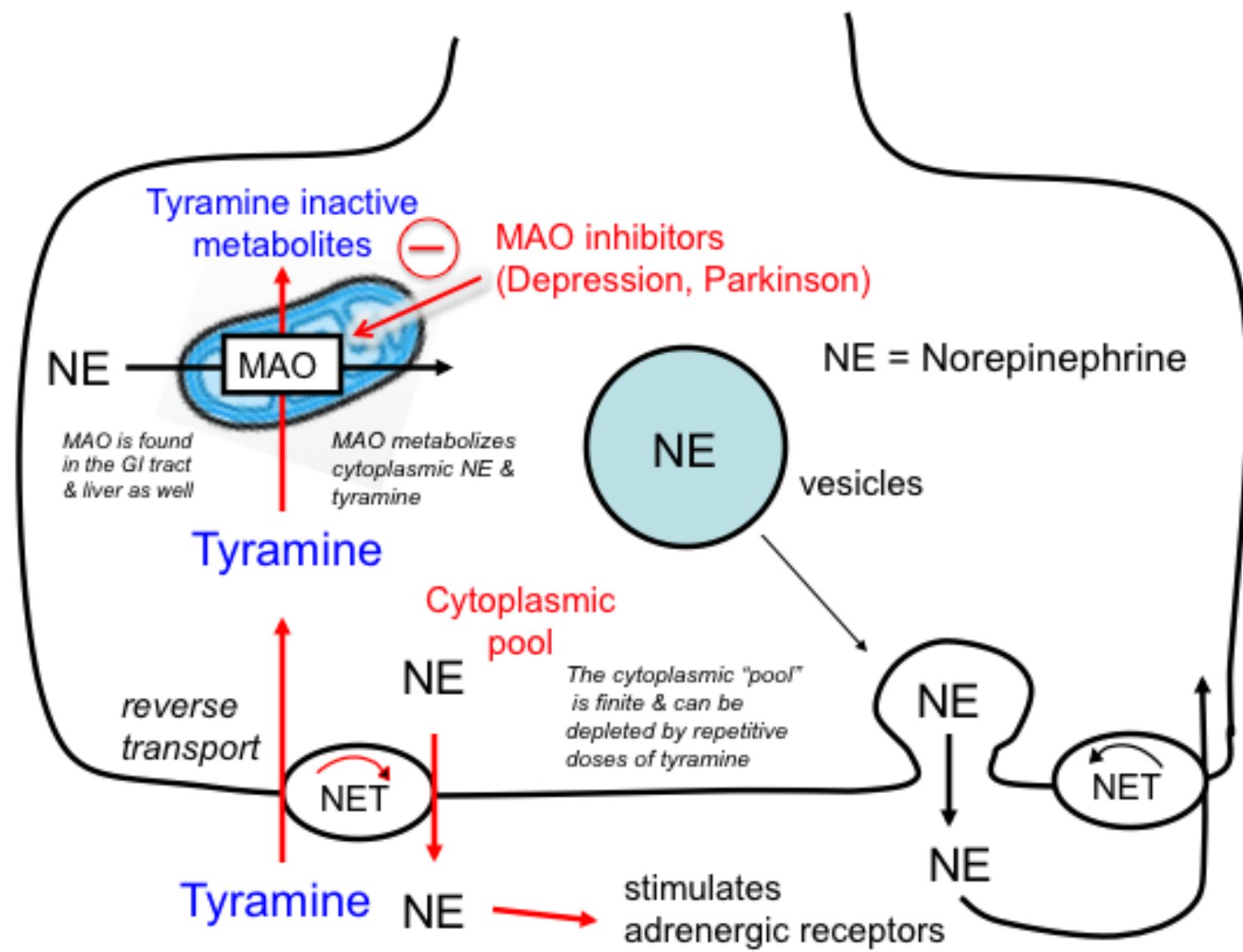
Normally, it is **oxidized by MAO** in the gastrointestinal tract, but, if the patient is taking **MAOIs**, it can precipitate serious **vasopressor episodes**.

Like amphetamines, tyramine can enter the nerve terminal and displace stored norepinephrine.

The released catecholamine then acts on adrenoceptors.

INDIRECT-ACTING ADRENERGIC AGONISTS/ B. Tyramine

Tyramine Mechanism



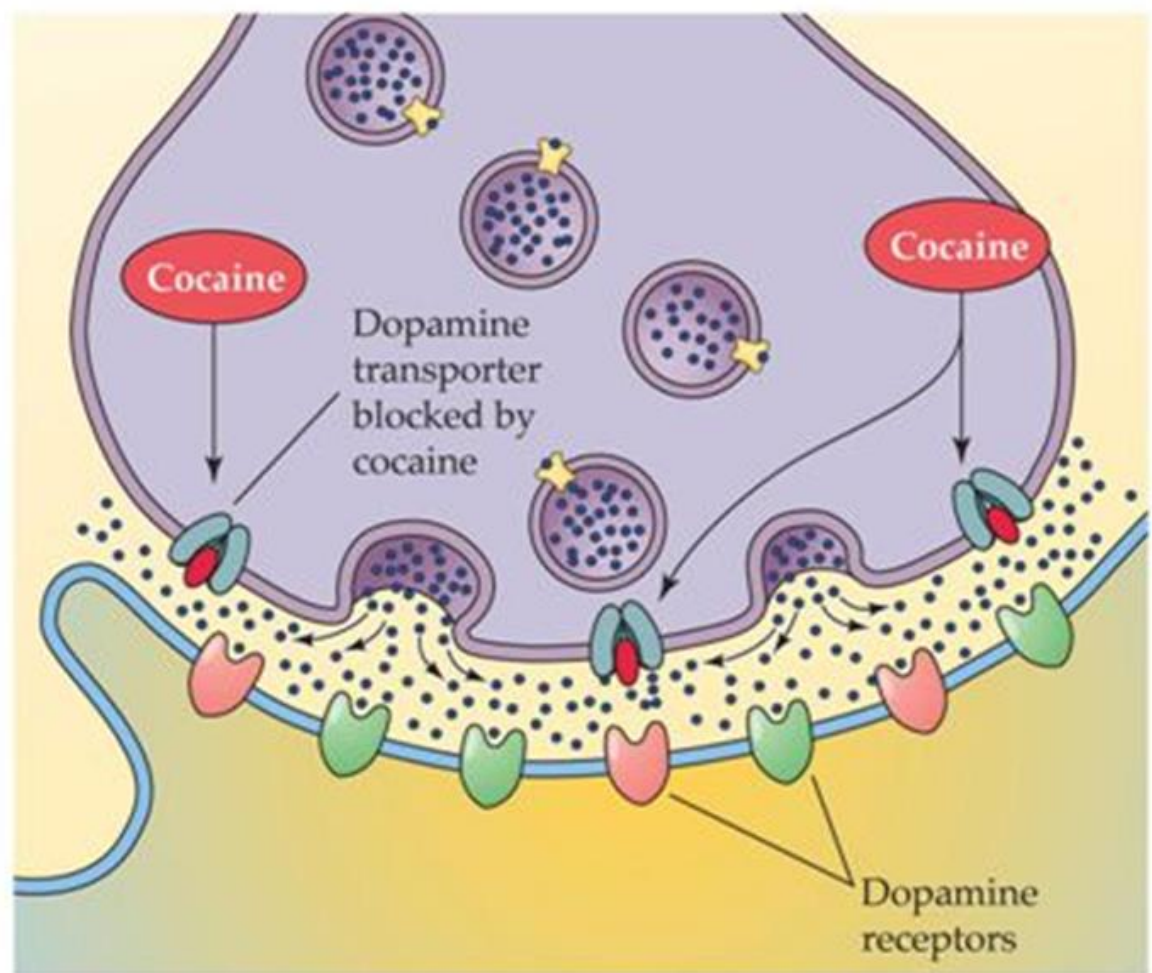
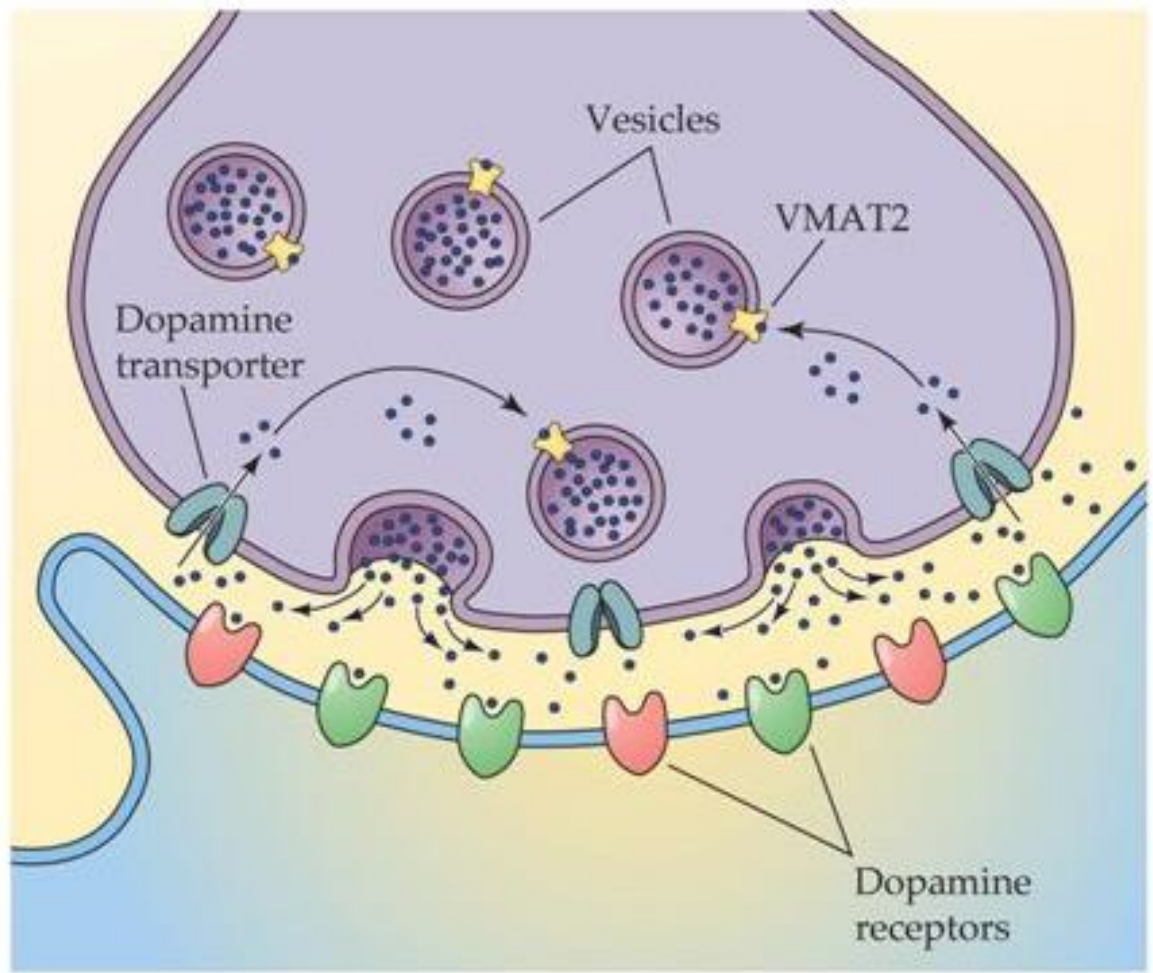
INDIRECT-ACTING ADRENERGIC AGONISTS/ C. Cocaine

Cocaine is unique among **local anesthetics** in having the ability to **block the sodium-chloride (Na⁺/Cl⁻)-dependent norepinephrine transporter** required for cellular **uptake** of norepinephrine into the adrenergic neuron.

Consequently, norepinephrine accumulates in the synaptic space, resulting in enhanced sympathetic activity and potentiation of the actions of epinephrine and norepinephrine.

Like amphetamines, it can **increase blood pressure** by **α₁** agonist actions and β stimulatory effects.

INDIRECT-ACTING ADRENERGIC AGONISTS/ C. Cocaine



MIXED-ACTION ADRENERGIC AGONISTS

Ephedrine and pseudoephedrine are mixed-action adrenergic agents.

They not only **release** stored norepinephrine from nerve endings but also **directly stimulate** both α and β receptors.

Thus, a wide variety of adrenergic actions ensue that are similar to those of epinephrine, although less potent.

Ephedrine and pseudoephedrine are **not catechols** and are **poor substrates for COMT and MAO**.

Therefore, these drugs have a long duration of action. Ephedrine and pseudoephedrine have excellent absorption orally and penetrate into the CNS, but pseudoephedrine has fewer CNS effects.

MIXED-ACTION ADRENERGIC AGONISTS

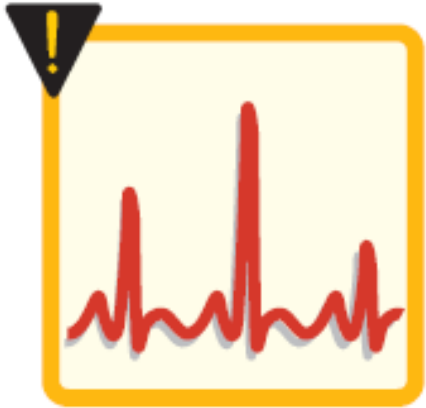
Ephedrine is eliminated largely **unchanged in urine**, and **pseudoephedrine** undergoes incomplete **hepatic** metabolism before elimination in urine.

Ephedrine raises systolic and diastolic blood pressures by vasoconstriction and cardiac stimulation and can be used to treat hypotension.

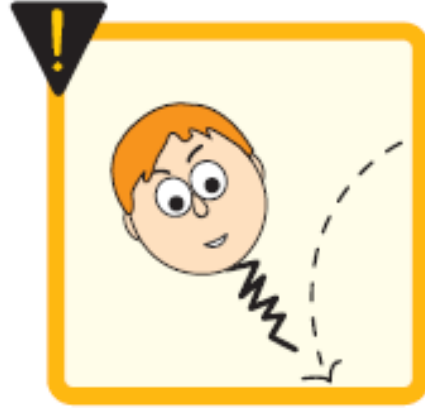
Ephedrine produces **bronchodilation**, but it is less potent and slower acting than epinephrine or isoproterenol.

It was previously used to prevent asthma attacks but has been replaced by more effective medications.

Ephedrine produces a mild **stimulation of the CNS**. This increases alertness, decreases fatigue, and prevents sleep.



Arrhythmias



Hyperactivity



Nausea



Headache



Insomnia



Tremors

Some adverse effects observed with adrenergic agonists

MIXED-ACTION ADRENERGIC AGONISTS

It also improves **athletic performance**.

Pseudoephedrine is primarily used **orally** to treat nasal and sinus **congestion**.

Pseudoephedrine has been illegally used to produce methamphetamine.

TISSUE	RECEPTOR TYPE	ACTION	OPPOSING ACTIONS
Heart <ul style="list-style-type: none"> • Sinus and AV • Conduction pathway • Myofibrils 	β_1 β_1 β_1	\uparrow Automaticity \uparrow Conduction velocity, automaticity \uparrow Contractility, automaticity	Cholinergic receptors Cholinergic receptors
Vascular smooth muscle	β_2	Vasodilation	α -Adrenergic receptors
Bronchial smooth muscle	β_2	Bronchodilation	Cholinergic receptors
Kidneys	β_1	\uparrow Renin release	α_1 -Adrenergic receptors
Liver	β_2, α_1	\uparrow Glycogenolysis and gluconeogenesis	—
Adipose tissue	β_3	\uparrow Lipolysis	α_2 -Adrenergic receptors
Skeletal muscle	β_2	\uparrow Increased contractility Potassium uptake; glycogenolysis Dilates arteries to skeletal muscle Tremor	—
Eye-ciliary muscle	β_2	Relaxation	Cholinergic receptors
GI tract	β_2	\downarrow Motility	Cholinergic receptors
Gall bladder	β_2	Relaxation	Cholinergic receptors
Urinary bladder detrusor muscle	β_2	Relaxation	Cholinergic receptors
Uterus	β_2	Relaxation	Oxytocin

Summary of β -adrenergic receptors. AV = atrioventricular; GI = gastrointestinal.

	DRUG	RECEPTOR SPECIFICITY	THERAPEUTIC USES
CATECHOLAMINES <ul style="list-style-type: none"> ● Rapid onset of action ● Brief duration of action ● Not administered orally ● Do not penetrate the blood-brain barrier 	<i>Epinephrine</i>	α_1, α_2 β_1, β_2	Acute asthma Anaphylactic shock In local anesthetics to increase duration of action
	<i>Norepinephrine</i>	α_1, α_2 β_1	Treatment of shock
	<i>Isoproterenol</i>	β_1, β_2	As a cardiac stimulant
	<i>Dopamine</i>	Dopaminergic α_1, β_1	Treatment of shock Treatment of congestive heart failure Raise blood pressure
	<i>Dobutamine</i>	β_1	Treatment of acute heart failure
NONCATECHOLAMINES Compared to catecholamines: <ul style="list-style-type: none"> ● Longer duration of action ● All can be administered orally or via inhalation 	<i>Oxymetazoline</i>	α_1	As a nasal decongestant
	<i>Phenylephrine</i>	α_1	As a nasal decongestant Raise blood pressure Treatment of paroxysmal supraventricular tachycardia
	<i>Clonidine</i>	α_2	Treatment of hypertension
	<i>Albuterol</i> <i>Terbutaline</i>	β_2	Treatment of bronchospasm (short acting)
	<i>Salmeterol</i> <i>Formoterol</i>	β_2	Treatment of bronchospasm (long acting)
	<i>Amphetamine</i>	$\alpha, \beta, \text{CNS}$	As a CNS stimulant in treatment of children with attention deficit syndrome, narcolepsy, and for appetite control
	<i>Ephedrine</i> <i>Pseudoephedrine</i>	$\alpha, \beta, \text{CNS}$	As a nasal decongestant Raise blood pressure

Summary of the therapeutic uses of adrenergic agonists.
CNS = central nervous system.

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.

Numerous adrenergic antagonists have important roles in clinical medicine, primarily to treat diseases associated with the cardiovascular system.

α BLOCKERS

Alfuzosin UROXATRAL

Doxazosin CARDURA

Phenoxybenzamine DIBENZYLINE

Phentolamine REGITINE

Prazosin MINIPRESS

Tamsulosin FLOMAX

Terazosin HYTRIN

Yohimbine YOCON

β BLOCKERS

Acebutolol SECTRAL

Atenolol TENORMIN

Betaxolol BETOPTIC-S, KERLONE

Bisoprolol ZEBETA

Carteolol CARTROL

Carvedilol COREG, COREG CR

Esmolol BREVIBLOC

Labetalol TRANDATE

Metoprolol LOPRESSOR, TOPROL-XL

Nadolol CORGARD

Nebivolol BYSTOLIC

Penbutolol LEVATOL

Pindolol VISKEN

Propranolol INDERAL LA, INNOPRAN XL

Timolol BETIMOL, ISTALOL, TIMOPTIC

DRUGS AFFECTING NEURO-TRANSMITTER UPTAKE OR RELEASE

Reserpine SERPASIL

Adrenergic Antagonists/ α -ADRENERGIC BLOCKING AGENTS

Drugs that block α adrenoceptors profoundly affect blood pressure.

Blockade of α -adrenergic 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.

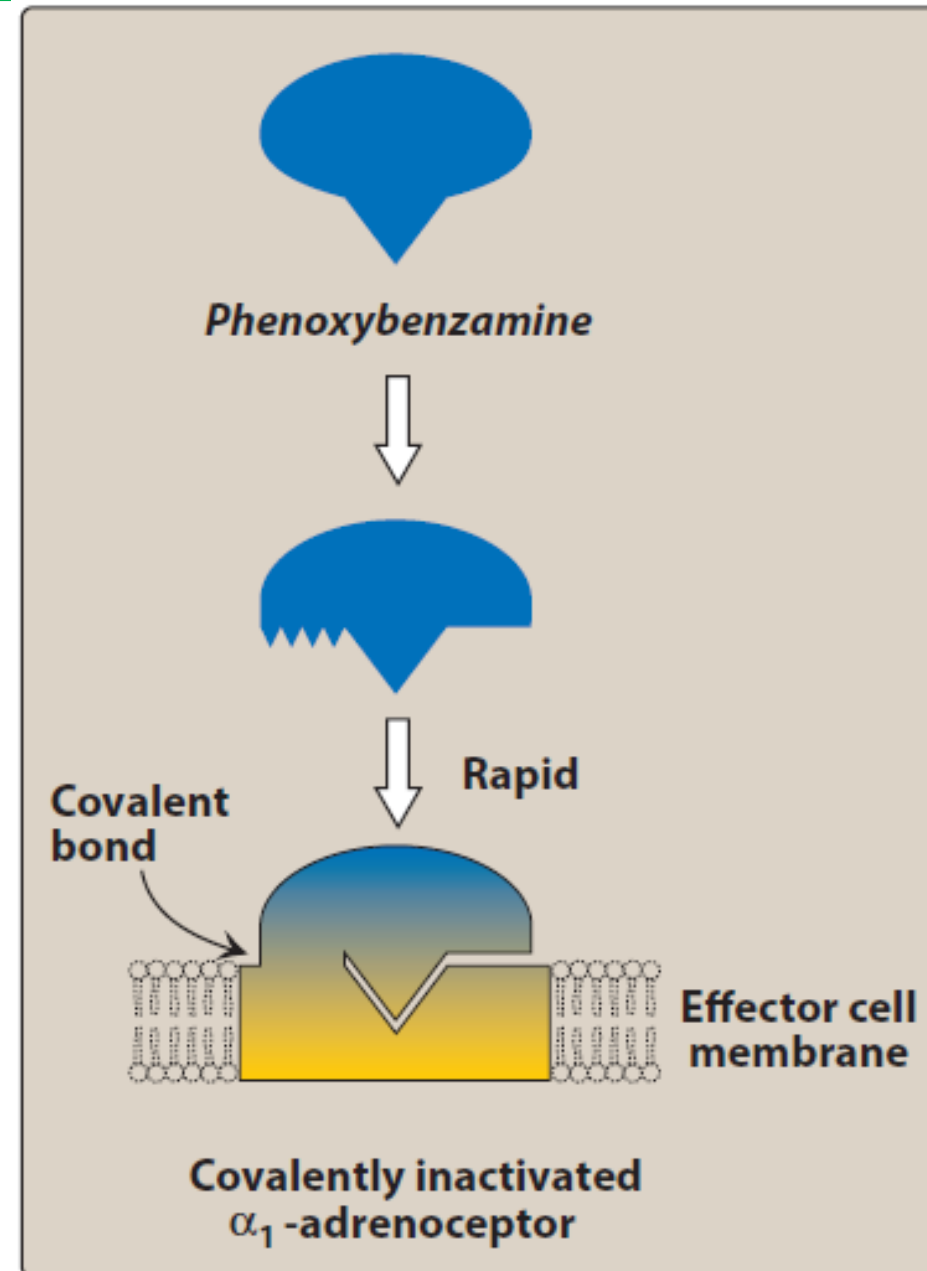
The α -adrenergic blocking agents, **phenoxybenzamine and phentolamine**, have limited clinical applications.

Adrenergic Antagonists/ α -ADRENERGIC BLOCKING AGENTS/ A. Phenoxybenzamine

Phenoxybenzamine is **nonselective**, linking covalently to both **α_1 and α_2 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.



Adrenergic Antagonists/ α -ADRENERGIC BLOCKING AGENTS/ A. Phenoxybenzamine

1. Actions:

a. Cardiovascular effects: By blocking α 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 **α_2** receptors in the heart can contribute to an **increased cardiac output**.

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

Adrenergic Antagonists/ α -ADRENERGIC BLOCKING AGENTS/ A. Phenoxybenzamine

1. 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 β_2 receptors is not blocked.

Therefore, in the presence of phenoxybenzamine, the systemic blood pressure decreases in response to epinephrine.

Adrenergic Antagonists/ α -ADRENERGIC BLOCKING AGENTS/ A. Phenoxybenzamine

2. Therapeutic uses:

Phenoxybenzamine is used in the treatment of **pheochromocytoma**, a catecholamine-secreting tumor of cells derived from the adrenal medulla.

It may be used prior to surgical removal of the tumor to prevent a hypertensive crisis, and it is also useful in the chronic management of inoperable tumors.

Phenoxybenzamine is sometimes effective in treating **Raynaud disease and frostbite**.

Adrenergic Antagonists/ α -ADRENERGIC BLOCKING AGENTS/ A. Phenoxybenzamine

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.

Adrenergic Antagonists/ α -ADRENERGIC BLOCKING AGENTS/ B. Phentolamine

In contrast to phenoxybenzamine, phentolamine produces a **competitive block** of α_1 and α_2 receptors that **lasts for approximately 4 hours** after a single injection.

Like phenoxybenzamine, it produces postural hypotension and causes epinephrine reversal.

Phentolamine-induced reflex cardiac stimulation and **tachycardia** are mediated by the baroreceptor reflex and by blocking the α_2 receptors of the cardiac sympathetic nerves.

The drug can also trigger arrhythmias and anginal pain, and phentolamine is **contraindicated in patients with coronary artery disease**.

Phentolamine is used for the short-term management of **pheochromocytoma**.

Adrenergic Antagonists/ α -ADRENERGIC BLOCKING AGENTS/ B. Phentolamine

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 and from ingesting tyramine-containing foods in patients taking monoamine oxidase inhibitors.

Adrenergic Antagonists/ α -ADRENERGIC BLOCKING AGENTS/ C. Prazosin, terazosin, doxazosin, tamsulosin, and alfuzosin

Selective competitive blockers of the α_1 receptor.

In contrast to phenoxybenzamine and phentolamine, they are useful in the treatment of **hypertension**.

Tamsulosin and alfuzosin are examples of other selective α_1 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.

Adrenergic Antagonists/ 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.**

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 decreases tone in the smooth muscle of the bladder neck and prostate and improves urine flow.

Adrenergic Antagonists/ α -ADRENERGIC BLOCKING AGENTS/ C. Prazosin, terazosin, doxazosin, tamsulosin, and alfuzosin

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.

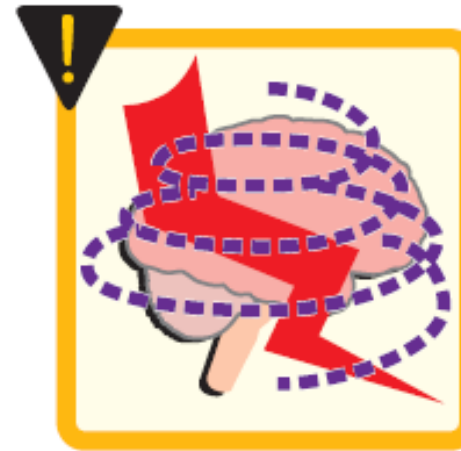
Because of inferior cardiovascular outcomes as compared to other antihypertensives, α_1 antagonists are not used as monotherapy for the treatment of hypertension.

Adrenergic Antagonists/ α -ADRENERGIC BLOCKING AGENTS/ C. Prazosin, terazosin, doxazosin, tamsulosin, and alfuzosin

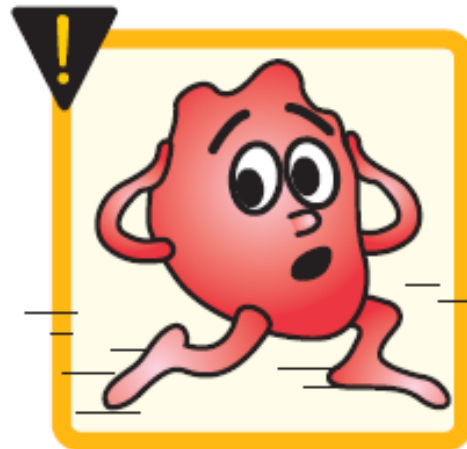
3. Adverse effects:



Orthostatic hypotension



Dizziness and headache



Tachycardia



Sexual dysfunction

Adrenergic Antagonists/ α -ADRENERGIC BLOCKING AGENTS/ C. Prazosin, terazosin, doxazosin, tamsulosin, and alfuzosin

3. Adverse effects:

α 1-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).

An additive antihypertensive effect occurs when α 1 antagonists are given with vasodilators such as nitrates or PDE-5 inhibitors (for example, sildenafil), thereby necessitating cautious dose titration and use at the lowest possible doses.

By blocking α receptors in the ejaculatory ducts and impairing smooth muscle contraction, α 1 antagonists may cause **inhibition of ejaculation** and retrograde ejaculation.

Adrenergic Antagonists/ α -ADRENERGIC BLOCKING AGENTS/ D. Yohimbine

Yohimbine is a selective **competitive α_2 -blocker**.

It is found as a component of the bark of the yohimbe tree 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.

Yohimbine works at the level of the CNS to increase sympathetic outflow to the periphery.

It is contraindicated in cardiovascular disease, psychiatric conditions, and renal dysfunction because it may worsen these conditions.