INDIRECT-ACTING ADRENERGIC AGONISTS

I. **Amphetamine**
II. **Tyramine**
III. **Cocaine**

Amphetamine

Methylphenidate, Dextroamphetamine

CNS stimualtion	• Enhance Dopamine and NE release
Peripheral Stimulation	• Enhance NE release, increase BP
Therapeutic uses	• ADHD, " student abuse" • Nacrolepsy • Appetite control

Anorexia, Insomnia, nervousness, fever,

CVS (palpitation, hypertension), C/I in glaucoma, HTN, CVD, and MAOI users

Tyramine

- Clinically inuseful CNS stimulant, *tyramine can enter the nerve terminal and* displace stored norepinephrine
- Fermented foods, such as aged cheese
- It is oxidized by MAO in the gastrointestinal tract
- Serious HTN if co-administered with MAOI

Cocaine

- Blocks the Na+/K+-activated ATPase (required for cellular uptake of norepinephrine)
- Causes NE accumulation in the synapse thus inducing sympathatic activity

MIXED-ACTION ADRENERGIC AGONISTS

I. Ephedrine and pseudoephedrine

- plant alkaloids that are now made synthetically

- MOA :

1. Release stored norepinephrine from nerve endings
2. Directly stimulate both **α** and **β** receptors

- ❖ Not catecholamines i.e not COMT or MAO substrate (long duration)
- ❖ Readily absorbed and reach CNS
- ❖ Epherdine : vasoconstriction & Bronchodilatation

- ❖ Both cause insomnia , hyperactivity, tremors

Epherdine

- More CNS actions
- Previously used in asthma
- Cause mild CNS stimulation
- Improves athlete performance
- Banned by FDA due CVS issues
- Excreted unchanged in Urine

Pseudoephedrine

- Less CNS actions
- Undergoes extensive first pass effect
- Used as local nasal decongestant
- Illegally converted to methamphetamine (restriction on Pseudoephedrin products)

TISSUE	RECEPTOR TYPE	ACTION	OPPOSING ACTIONS
Heart			
• Sinus and AV	β_1	↑ Automaticity	Cholinergic receptors
• Conduction pathway	β_1	↑ Conduction velocity, automaticity	Cholinergic receptors
• Myofibrils	β_1	↑ Contractility, automaticity	
Vascular smooth muscle	β_2	Vasodilation	α-Adrenergic receptors
Bronchial smooth muscle	β_2	Bronchodilation	Cholinergic receptors

Kidneys	β_1	↑ Renin release	α_1-Adrenergic receptors
Liver	β_2, α_1	↑ Glycogenolysis and gluconeogensis	–
Adipose tissue	β_3	↑ Lipolysis	α_2-Adrenergic receptors
Skeletal muscle	β_2	↑ Increased contractility Potassium uptake; glycogenolysis Dilates arteries to skeletal muscle Tremor	–
Eye-ciliary muscle	β_2	Relaxation	Cholinergic receptors

GI tract	β_2	↓ Motility	Cholinergic receptors
Gall bladder	β_2	Relaxation	Cholinergic receptors
Urinary bladder detrusor muscle	β_2	Relaxation	Cholinergic receptors
Uterus	β_2	Relaxation	Oxytocin

Summing up Adrenergic Agonists

CATECHOLAMINES :

Epinephrine	α_1, α_2 β_1, β_2	Acute asthma Anaphylactic shock In local anesthetics to increase duration of action
Norepinephrine	α_1, α_2 β_1	Treatment of shock
Isoproterenol	β_1, β_2	As a cardiac stimulant
Dopamine	Dopaminergic α_1, β_1	Treatment of shock Treatment of congestive heart failure Raise blood pressure
Dobutamine	β_1	Treatment of acute heart failure

NONCATECHOLAMINES

Oxymetazoline	α_1	As a nasal decongestant
Phenylephrine	α_1	As a nasal decongestant Raise blood pressure Treatment of paroxysmal supraventricular tachycardia
Methoxamine	α_1	Treatment of supraventricular tachycardia
Clonidine	α_2	Treatment of hypertension
Albuterol *Terbutaline*	β_2	Treatment of bronchospasm (short acting)
Salmeterol *Formoterol*	β_2	Treatment of bronchospasm (long acting)
Amphetamine	α, β, CNS	As a CNS stimulant in treatment of children with attention deficit syndrome, narcolepsy, and for appetite control
Ephedrine *Pseudoephedrine*	α, β, CNS	As a nasal decongestant Raise blood pressure

SABA

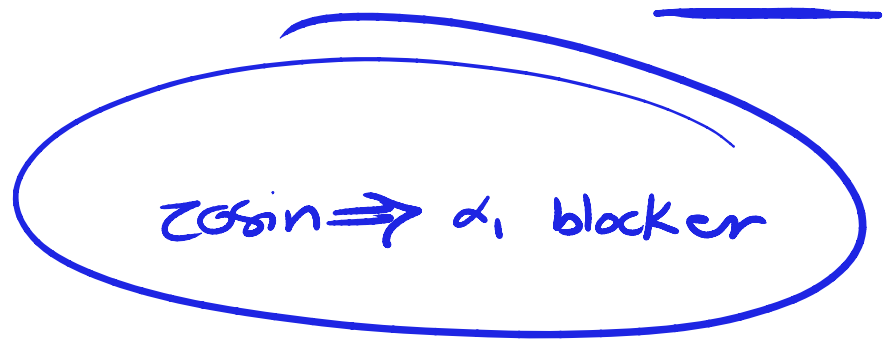
LABA

ADRENERGIC ANTAGONISTS

- Blockers or sympatholytic agents
- Bind reversibly or irreversibly with receptors
- Many play important roles in medicine
- Essential in HTN management

α-ADRENERGIC BLOCKING AGENTS

I. **Phenoxybenzamine**
II. **Phentolamine**
III. **Prazosin, terazosin, doxazosin, tamsulosin, and alfuzosin**
IV. **Yohimbine**



Phenoxybenzamine

- Nonselective antagonist linking covalently to both α1- and α2-receptors
- A Noncompetitive , Irreversibe Antagonist.
- How its action can be terminated?
- 24 hours duration
- After injection, few hrs to block the receptors.

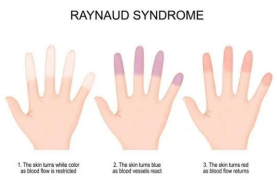
why ? عشانه irreversable receptors بحاول الجسم يفلح جديدة وهاد بده وقت طويل حوالي 24 ساعة !

reflex mechanism

➢ Not used in CVS system due to reflex tachycardia (α_1) and higher myocardial contractility due to increase NE release upon α_2 blockage

Phenoxybenzamine

- Pheochromocytoma treatment prior to surgery to preclude HTN crisis.



- Other possible indications :
  - ✓ Raynaud disease
  - ✓ Frostbite


Frostbitten toes two to three days after mountain climbing

Adverse Effects :

- postural hypotension,
- nasal congestion,
- nausea, and vomiting.
- It may inhibit ejaculation
- It also may induce reflex tachycardia

Phentolamine

more selective

- Competitive block of α1 and α2 receptors.
- Drug's action lasts for approximately 4 hours after a single administration
- As phenoxybenzamine, phentolamine causes postural hypotension
- Blocking α2 leads to relfex tachycardia

phentolamine

- C/I with coronary artery disease
- Used in HTN crisis induced by tyramine

Prazosin, terazosin, doxazosin, tamsulosin, and alfuzosin

- **Selective competitive blockers of the α1 receptor.**
- Useful in HTN treatment
- Postural hypotension
- All are inactivated by metabolism vial renal system,
- however Doxazocin appear in feces

lipophilic ← metabolism صعب →

Cardiovascular effects

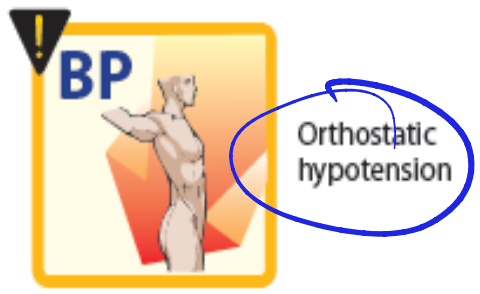
- Reduces PR and lowers BP by relaxing arterial &venous smooth muscles
- Minimal effect on CO, Renal BF .
- Better than phenoxybenzamine and Phentolamine for HTN management.
- **Mainly First dose orthostatic hypotension and syncope**
- Improve lipid & glucose metabolism

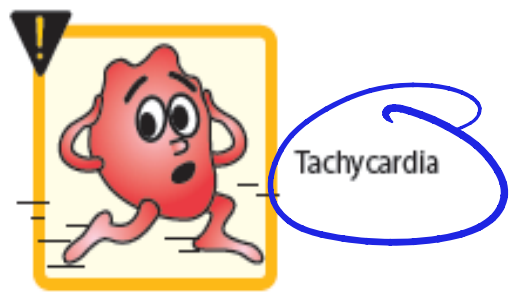
Benign Prostate Hyperplasia

- Blockade of the α receptors decreases tone in the smooth muscle of the bladder neck and prostate and improves urine flow.

omnic

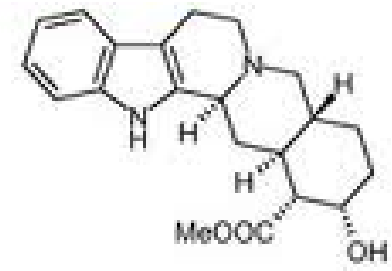
- ***Tamsulosin*** *is an inhibitor (with* some selectivity) of the α1A receptors found on the smooth muscle of the prostate. This selectivity accounts for *tamsulosin's relatively* minimal effect on blood pressure, though dizziness (orthostasis) may rarely occur





-Newer agents are more selective with less s/e
-Doxazocin retains Na+ and so its given with a diuretic
-For Ejaculation to occur, the smooth muscles in the ejaculatory duct must contract properly and this may be inhibited with this class (non selectives)
-- Alpha antagonist use in HTN is now limited due to the emergence of better classes.

Yohimbine



- Selective competitive α2 blocker
-Found in the bark of Yohimbine tree
- *Yohimbine works at the level of the* CNS to increase sympathetic outflow to the periphery.
-CNS and cardiovascular stimulant
- May be used as a sexual stimulant