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Drugs acting on PNS

DRUGS AFFECTING THE SYMPATHETIC NERVOUS SYSTEM

(Drugs Affecting Adrenergic Synapses, Adrenergic Substances)

1. **Adrenoblockers**
2. **Sympatholytics**
3. **Dopaminergic drugs:**
   - **Dopaminomimetics**
   - **Dopaminolytics**

A. α-Adrenoblockers (α-receptor competitive antagonists)

1. **Nonselective ($\alpha_1 + \alpha_2$)**
   - a) **Hydrogenated derivatives of ergot alkaloids**
     - Dihydroergotamine
     - Dihidroergotoxine
     - Nicergoline (sermion)
   - b) **Synthetic**
     - Phenoxybenzamine
     - Phentolamine
     - Tropodiphen (tropafen)
     - Proroxan (pyroxan)
     - Butiroxan
2. **Selective (α_1)**
   - Prazosin
   - Doxazosin
   - Terazosin
   - Alfuzosin
   - Tamsulosin (α_{1A}) (omnic)
   - Indoramin
3. **Selective (α_2)**
   - Yohimbine

B. β-Adrenoblockers (β-receptor competitive antagonist)

1. **Nonselective (β_1 + β_2) without intrinsic sympathomimetic activity (ISA)**
   - Propranolol
   - Timolol
   - Nadolol
   - Sotalol
2. **Nonselective (β_1 + β_2) with ISA**
   - Alprenolol
   - Oxprenolol
   - Pindolol
3. **Selective (β_1) without ISA (cardioselective)**
   - Atenolol
   - Metoprolol
   - Talinolol
   - Betaxolol
   - Bisoprolol
4. **Selective (β_1) with ISA**
   - Acebutolol
   - Practolol
5. **Supraselective (β_1) (3rd generation)**
   - Nebivolol (nebilet)

C. α, β-Adrenoblockers

- Labetolol
- Proxodolol
- Carvedilol

D. Acting on multiple receptors

- Urapadil ($\alpha_{1,2}$ and 5-HT)
- Chlorpromazine
- Haloperidol
- Levomepromazine

E. Sympatholytics

- Centrally acting
  - Methyldopa
- Peripherally acting
  - Guanethidine
  - Bretylium
- With central and peripheral action
  - Reserpine

F. Dopaminergic drugs

1. Dopaminomimetics

- Dopamine
- Levodopa
- Apomorphine
- Bromocriptine

2. Dopaminolytics

a) Neuroleptics

- Chlorpromazine
- Droperidol
- Haloperidol
- Sulpiride

b) Anti-vomiting drugs

- Metoclopramide (Reglan, cerucal)
- Domperidone
- Dimetpramid

Agents that inhibit responses mediated by direct adrenoceptor activation.

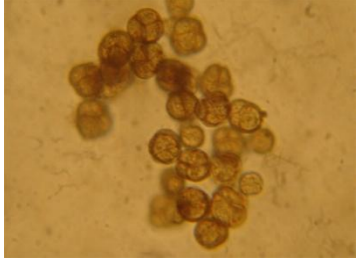
- **adrenoblockers**
- **adrenoceptor antagonists,**
- **adrenergic antagonists,**
- **adrenergic blocking agents.**

Adrenoceptor-blocking agents:

1. **Prevent the agonist from interacting with its receptor.**
2. **Do not prevent the release of transmitters from adrenergic nerves**
3. **Are not catecholamine-depleting agents**

α-Adrenoblockers

Nonselective (α1 + α2)



Hydrogenated derivatives of ergot alkaloids

Ergot alkaloids are produced by *Claviceps purpurea*, a fungus that infects grasses and grains—especially rye—under damp growing or storage conditions.

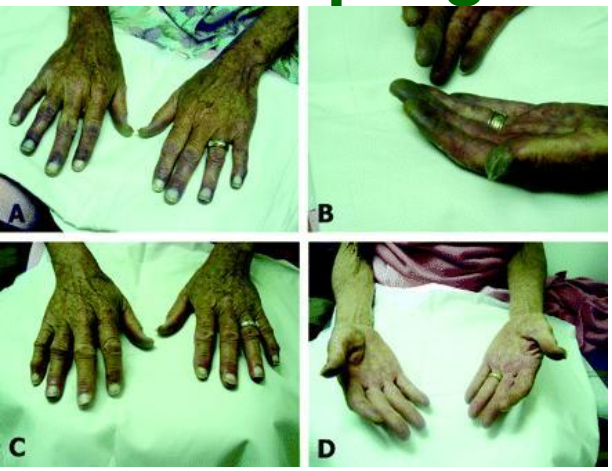
- **This fungus synthesizes alkaloids:**
  - **Ergotamine**
  - **Ergotoxine**
    - **Ergocriptine**
    - **Ergonovine**
    - **Ergocristine**

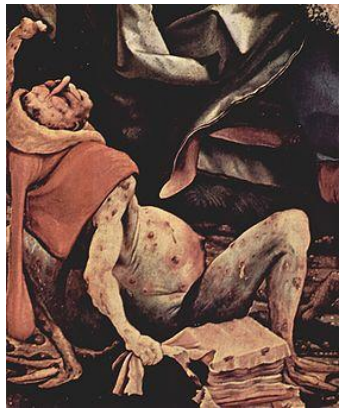
PLATE XXXVII.—*Claviceps purpurea* (Rye ergot). (From Jackson: *Experimental Pharmacology and Materia Medica.*)

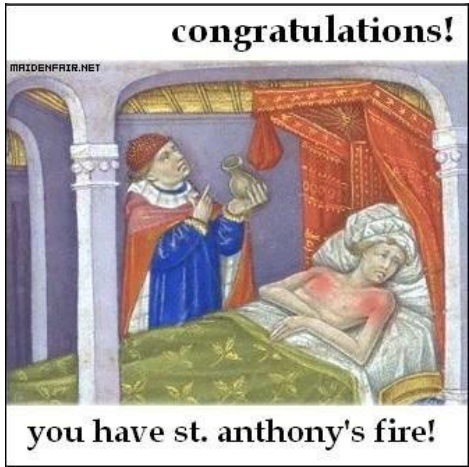
- These alkaloids affect adrenoreceptors (partial agonists), dopamine receptors, 5-HT receptors

Ergot poisoning (ergotism, St. Anthony's fire).

- dementia with florid hallucinations;
- prolonged vasospasm, which may result in gangrene;
- stimulation of uterine smooth muscle, which in pregnancy may result in abortion.







Hydrogenated derivatives of ergot alkaloids

- are semisynthetic drugs
- block α-adrenoreceptors more pronounced
- less vasoconstriction
- do not act on nonpregnant uterus
- less toxic

Hydrogenated alkaloids of ergotoxine produce vasodilation with hypotension

Indications

- **complex treatment of hypertension**
- **cerebral vascular disorders**
  - migraine headache,
  - cluster headache,
  - vascular headaches
- **peripheral circulatory disorders (PVD)**
- **uterine bleeding** after delivery,

Contraindications

- pregnancy,
- ischemic heart disease,
- uncontrolled hypertension,
- peripheral arterial disease,
- sepsis,
- recent vascular surgery,
- ischemic bowel,
- hypersensitivity to ergot,
- high-dose aspirin therapy,
- known alcohol intolerance.
- Raynaud's disease,
- severe liver or kidney disease,

Adverse reactions

- MI,
- myocardial ischemia,
- ventricular tachycardia,
- ventricular fibrillation,
- CVA,
- pleural and retroperitoneal fibrosis,
- cyanosis,
- ergotism or gangrene (if used over prolonged period).

2. Synthetic
Phenoxybenzamine and Phentolamine

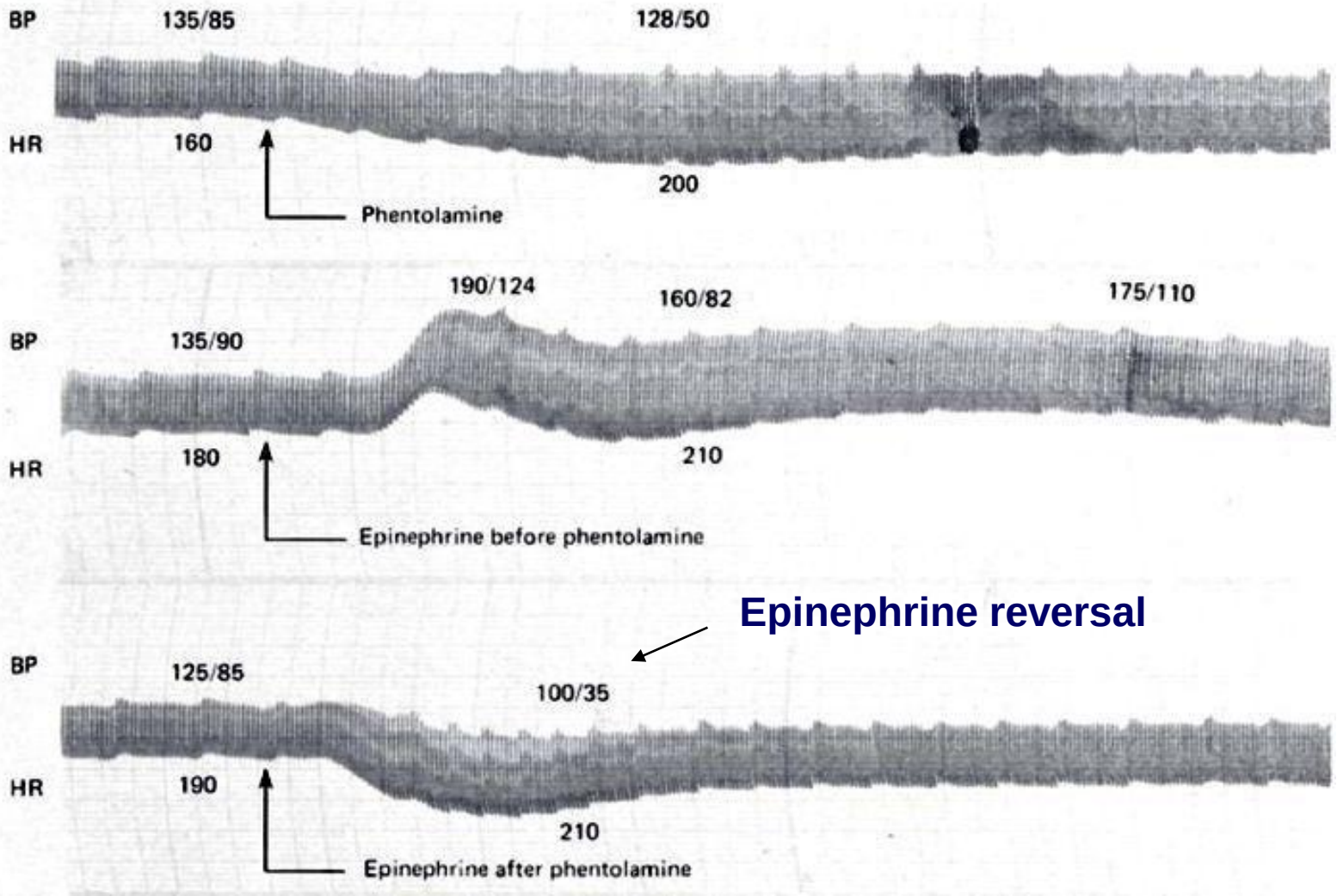
- **Phenoxybenzamine – haloalkylamine compound – irreversible antagonist;**
- **Phentolamine – imidazoline - competitive antagonist.**

2. Synthetic
Phenoxybenzamine and Phentolamine

A. The actions on the **cardiovascular system**:

1. **decrease total peripheral resistance (due to antagonism of receptors in the vasculature) =>**
2. **↓ BP**
3. **improve microcirculatory disturbances**
4. **increase in cardiac output and tachycardia:**
   - **reflex sympathetic nerve stimulation**
   - **enhanced release of NE (antagonism of presynaptic alpha-2 receptors)**

- **These drugs can prevent the pressor effects of usual doses of agonists;**
- **Indeed, in the case of agonists with β_2 action (eg, epinephrine), α selective - receptor antagonism may convert a pressor to a depressor response**



Synthetic
Phenoxybenzamine and Phentolamine

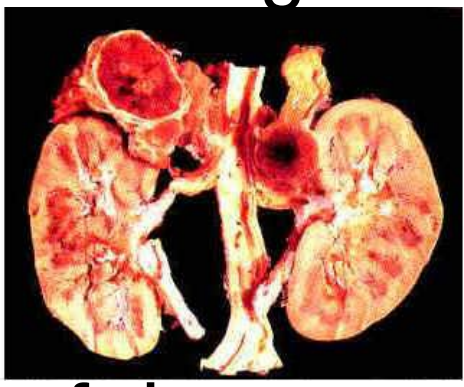
B. The actions on the respiratory system:

- ↑ sensitivity of $beta_2$ AR
- Dilate prealveolar sphincters

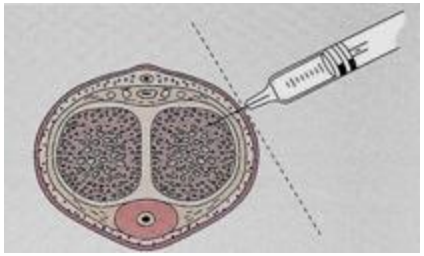
Synthetic

Indications

- **Hypertension**, immediately before or during surgery for **pheochromocytoma**

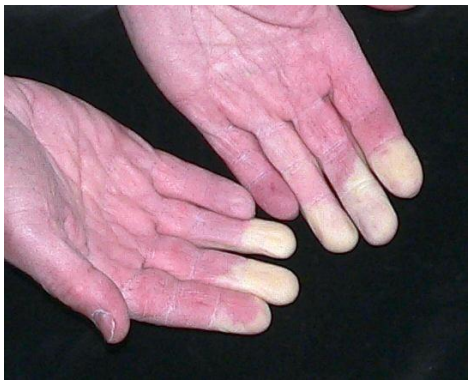


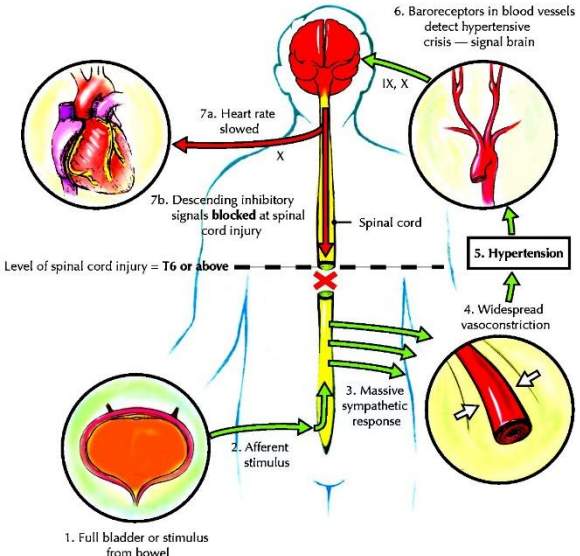
- Diagnosis of pheochromocytoma
- Treatment of **dermal necrosis** from extravasation after IV administration of drugs.
- Adjunct therapy of **impotence**
- Hypertensive crisis caused by MAO inhibitor–sympathomimetic amine **interaction**



Synthetic
Indications

- Endarteriitis, Raynaud's disease (**peripheral circulatory disorders**).
- **Autonomic hyperreflexia** in patients with spinal cord transection
- To **reverse or shorten** the duration of soft-tissue anesthesia





Synthetic

Indications

- **Hypertensive crisis** treatment, treatment of hypertension,
- Treatment of traumatic, cardiogenic, hemorrhagic, combustion **shock** – removing the spasm of arterioles - improving microcirculation,
- Acute and chronic **heart failure**,
- Complex treatment of **asthma**,

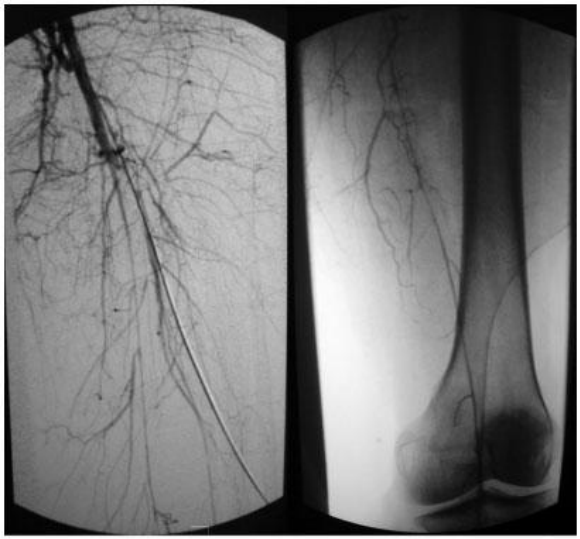
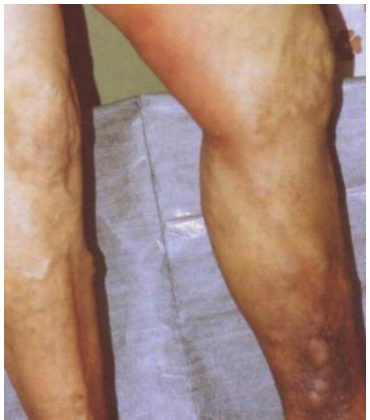


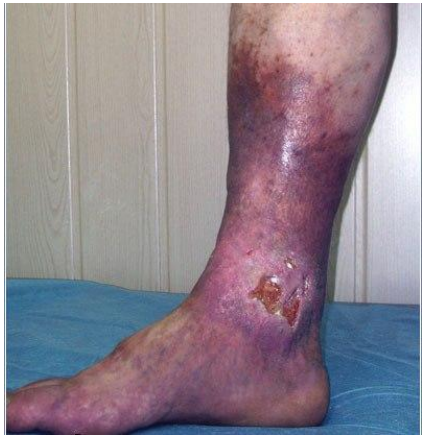
Figure 2 - Arteriography of left lower limb showing signs of severe spasm of the superficial femoral artery

Synthetic

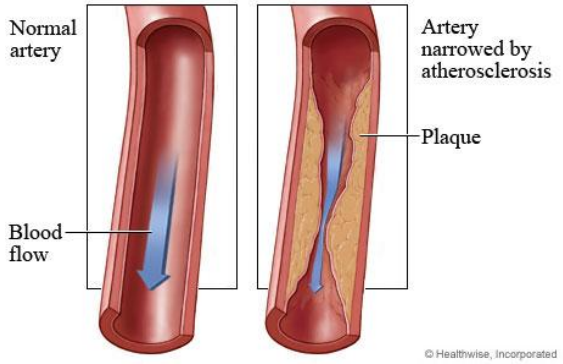
Indications

- Complex treatment of **trophic ulcers** of the leg,
- Complex treatment of postoperative **intestinal atonia**,
- **Pulmonary hypertension**
- Prevention and treatment of **phlebitis and thrombophlebitis**

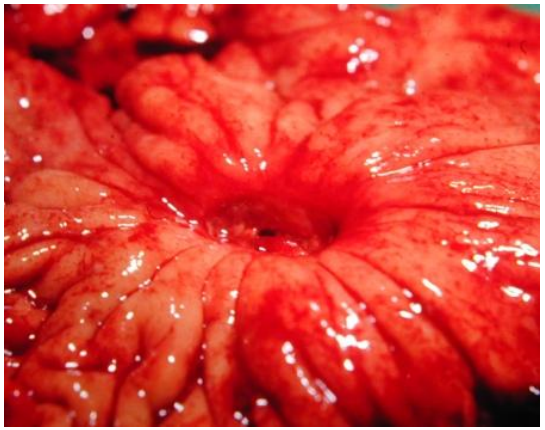




Synthetic
Contraindications:



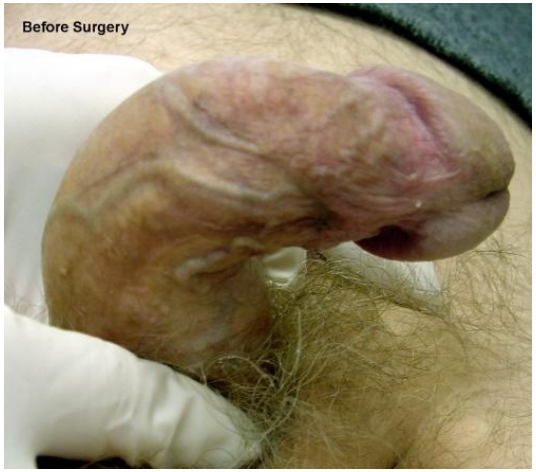
- organic heart disease
- coronary artery disease with angina or coronary insufficiency
- history of MI
- cerebrovascular disease
- hypovolemia
- gastritis and gastric ulcer (with caution)



Side effects:

Common:

- **nausea,**
- **vomiting,**
- **nasal congestion,**
- **abdominal pain.**



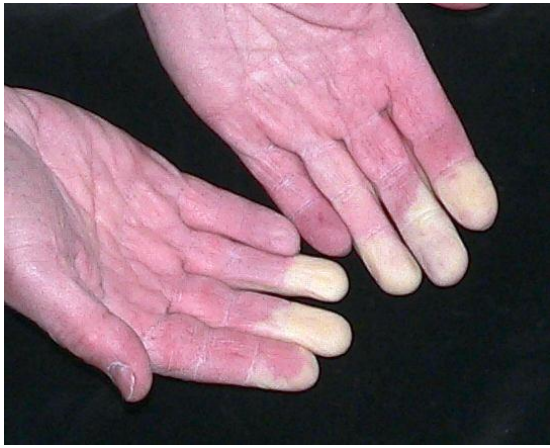
Serious:

- **arrythmias,**
- **angina,**
- **orthostatic hypotension,**
- **cerebral vascular spasm,**
- **severe hypotension,**
- **MI,**
- **worsening of peptic ulcer**
- **delay ejaculation**
- **priapism and fibrosis of the penis**

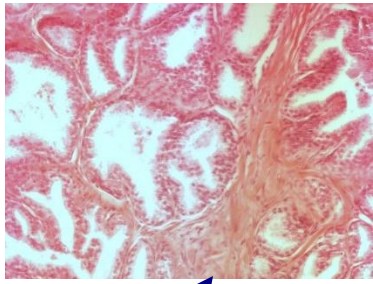
Selective (α1)

1. direct alpha1-antagonism in blood vessels,
2. high doses – inhibition of phosphodiesterases – vasodilation
   - decrease in arterial and venous resistance
   - decrease venous return (preload) and heart work
   - HR changes little (moderate tachycardia)
3. Block adrenergic receptors (α_{1A}) in neck of urinary bladder and in prostate:
   - smooth muscle relaxation
   - improved urine flow.

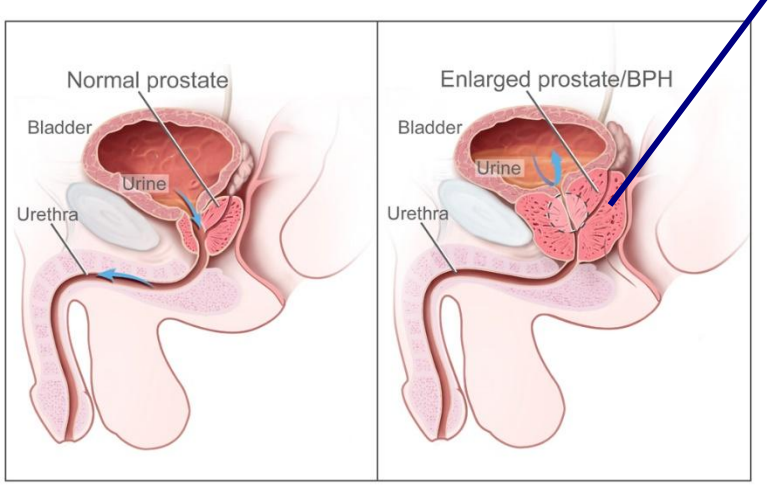
Indications



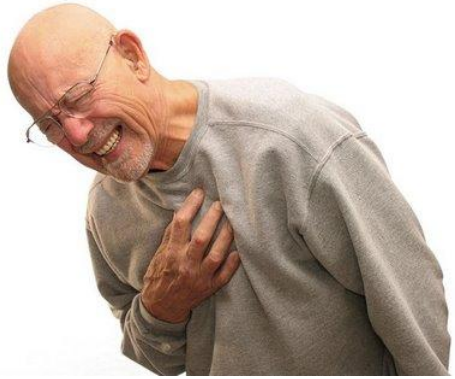
- **Hypertension**
- **Benign prostatic hyperplasia**
- **Congestive heart failure**
- Mitral or aortic **valvular insufficiency** (adjunct therapy)



- **Peripheral vasospastic diseases** (Raynaud's d., etc.)



Side effects



Common:

- dizziness,
- headache,
- fatigue.

Serious:

- orthostatic hypotension,
- syncope,
- depression,
- priapism,
- ejaculation abnormalities.
- angina,
- arrhythmias,
- retinopathy,
- pancreatitis.

Contraindications

- Hypersensitivity to prazosin and other quinazoline drugs (-osin).
- Children (some drugs)

Use with caution

In patients with pulmonary embolism, aortic and mitral valve stenosis, liver disease.

Selective (α_2)
Yohimbine

- It is an indolealkylamine alkaloid found in the bark of the tree *Pausinystalia yohimbe* and in *Rauwolfia* root

Yohimbine

Blockade of α_2 receptors

- **in the pontomedullary region of the CNS**
  - **increase sympathetic outflow**
- **nerve endings**
  - **potentiate the release of NE, leading to activation of β1 and α1 receptors in the heart and peripheral vasculature**

- **Increases blood pressure and heart rate**
- **Enhances motor activity and produces tremors**

Yohimbine
Indications

- male sexual dysfunction
- SSRI-induced sexual dysfunction,
  - erectile dysfunction,
  - decreased libido
  - anorgasmia
- diabetic neuropathy
- postural hypotension

Side effects

- Anxiety,
- nausea,
- fine tremor,
- increased BP,
- sweating,
- fatigue

- β-adrenoblockers

Nonselective (β_1 + β_2) without intrinsic sympathomimetic activity (ISA)

Propranolol

- **MA: blocks stimulation of beta1 (myocardial) and beta2 (pulmonary, vascular, and uterine)-adrenergic receptor sites.**

Effects:

- **Heart:**
  - ↓ HR – negativ chronotropic
  - ↓ contractility – negativ inotropic => ↓ cardiac output => heart work and oxygen demand
  - ↓ conductance – negativ dromotropic
  - ↓ automatism – negativ batmotropic
- **Blood pressure ↓ due to:**
  - ↓ cardiac output (β_1-AB action)
  - Blockade of presynaptic β_2-AR => ↓ release of NA
  - Blockade of β_1-AR of juxtaglomerular apparatus => ↓ renin release => ↓ conversion AGen to AT-I => ↓ ATII and aldosteron
  - Decreased central sympathetic outflow
  - Resetting of baroreceptor

Effects:

- Moderate psycho-sedative activity because of penetration through the BBB (considered as day-time tranquilizers) resulting in the removal of fear, excitability, negative emotions, insomnia.
- The constrictor action of Adr on the background of propranolol administration is similar to the Nor (missing phase II hypotension) as β2-AR of vessels are blocked).
- Bronchi - increases tone and may cause bronchospasm (in asthma)
- Propranolol is an antagonist of Adr on its hyperglycaemic and lipolytic actions (inhibits glycogenolytic and lipolytic effects of catecholamines).

Indications

- **Angina pectoris (blockade of β1-AR decrease the work of the heart, which reduces its O2 demand);**
- **Hypertensive disease;**
- **Supraventricular tachyarrhythmias (in atrial fibrillation) - β1-AR inhibition decrease the automaticity and increases AV conduction time;**
- **Hipertireoidism, thyrotoxicosis;**
- **Tachycardias of different etiology (in mitral stenosis, thyrotoxicosis and arrhythmia caused by adrenomimetics and cardiac glycosides);**

Indications

- **Open-angle glaucoma, topically - decreases production of aqueous humor and decrease the intraocular pressure (timolol, levobunolol, etc.);**
- **Anxiety;**
- **Tremor in Parkinson's disease;**
- **Migraine;**
- **Withdrawal syndrome in alcoholics;**
- **Combined with α-AB in pheochromocytoma.**

Adverse Reactions / Side Effects

- **Rebound syndrome;**
- **CNS: fatigue, weakness, anxiety, dizziness, drowsiness, insomnia, memory loss, mental depression, mental status changes, nervousness, nightmares.**
- **EENT: blurred vision, dry eyes, nasal stuffiness.**
- **Resp: bronchospasm, wheezing.**
- **CV: ARRHYTHMIAS, BRADYCARDIA, CHF, PULMONARY EDEMA, orthostatic hypotension, peripheral vasoconstriction.**

Adverse Reactions / Side Effects

- **GI: constipation, diarrhea, nausea.**
- **GU: erectile dysfunction, ↓ libido.**
- **Derm: itching, rashes.**
- **Endo: hyperglycemia, hypoglycemia (↑ in children).**
- **MS: arthralgia, back pain, muscle cramps.**
- **Neuro: paresthesia.**
- **Misc: drug-induced lupus syndrome.**

Contraindications:

- Uncompensated CHF
- Bradycardia or heart block
- Cardiogenic shock
- Asthma attacks
- Gastric ulcer disease
- Diabetes
- Pregnancy
- Pulmonary hypertension, Pulmonary edema
- Disorders of the vascularity of the limbs

Nonselective (β_1 + β_2) with ISA

- **These drugs are preferred in hearts' diseases with normal rhythm, sometimes with slight bradycardia.**

Selective (β_1) without ISA (cardioselective)

Metoprolol

- Blocks stimulation of beta1 (myocardial)-adrenergic receptors.
- Does not usually affect beta2 (pulmonary, vascular, uterine)-adrenergic receptor sites.

Metoprolol
Indications

- Hypertension.
- Angina pectoris.
- Prevention of MI and decreased mortality in patients with recent MI.
- Management of stable, symptomatic (class II or III) heart failure due to ischemic, hypertensive or cardiomyopathc origin
- Ventricular arrhythmias / tachycardia.
- Migraine prophylaxis.
- Tremors.
- Aggressive behavior.
- Drug-induced akathisia.
- Anxiety.

Selective (β_1) with ISA

Acebutolol

Practolol

- Are cardioselective (β1), intrinsic sympathomimetic activity is less expressed than in the non-selective with ISA.
- Less effect on cardiac output and reduce HR at rest.

Nebivolol

MA

- the most β1-selective of the β-blockers tested (D-isomer)
- it has a nitric oxide (NO)-potentiating, vasodilatory effect (L-isomer) – causes dilation of blood vessels in addition to effects on the heart – vasodilator action.

Indications

- Hypertension (alone and with other antihypertensives);
- Ischemic heart disease.

Carvedilol

MA:

- Blocks stimulation of beta1 (myocardial => ↓ heart work, juxtaglomerular => ↓ renin release) and beta2 (pulmonary, vascular, and uterine)-adrenergic receptor sites.
- Has alpha1 blocking activity => ↓ TPR, afterload and preload.

Indications

- Hypertension.
- CHF (ischemic or cardiomyopathic) with digoxin, diuretics, and ACE inhibitors.
- Ischemic heart disease.
- Left ventricular dysfunction after myocardial infarction.

Sympatholytics:

- **Affect noradrenaline synthesis (methyldopa, rezerpine)**
- **Affect noradrenaline release (guanethidine)**
- **Affect noradrenaline uptake. (guanethidine)**
- **Inhibit the influx of Ca 2+ through presynaptic membrane and inhibit in this way mediators release (Bretylium)**

α-Methyldopa

MA:

- **It is taken up by noradrenergic neurons, where it is converted to the false transmitter α-methylnoradrenaline. This substance is not deaminated within the neuron by MAO, so it accumulates and displaces noradrenaline from the synaptic vesicles.**
- **α-Methylnoradrenaline is released in the same way as noradrenaline, but is less active than noradrenaline on α1 receptors and thus is less effective in causing vasoconstriction. On the other hand, it is more active on presynaptic (α2) receptors, so the autoinhibitory feedback mechanism operates more strongly than normal, thus reducing transmitter release below the normal levels.**
- **Stimulates CNS alpha2-adrenergic receptors, producing a decrease in sympathetic outflow to heart, kidneys, and blood vessels.**
- **Result is decreased blood pressure and peripheral resistance, a slight decrease in heart rate, and no change in cardiac output.**

Indications

- Management of moderate to severe hypertension (with other agents).
- May be used for treatment of hypertension in pregnancy >6 month

Adverse Reactions/Side Effects

- CNS: sedation, ↓mental acuity, depression.
- EENT: nasal stuffiness.
- CV: MYOCARDITIS, bradycardia, edema, orthostatic hypotension.
- GI: DRUG INDUCED HEPATITIS, diarrhea, dry mouth.
- GU: erectile dysfunction.
- Hemat: eosinophilia, hemolytic anemia.
- Misc: fever.

Contraindications/Precautions

- **Contraindicated in:**
  - **Hypersensitivity;**
  - **Active liver disease.**
- **Use Cautiously in:**
  - **Previous history of liver disease;**
  - **Pheochromocytoma;**
  - **Geri: ↑ risk of adverse reactions; consider age-related impairment of hepatic, renal and cardiovascular function as well as other chronic illnesses. May cause bradycardia and exacerbate depression.**

Guanethidine

MA:

- **It is selectively accumulated by noradrenergic nerve terminals, being a substrate for NET.**
- **Its initial blocking activity is due to block of impulse conduction in the nerve terminals that selectively accumulate the drug. Its action is prevented by drugs, such as *tricyclic antidepressants*, which block NET.**
- **Guanethidine is also concentrated in synaptic vesicles by means of the vesicular transporter VMAT, possibly interfering with their ability to undergo exocytosis, and also displacing noradrenaline.**
- **In this way, it causes a gradual and long-lasting depletion of noradrenaline in sympathetic nerve endings, similar to the effect of reserpine.**
- **Given in large doses, guanethidine causes structural damage to noradrenergic neurons, which is probably due to the fact that the terminals accumulate the drug in high concentration.**

Guanethidine

In:

- **Antihypertensive**
- **Glaucoma**

Side effects:

- **associated with the loss of sympathetic reflexes.**
  - **postural hypotension,**
  - **diarrhoea,**
  - **nasal congestion**
  - **failure of ejaculation.**

Reserpine

- **Is an alkaloid from the shrub *Rauwol***

MA:

- **Reserpine, at very low concentration, blocks the transport of noradrenaline and other amines into synaptic vesicles, by blocking the vesicular monoamine transporter.**
- **Noradrenaline accumulates instead in the cytoplasm, where it is degraded by MAO. The noradrenaline content of tissues drops to a low level, and sympathetic transmission is blocked.**
- **Reserpine also causes depletion of 5-HT and dopamine from neurons in the brain, in which these amines are transmitters.**

Reserpine

In:

- **Hypertension**
- **Dyskinesia in patients suffering from Huntington's disease**
- **Psychotic diseases**

Reserpine

Side effects

- nasal congestion, nausea, vomiting, weight gain, gastric intolerance, gastric ulceration (due to increased cholinergic activity in gastric tissue and impaired mucosal quality), stomach cramps, diarrhea.
- hypotension and bradycardia, may worsen asthma.
- erectile dysfunction
- depression - sometimes lead to suicide
- drowsiness, dizziness, and nightmares.
- Parkinsonism
- general weakness or fatigue
- hyperprolactinemia
- passes into breast milk - should be avoided during breastfeeding if possible.