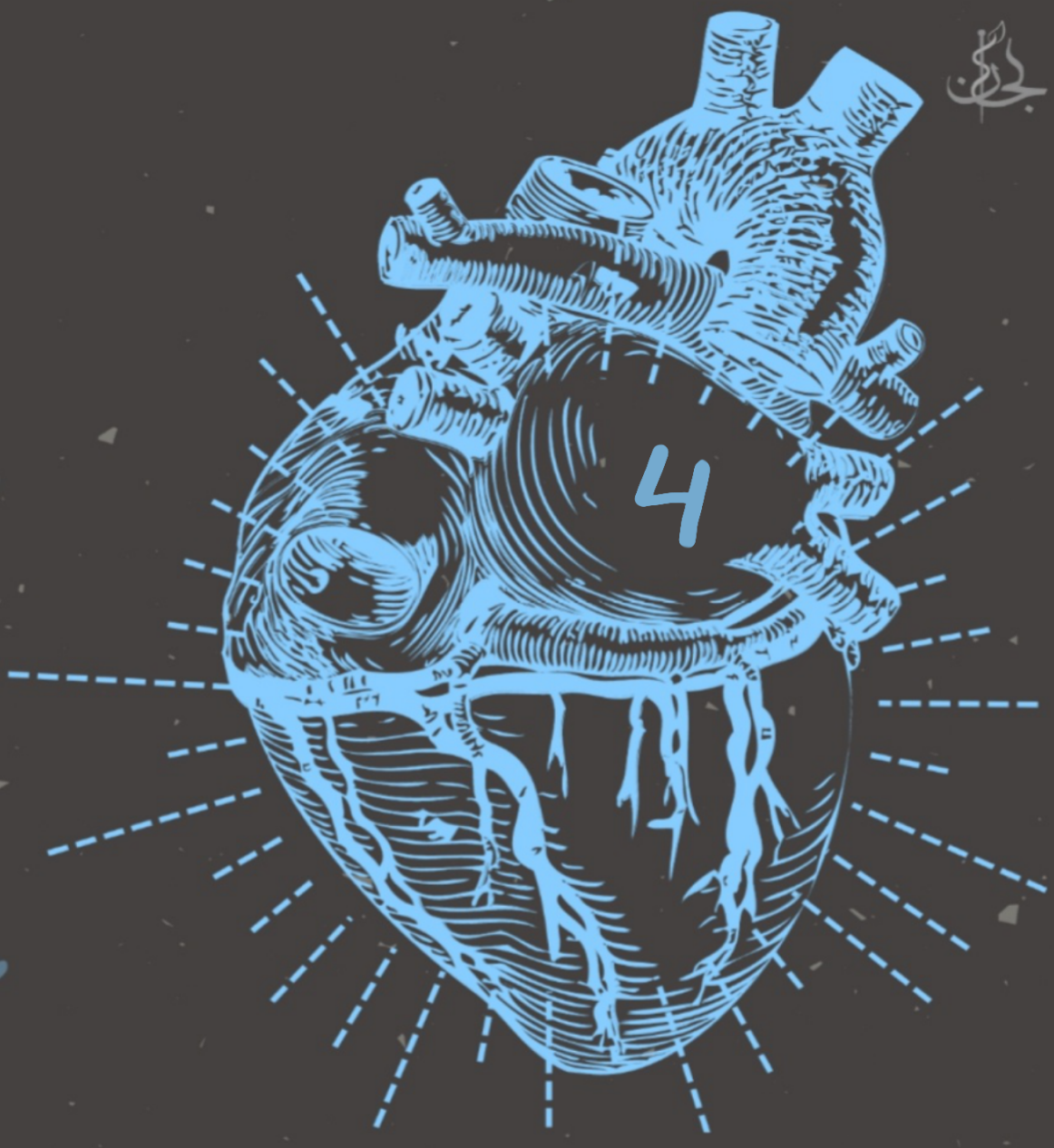
CVS



PHARMACOLOGY

WRITER: Doctor 018 ENTER

CORRECTOR: ENTER

DOCTOR: ENTER

Hypertension

Hypertension is a common, incurable, persistent, but usually asymptomatic disease whose treatment provides no obvious benefit. It is usually found incidentally.

Why do we treat hypertension?

- 40% reduction in stroke incidence.
- 25% reduction in myocardial infarction.
- 50% reduction in heart failure.
- And to reduce other complications such as retinal detachment, nephrotoxicity, chronic renal failure.

The diagnosis of hypertension is standardized. We take an average of 14 readings, two per session, taken morning and evening for 7 days. Here we talk about borderline hypertension, but in case of a very high blood pressure, diagnosis could be made immediately from a single reading.

- 30% patients don't even know they have hypertension.
- 11% do know but for a reason or another, they are not on therapy.
- 25% are on inadequate therapy.
- 34% are on adequate therapy. ONLY ONE THIRD!!

Adequate therapy means the patient's BP is controlled, they take their medication, follow up with their doctor, and regularly check their BP.

BP variations

In healthy people blood pressure varies from one day to another. However, Increased BP variability is associated with increased organ damage and cardiovascular morbidity.

In the case of hypertension, the blood pressure elevation is persistent.

- "White Coat" or isolated office hypertension: Some patients don't actually have hypertension but due to the stress of visiting physicians, their blood pressure will be elevated.
- Masked hypertension: Patients would show normal blood pressure when it is taken at the clinic, but when taken at home their blood pressure is elevated.
- Morning surge of BP: Patients show high blood pressure only in the morning but later during the day it drops back to normal.
- During Sleep, "Non dipping" and "extreme dipping",

Normally during sleep, there is dipping of BP, meaning the BP is lower than when a person is awake. What isn't normal is when some people have no decrease in BP at all while sleeping (non-dipping) or extreme dipping (extreme decrease in BP).

Systolic/Diastolic pressure (mm Hg)	Category
< 120/80	Normal
120-135 / 80-89	Prehypertension
>= 140/90	hypertension
140-159 / 90-99	Stage 1
>= 160/100	Stage 2

The above table shows the classification of hypertension on the basis of blood pressure.

There is a condition known as malignant hypertension, in which there is a very high increase in BP, but this condition is not related to malignancies (cancers) at all.

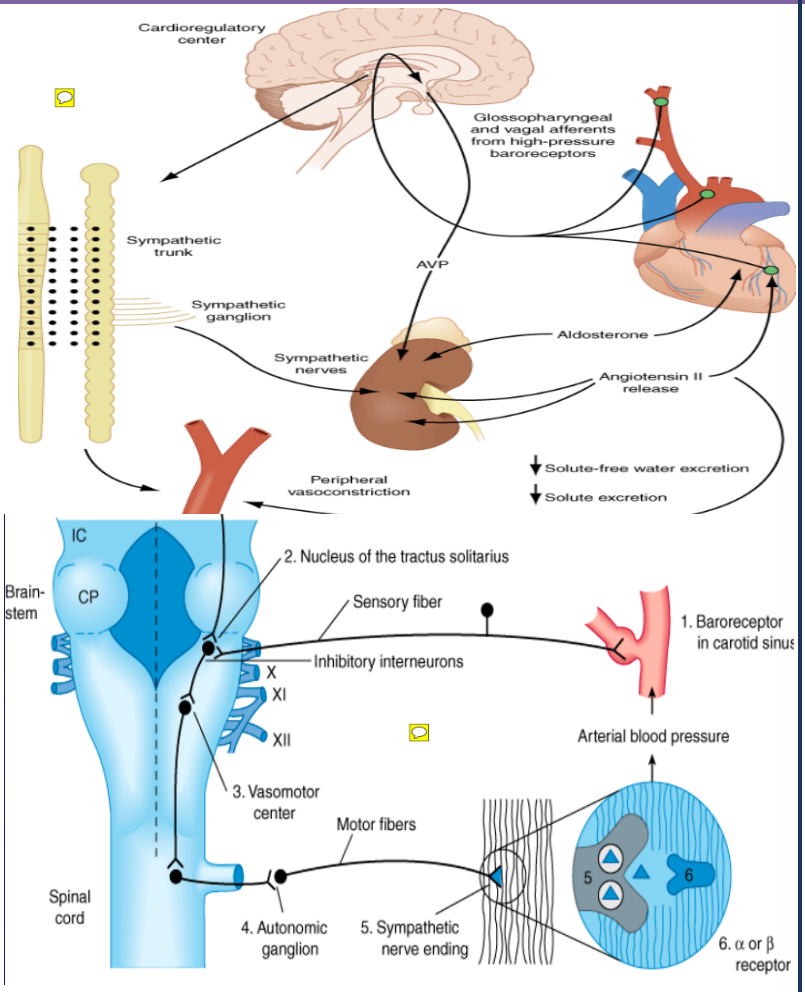
BP Control

BP is controlled by many systems in the body, including the CNS, heart, kidneys, blood vessels, and parasympathetic and sympathetic nervous systems.

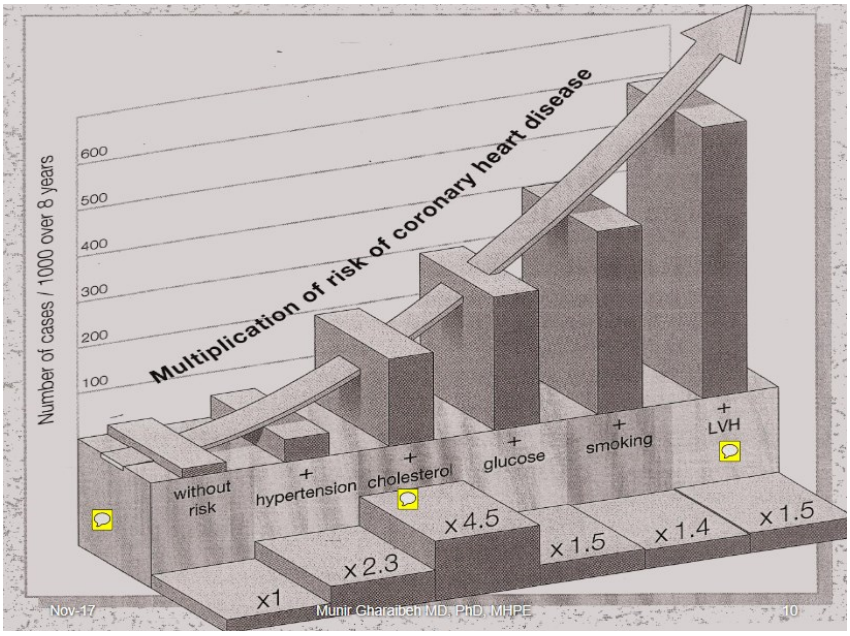
Neural control of BP:

1. Baroreceptors in carotid sinuses detect changes in BP and send signals to the brain.
2. Activation of vasomotor center.
3. The vasomotor center then sends signals back to the blood vessels and heart through the sympathetic and parasympathetic systems.

Also, the nervous system can control the kidneys.



The figure to the right illustrates how hypertension and other factors contribute to increasing risk of coronary heart disease. We notice that hypertension can increase the risk by 2.3 times, while glucose and smoking each increase the risk merely by 1.5 times.



Goals of Therapy

- To provide maximal protection against cardiovascular consequences with minimal side effects to the patient.
- On the other hand, a severe decrease in blood pressure causes a drop in the blood supply to vital organs which could lead to complications such as stroke, coronary, and renal complications. That's why drug doses should be controlled well.

Non-pharmacologic Treatment

Some people only rely on these, unfortunately, they are not enough alone.

Mostly they are just lifestyle modifications such as:

- Weight reduction
- Diet rich in potassium↑ and calcium↑ and sodium↓ reduction.
- A special kind of diet called Dietary Approaches to Stop Hypertension (DASH) is an eating plan where patients take just 1600 mg sodium per day. This has proved to have efficacy similar to single drug therapy. (we usually use a combination of two or three drugs to treat BP)
- Physical activity

Determinants of Blood Pressure

The doctor read the figure quickly and said you must already know this from physiology lectures.

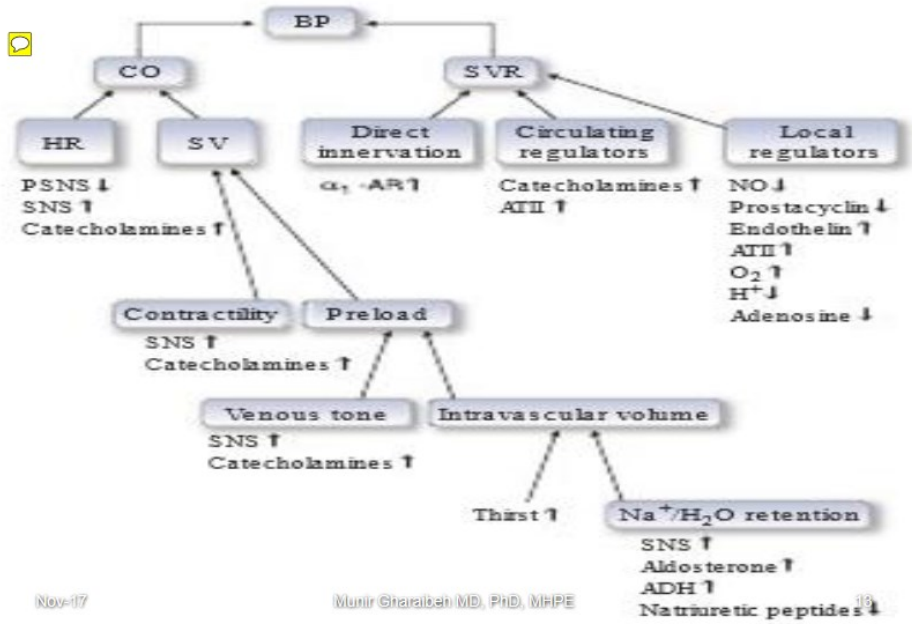
**SVR stands for Systemic Vascular Resistance

**SV stroke volume

**CO cardiac output

**AR Angiotensin Receptors

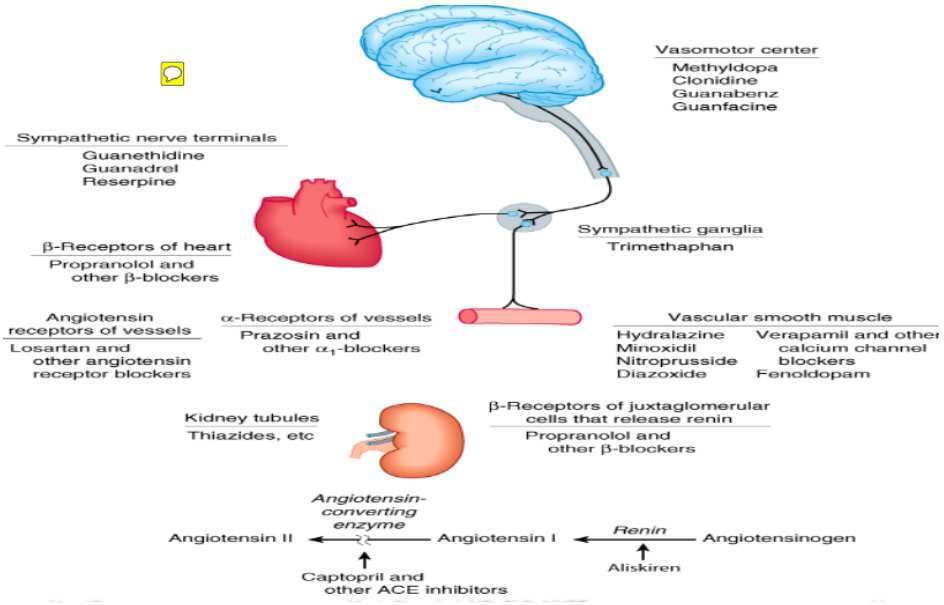
**ATII Angiotensin II



Antihypertensive drugs

Sites of action of antihypertensive drugs

We have many different types of antihypertensive drugs and they work on different sites as shown in the figure.



- Sympathetic nerve terminals.
- Beta receptors of heart
- Alpha receptors of vessels
- Vasomotor center
- Sympathetic ganglion
- Vessels smooth muscles
- Angiotensin receptors on vessels
- Renin-angiotensin I & II

Hemodynamic Effects of Antihypertensive Drugs

Every class of drugs have different hemodynamic effects so we should use a suitable agent for each patient.

This table (and the one about pharmacokinetics in the slides) are not for memorization.

	HEART RATE	CARDIAC OUTPUT	TOTAL PERIPHERAL RESISTANCE	PLASMA VOLUME	PLASMA RENIN ACTIVITY
Diuretics	↔	↔	↓	–↓	↑
Sympatholytic agents					
Centrally acting	–↓	–↓	↓	–↑	–↓
Adrenergic neuron blockers	–↓	↓	↓	↑	–↑
α receptor antagonists	–↑	–↑	↓	–↑	↔
β receptor antagonists					
No ISA	↓	↓	–↓	–↑	↓
ISA	↔	↔	↓	–↑	–↓
Arteriolar vasodilators	↑	↑	↓	↑	↑
Ca^{2+} channel blockers	↓ or ↑	↓ or ↑	↓	–↑	–↑
ACE inhibitors	↔	↔	↓	↔	↑
AT_1 receptor antagonists	↔	↔	↓	↔	↑
Renin inhibitor	↔	↔	↓	↔	↓ (but [renin] ↑)

Diuretics (Saluretics)

- These drugs cause diuresis leading to loss of fluids and sodium.
- Widely recommended as first-line therapy, especially in the elderly, the obese, and black patients. But they're not preferred by some patients because they cause diuresis.
- They are better at reducing coronary heart disease, heart failure, stroke, and mortality.
- Inexpensive: they are the cheapest antihypertensives.
- Combine well with other drugs.
- Lower doses along with sodium restriction (less dietary sodium intake) can cause fewer metabolic side effects while retaining antihypertensive activity.

All diuretics have same efficacy in lowering BP, although not the same diuretic activity.

These drugs have two categories of effects that occur according to the time since beginning drug administration: early and late.

Early Effects (in the first 3-4 days):

- Mainly affects the systolic BP.
- Diuresis lowers the blood volume (plasma) and cardiac output, consequently causing a drop in systolic BP.

Late Effects (appear after 3-4 weeks):

- The decreased Na+ & Cl- in the blood vessels lowers blood vessel contractility, causing vasodilation leading to decreased BP. This will occur even with low doses. (This will be the cause of sustained decrease in BP)

- Increased Plasma Renin, which is disadvantageous, because increased renin will increase angiotensin I & II and aldosterone, ultimately increasing the blood pressure. Due to this mechanism, some patients might develop tolerance to diuretics.

{ Renin release is stimulated by blood pressure in the afferent arterioles which supply nephrons as well as sodium content in afferent arterioles so decreasing Na content in afferent arterioles will enhance the release of renin which will activate renin-angiotensin system }

- *Side Effects:*
  - The most bothersome but least serious is diuresis, meaning having to urinate a lot more than usual.
  - Metabolic side effects are the major side effects. They include hyperglycemia, hyperuricemia, and hyperlipidemia. They are dose dependent.

Thiazide diuretics

- Most commonly used diuretics.
- Effective in mild and moderate hypertension with normal renal and heart function.
- Examples:
  - Hydrochlorthiazide.
  - Chlorthalidone: It is long acting.
  - Bendrofluazide.
  - Indapamide ("Natrilex") has vasodilating effects and is lipid neutral, meaning it doesn't cause lipid abnormalities like other thiazides. It also induces regression of left ventricular hypertrophy (LVH).

Loop Diuretics

- They are needed in severe hypertension, and patients with renal insufficiency, heart failure or cirrhosis, in contrast to thiazides which would be ineffective in this case because they will not be able to reach the site of action.
- Remember that all diuretic drugs have the same antihypertensive effect.
- Very potent, causes severe diuresis. That's why they're not preferred by patients
- Furosemide: Very potent yet very short acting so it is not ideal.
- Torsemide: Free of metabolic side effects.

Potassium-Sparing Diuretics

- In contrast to the previous drugs, these drugs spare potassium from being excreted. They are useful in heart failure, renal insufficiency and cirrhosis. This is because these drugs antagonize aldosterone, which is elevated in those diseases (secondary hyperaldosteronism).
- Examples
  - Spironolactone
  - Eplerenone
  - Ameloride
  - Triamterene

Sympatholytics or Adrenergic Blockers

- Alpha Adrenergic Antagonists, alpha receptors found in blood vessels causes vasoconstriction, so by giving alpha antagonists we prevent this and the vessels stay dilated and blood pressure goes down.
  - Non selective antagonists
  - Alpha1-selective antagonists
- Beta adrenergic blockers
- Adrenergic neuron blockers
- Ganglionic blockers

There are two types of alpha receptors. Alpha1 are present in the postsynaptic membrane, alpha2 are in presynaptic membrane. Alpha2 receptors inhibit NE release from the vesicles, thus, inhibiting alpha2 receptors alone will increase blood pressure. Inhibiting alpha1 receptors alone will decrease the blood pressure, while inhibiting both causes tachycardia and increase contractility.

Non selective Alpha-Adrenergic Antagonist

- They block both α1 and α2 receptors, causing reflex tachycardia and increased contractility.
- Blockade of α2-presynaptic receptors leads to augmented release of NE leading to tachycardia and increased contractility of the heart.
- Used only for pheochromocytoma (a tumor of the adrenal medulla which secretes epinephrine and norepinephrine in large amount, causing hypertension and increasing HR and CO). Therefore, we need a drug that works on both alpha1 and alpha2 receptors.
- EXTRA: in pheochromocytoma we initially give alpha blocker to control the hypertension (even though it causes further increase in HR & CO), then later we give the patient beta blockers to control the heart rate and cardiac output.

Examples:

- Phentolamine
- Phenoxybenzamine

α1-selective Alpha-Adrenergic Antagonists

- These drugs are selective, meaning they favor α1 rather than α2 (α1 > α2). However, they are not **specific** only for α1.
- α1 blockers will lower the BP but will not cause tachycardia.
- First-dose phenomenon, similar to ACE inhibitors, a sudden drop in blood pressure that might lead to fainting and tachycardia.
- All are free of metabolic effects, but can cause drowsiness, diarrhea, postural hypotension, tachycardia, and tolerance **due to fluid retention**. Similar to short-acting vasodilators.
- Effective in moderate hypertension as well as benign prostatic hypertrophy.

Examples:

- Prazosin, Terazosin, Doxazosin.

Non selective Beta Adrenergic Blockers

They work on beta receptors which are mainly present in heart.

Antihypertensive Mechanisms:

- Decrease HR, SV, and consequently cardiac output (CO).
- Central action in the **vasomotor center**, since many of them can cross the blood brain barrier (Beta Blockers can cross the BBB).
- Decrease rennin release↓ & Inhibit NE release↓.

There are 30 different preparations found in the market including:

- Propranolol, which is lipophilic, is a prototype of these of drugs and is the oldest and most widely used nonselective β-adrenoblocker (discovered in 1957).
- Timolol: Lipophilic
- Nadolol: Long acting
- Pindolol: intrinsic sympathomimetic activity (ISA)
- Acebutolol: ISA
- Esmolol: β1 selective, and has a short half life
- Metoprolol: β1 selective
- Atenolol: β1 selective
- Betaxolol: β1 selective
- Bisoprolol: β1 selective

Intrinsic sympathomimetic activity: being able to stimulate β-adrenergic receptors (agonist effect) and to oppose the stimulating effects of catecholamines (antagonist effect) in a competitive way.

Therapeutic Effectiveness:

- Effect is not immediate
- Useful in high-rennin hypertension (they inhibit renin release).
- Monotherapy or combination with vasodilators or ACEIs.
- Hyperkinetic hearts- to calm the heart.
- Used in other cardiovascular conditions, such as ischemic heart disease (IHD) and cardiac arrhythmias.
- Ineffective in blacks, maybe due to genetic predisposition.
- Doesn't cause postural hypotension (in contrast to vasodilators, CCBs, and diuretics).

Side Effects:

- Bronchospasm, especially with the non-selective blockers, because beta2 receptors are found in the lungs and bronchi.
- Heart failure, beta receptors normally stimulate the heart muscle, so blocking these receptors can reduce the activity of the heart. That's why they are not advisable in elderly patients.
  In general, beta blockers are contraindicated in patients with heart problems.
- CNS effects like fatigue, depression, impotence ...etc.
- Impair lipid and glucose metabolism, therefore not used for treatment of hypertensive diabetics.
- Mask hypoglycemia, normally during hypoglycemia sympathetic nervous system gets activated to warn the body, producing severe hunger, increased blood pressure, and increased heart rate. Additionally, you know that beta receptors, in the liver, stimulate gluconeogenesis and glycogenolysis to elevate glucose blood levels. But, if beta receptors are blocked, the body will go into severe hypoglycemia without even noticing.
- Claudication- pain caused by too little blood flow to your leg or arm, due to blockade of beta receptors.

Norepinephrine will overly activate alpha receptors causing vasoconstriction of peripheral blood vessels, usually in upper and lower limbs leading to cold extremities, cold and cyanotic nose and ear lobes, especially in winter.

- Withdrawal syndrome due to up-regulation of these receptors. This might happen upon sudden stop of using beta blockers.
  Over-activity of sympathetic systems happens which leads to stimulation of the heart, and increase in blood pressure to levels above that of pretreatment. So beta blockers should be stopped gradually over a two to three days.