MED441
KING SAUD UNIVERSITY

Revised & Reviewed by: Abdulaziz Bahammam & Faye Wael Sendi

7&8
Treatment of hypertension

Pharmacology
TEAM 441

Objectives:

- Outline the pharmacologic classes of drugs used in treatment of hypertension
- Describe the mechanism of action , therapeutic uses & common ADRs of each class of drugs.
- Select an antihypertensive drug to treat a specific patient according to efficacy, safety, suitability & cost

HELPFUL VIDEO:

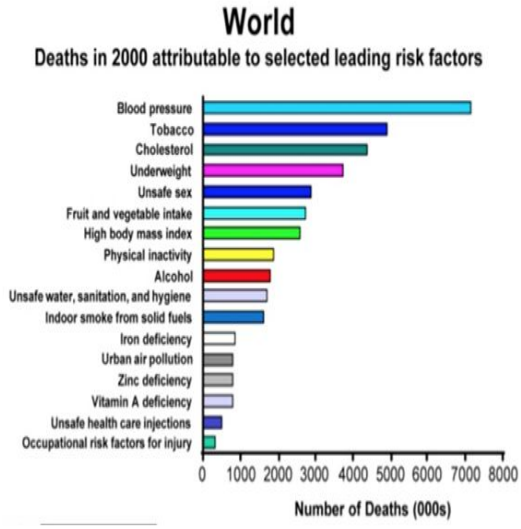
Antihypertensives

Editing file

Color index:
Important
In male's slides only
In female's slides only
Extra information
Doctors notes

Hypertension General information:

1. Prevalence: 25-30%
2. FIRST CAUSE OF DEATH WORLDWIDE
3. In majority of cases it is Symptomless (Silent killer)



The rule of halves of Hypertension:

For every 800 adults in the community:

400 are Hypertensive (Either high SBP or High DBP or both)

Of them, only 200 are diagnosed with hypertension

Of them, only 100 started treatment

Of them, only 50 are on correct drug therapy

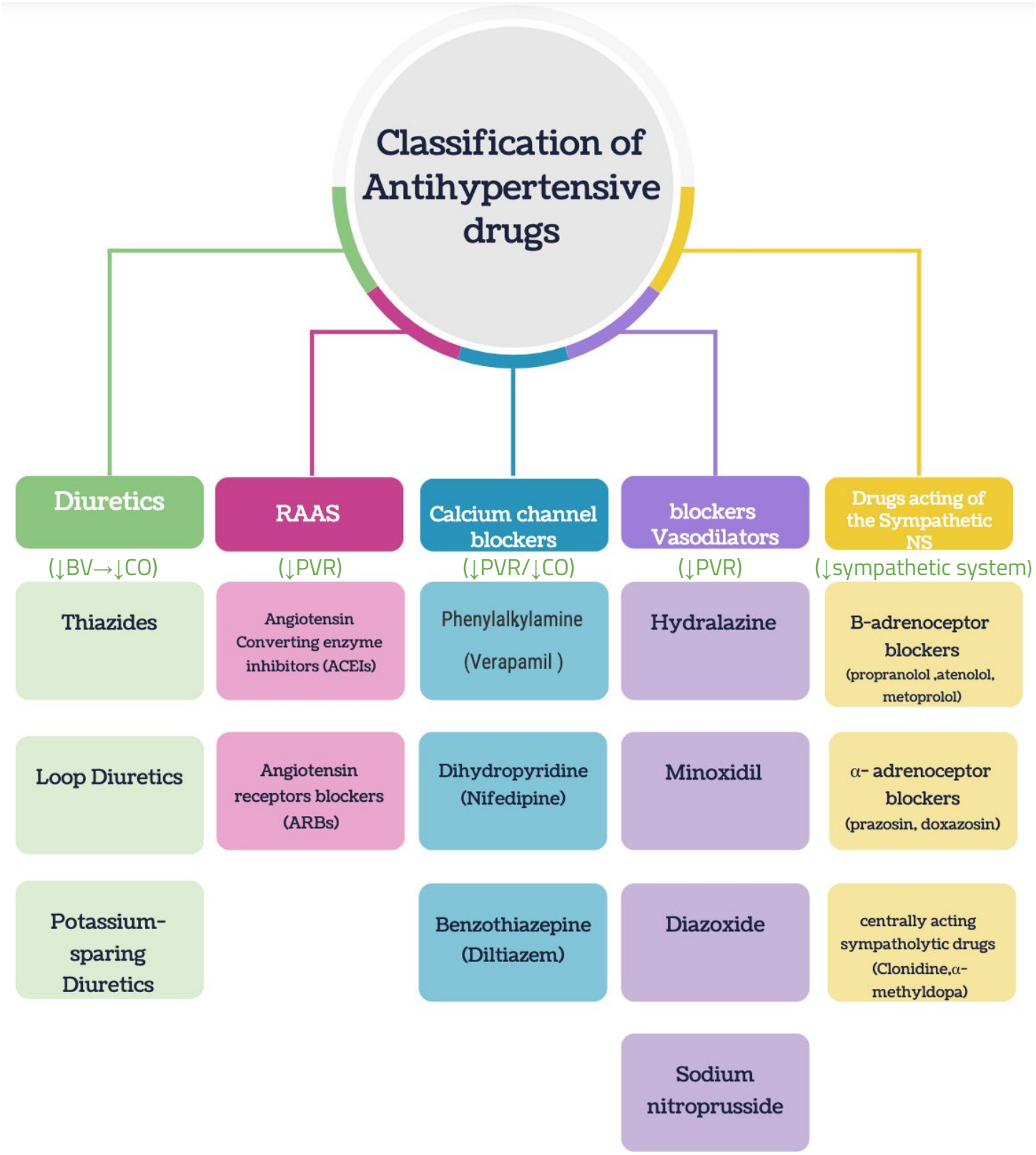
Of them, only 25 attained the goal BP

Which means : 25/400= 6% have goal BP

Summary of Robbins (thanks 439)

- Hypertension is a common disorder affecting 25% of the population; it is a major risk factor for atherosclerosis, congestive heart failure, and renal failure.
- Hypertension may be primary (idiopathic) or less commonly secondary to an identifiable underlying condition. In close to 95% of cases hypertension is idiopathic or "essential." The remaining cases (secondary hypertension) are due to primary renal disease, renal artery narrowing (renovascular hypertension), or adrenal disorders.
- Essential hypertension represents 95% of cases and is a complex, multifactorial disorder, involving both environmental influences and genetic polymorphisms that may influence sodium resorption, aldosterone pathways, the adrenergic nervous system, and the renin-angiotensin system.
- Hypertension occasionally is caused by single-gene disorders or is secondary to diseases of the renal arteries, kidneys, adrenal glands, or other endocrine organs.

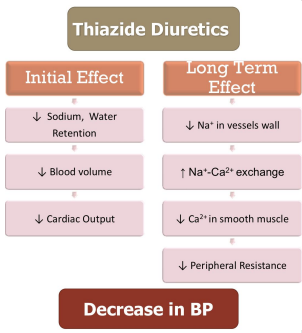
Classification of antihypertensive drugs



BV= Blood volume
CO= Cardiac output
PVR= Peripheral Vascular Resistance

Remember:
Blood pressure (BP)= Cardiac output (CO) × Peripheral Vascular Resistance (PVR)

1.Diuretics

<table>
<tr><th>Drug</th><th>Thiazides
(K losing Diuretic)</th><th>Loop Diuretics
(K losing Diuretic)</th><th>Potassium-sparing Diuretics</th></tr>
<tr><td>Example</td><td>Hydrochlorothiazide
Chlorthalidone
(less potent than Loop diuretics, but longer duration of action)</td><td>Furosemide
more potent diuresis but a smaller decrease in PVR
(Shorter duration of action)</td><td>Spironolactone</td></tr>
<tr><td rowspan="2">Uses</td><td>Routine management of hypertension (because of their effect on PVR and long duration of action)</td><td>Hypertension with renal impairment (Thiazides do not enhance the excretion of Na and water when kidney function is impaired) or heart failure (because they are very potent)</td><td>Minimal effect on lowering BP (less effect on PVR)</td></tr>
<tr><td colspan="3">Mild to moderate Hypertension (not very potent HT drugs)
Diuretics are very useful Anti HT drugs and should be the initial treatment of HT
(تأثيرها متوسط لكن جدا مفيدة وتعتبر الخيار الأول)</td></tr>
<tr><td>M.O.A
(of thiazides)</td><td colspan="3">Initially→ they reduce sodium and water retention
→decrease blood volume → decrease cardiac output
→Decrease blood pressure
Long term→↓ Na^+ in vessel wall
→ ↑Na^+-Ca^{2+} exchange (Na^+ in/ Ca^{2+}out)
→↓ Ca^{2+} in smooth muscle cell → ↓ Peripheral resistance
→Decrease blood pressure
 

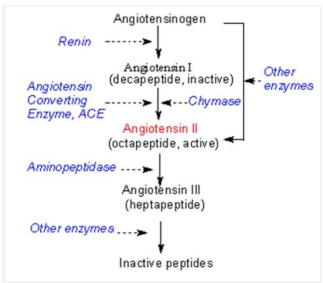
The initial diuresis lasts 4-6 weeks and then is replaced by a decrease in PVR</td></tr>
<tr><td></td><td colspan="3">According to ALLHAT trial, chlorthalidone is superior to an ACE inhibitor, a calcium channel blocker and an alpha1-adrenergic antagonist in preventing one or more cardiovascular event.</td></tr>
<tr><td>Contraindications</td><td colspan="3">• Gout (diuretics reduce the excretion of uric acid)
• Hypokalemia (K losing diuretics “they decrease the level of potassium”)
• Hyperkalemia (K sparing diuretics “they increase the level of potassium”)</td></tr>
</table>

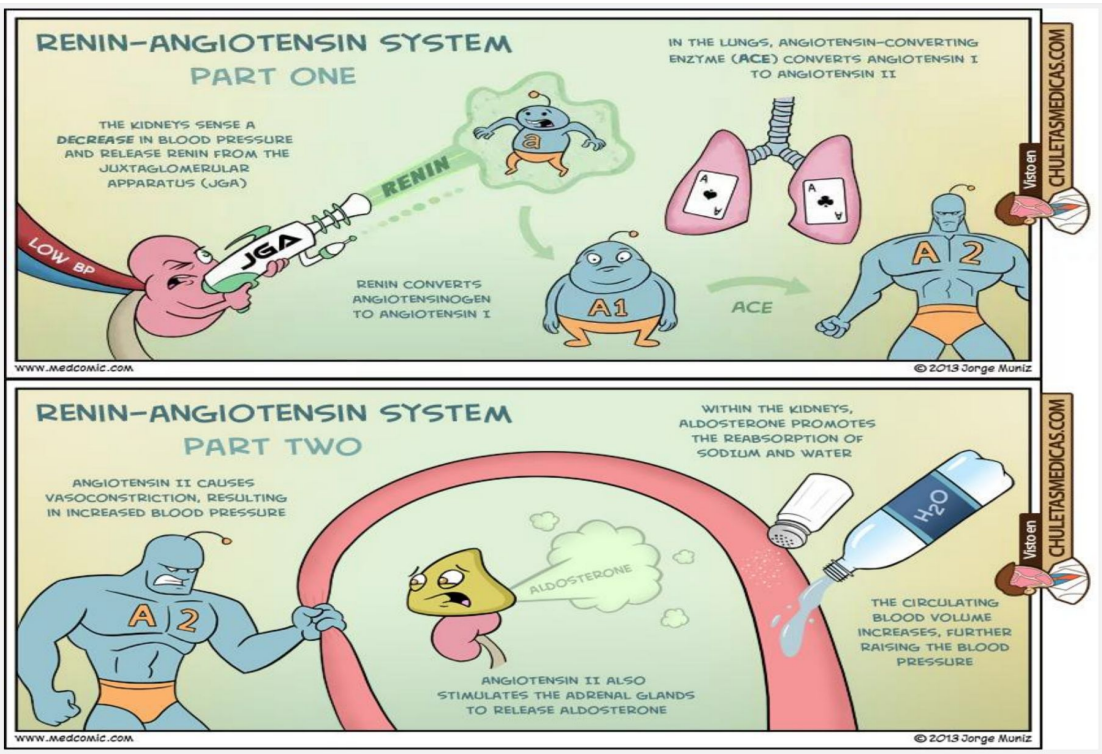
2.Drugs acting on the renin angiotensin aldosterone (RAAS) system:

a. Angiotensin Converting enzyme inhibitors (ACEIs)	
Drug	**Captopril, Lisinopril, Enalapril, Ramipril** Captopril is a sulfhydryl derivative→more toxic/more ADRs
M.O.A	• ACE inhibitors decrease angiotensin II (vasoconstrictor) and increase bradykinin levels (vasodilator) by preventing its degradation by ACE , so the antihypertensive effect results primarily from vasodilatation with little change in CO. • A fall in aldosterone production may also contribute. • Particularly effective when hypertension results from **excess renin production** (renovascular hypertension, white & young) "not very useful in black/old patients because they have less renin"
P.K	• Polar, excreted in urine. • Do not cross BBB • Have a long half life & given once daily. • Rapidly absorbed from GIT after oral administration. • Food reduce their bioavailability. • It takes 2-4 weeks to notice the full antihypertensive effect of ACEIs. "slow onset" • **Enalapril & Ramipril** are prodrugs, converted to the active metabolite in the liver. • **Enalaprilat** is the active metabolite of Enalapril, can be given by I.V. route in hypertensive emergency.
Uses	• Treatment of **essential hypertension.** • Hypertension in patient with **diabetes, chronic renal disease** (reduces the progression of damage to the kidneys) **and ischemic heart disease** (reduces the incidence of cerebrovascular event)**.** • Treatment of **Heart failure.**
Contraindication	• During the second and third trimesters of **Pregnancy** due to the risk of: fetal hypotension, anuria, renal failure & malformations. • **Renal artery stenosis.** "Chronic renal diseases يختلف عن" • **Potassium-sparing diuretics.** "Because ACEI increase the level of K by inhibiting aldosterone release so using them together causes hyperkalemia" • Patients using **NSAIDs**. " they block the synthesis of PGs so cause Na^+ and water retention therefore nullify the anti HT effect of ACEI"
ADRs	• **Dry Cough** "raised bradykinin" • **Acute renal failure, especially in patients with renal artery stenosis.** • **Severe hypotension in hypovolemic patients** • **Renal agenesis/failure in the fetus resulting in oligohydramnios.** "reduced amniotic fluid because its volume relies on the urine produced by the fetus" • **Angioneurotic edema** (swelling in the nose, tongue, throat & larynx) -caused by raised bradykinin levels "more in black patients". • **First dose effect** (remarkable fall in BP, depends on the level of renin in patients "if the level is high the hypotensive effect will be high") (Given at bedtime - start with small dose and increase the dose gradually) "to decrease the effect" • **Adverse effects Specific to captopril** "because of sulfhydryl group" ➔ skin rash, fever, dysgeusia (loss of taste),Proteinuria and neutropenia.

2.Drugs acting on the renin angiotensin aldosterone (RAAS) system:

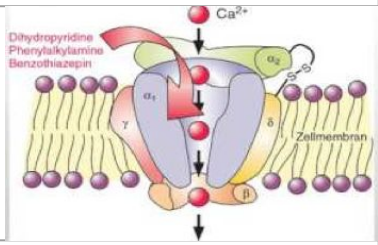
cont.

b. Angiotensin receptors blockers (ARBs)		
Drugs	**Losartan**	**Valsartan**
P.K	-Has a Potent active metabolite. -Effective Orally once daily. -long half life. -Do not cross BBB.	No active metabolite
M.O.A	- **selective** block of AT1 receptors. - **No effect** on bradykinin, **no** cough, **no** angioedema. "advantage" - Produce more **complete inhibition** of angiotensin than ACE inhibitors because there are other enzymes **(not only ACE)** that can generate angiotensin	
ADRs	Same as ACEI except dry cough & angioneurotic edema. "No bradykinin accumulation" It is more expensive than ACEI	
Contraindication	Same contraindications as ACEI.	



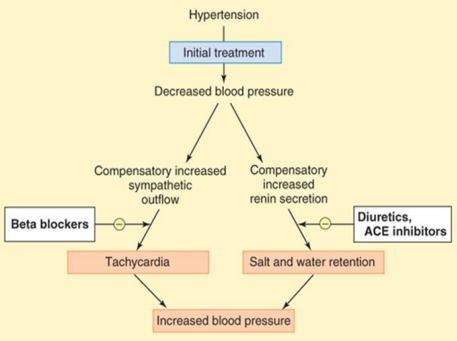
3.Calcium channel blockers

Very Nice Drugs

Class	Phenylalkylamine	Dihydropyridine	Benzothiazepine
Drug	**Verapamil**	**Nifedipine**	**Diltiazem**
Feature	Act mainly on myocardium	Act more on smooth muscle	Has intermediate effect
M.O.A	Block the influx of calcium through calcium channels resulting in: 1- Peripheral vasodilatation. 2- Decrease cardiac contractility. 		
P.K	given orally (onset: 0.5-2h) and I.V. injection (onset 1-3min), well absorbed. ● **Verapamil & diltiazem** have active metabolites, nifedipine has not. ● **Verapamil** and **nifedipine** are highly bound to plasma proteins (more than 90%) while **diltiazem** is less Bound (70-80%). ● Sustained-release preparations can permit once-daily dosing "longer DOA"		
Uses	Treatment of chronic hypertension. especially for **Nifedipine**. ● **Nicardipine** can be given by I.V. route & used in hypertensive Emergency. ● Sustained-release formulations are preferred for the treatment of hypertension due to the short half- life of CCBs		
ADRs	● Headache, Flushing, Hypotension. ● **Nifedipine:** reflex tachycardia."less effect on myocardium" ● **Verapamil & Diltiazem:** peripheral edema (ankle edema) "they dilate arterioles not venules, blood will pool inside the arterioles so it can't pass easily to the venules (they are not dilated) the blood will accumulate in the arterioles and capillaries, this will lead to leaking of fluid in the surrounding tissue and will result in Edema" ● **Verapamil:** constipation		

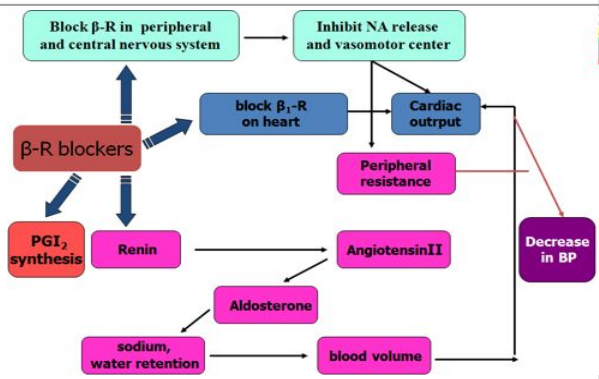
4.Vasodilators

- Classified into arterial, venous or mixed vasodilators .
- Once Vasodilators are administered,fall in BP produced will activate the sympathetic system & the RAAS. "We need to combine them with other drugs (beta blockers and diuretics/ACEI), check the image"



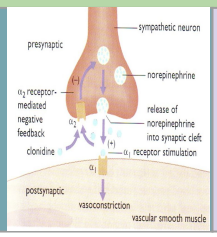
Drugs	Hydralazine	Minoxidil	Diazoxide	Sodium nitroprusside
Site of action	Artiodilator			Arterio & venodilator
M.O.A	Release of nitric oxide (NO)	Opening of potassium channels *in smooth muscle membranes by minoxidil sulfate (Active metabolite)*	Opening of potassium channels.	Release of nitric oxide (NO)
Administration	Oral "Routine management"		Rapid I.V "Emergency"	I.V infusion "Emergency"
Therapeutic uses	Moderate-severe hypertension		Hypertensive emergency	
	In combination with diuretics & β-blockers "to prevent tachycardia/ Na^+ water retention"			
	Hypertensive pregnant woman But not the first-line.	Baldness	Treat hypoglycemia due to Insulinoma (Tumor of the pancreas that increase the secretion of insulin)	Severe heart failure
ADRs	Hypotension, reflex tachycardia, palpitation, angina, salt and water retention (edema). "If not combined with diuretics/ β-blockers"			Severe hypotension
Specific ADRs	Lupus erythematosus like syndrome	Hypertrichosis excess hair growth thus contraindicated in females	Inhibit insulin release from β cells of the pancreas causing hyperglycemia. contraindicated in diabetics	-Methemoglobin during Infusion -Cyanide toxicity -Thiocyanate toxicity -Headache, palpitations which disappear when infusion is stopped. Cyanide accumulation cause cyanide poisoning (metabolic acidosis, arrhythmias, severe hypotension and death) "use is very limited" Cyanide inhibits oxidative phosphorylation.

5.Sympatholytic drugs

a. β-Adrenoceptor blockers			
Drugs	**Propranolol**	**Atenolol**	**Metoprolol**
Type	Non selective "Contradicted with asthma patients"	Selective beta 1 blocker	
Clinical uses	• Used in mild to moderate hypertension In severe cases used in combination with other drugs • Therapeutic response may take up to two weeks • Evidence support their use in patient with coronary heart disease "reduces O2 consumption/ prevents CVS events/ improves survival/ inhibit development of cardiac arrhythmia" • Shouldn't be the primary agent for primary prevention but are effective as add-on therapy "increase incidence of stroke" • When discontinued should be withdrawn gradually. "receptors are upregulated"		
M.O.A	1- Decrease cardiac output 2- Inhibit renin release 3- Centrally mechanism by inhibition of NE release from adrenergic nerves		
ADRs	• Aggravate peripheral arterial disease • hypoglycemia (blocks receptors on the liver) • increase triglycerides • erectile dysfunction	• bradycardia • hypotension	
	• mask hypoglycemia symptoms in diabetics (don't use with diabetics patients) • Fatigue		

5.Sympatholytic drugs

b. α- Adrenoceptor blockers		
Drugs	**Prazosin**	**Doxazosin**
P.K.	short- acting	preferred for its long half life
M.O.A	• Block α- receptors in arterioles and venules • Reduce blood pressure by decreasing both afterload & preload	
Clinical uses	treatment of hypertension in patients with benign prostatic hypertrophy	
ADRs	causes first dose hypotension (given in gradual dose),and postural hypotension	-

c. Centrally acting sympatholytic drugs			
Drugs	**Clonidine** (Direct α2-agonist)		**α- methyldopa** (Indirect α2 agonist, converted to methyl norepinephrine)
M.O.A	Diminish central adrenergic outflow from the CNS & increase parasympathetic outflow to the heart. This leads to reduced total peripheral resistance and decrease BP.		
Uses	• hypertension with renal disease (it does not decrease renal outflow or glomerular filtration) • Resistance hypertension		α -Methyldopa is the first line treatment of hypertension in pregnancy
ADRs	Abrupt Sudden withdrawal of clonidine can lead to rebound hypertension."down regulation of receptor"		-

Clinical case

Osman a 51-year-old man (95Kg weight, 176cm tall) is referred for further evaluation of his BP. He is a computer engineer and has a past history of type 2 diabetes for 5 years and high BP for 12 years. His somatic complaints include fatigue and dry mouth. He has no known history of hypertension target-organ damage, and his medications are listed in the accompanying table . He has no remarkable family history other than hypertension in both parents.
His examination was otherwise unremarkable (including normal heart sounds and no peripheral edema), aside from mild arteriolar narrowing in the fundus. His seated BP was 156/90 mmHg and 158/90 mmHg in the right arm (similar to the left arm), with a regular heart rate of 70 beats/min. His BP did not change on standing. His urinalysis showed an unremarkable dipstick evaluation. The patient was suspected as having drug- resistant hypertension*.
*"A condition when the patient is prescribed at least 3 anti HT drugs including diuretics but still not responding to the anti HT therapy"

Drug name	Dose	Frequency
Hydrochlorothiazide	25mg	Daily
Valsartan	160mg	Daily
Diltiazem (long acting)	300mg	Daily
Clonidine	0.2mg	Twice Daily
Metoprolol (long acting)	100mg	Daily
Simvastatin	40mg	Daily
Fenofibrate	145mg	Daily
Metformin	1g	Twice Daily

List as many reasons as you can, Why Osman failed to respond to Anti-Hypertensive Therapy?
1-Secondary hypertension.
2- Smoking
3-Obesity
4-Drug induced e.g NSAIDs

The seated BP of Osman was 156/90, what are the target BP values for treatment of hypertensive patients?
< 140/90 mm Hg

JNC VII CLASSIFICATION	SYSTOLIC BLOOD PRESSURE (SBP)		DIASTOLIC BLOOD PRESSURE (DBP)
LOW**	<90	or	<60
NORMAL	<120	and	<80
PREHYPERTENSION	120 – 139	or	80 – 89
HIGH: STAGE 1 HYPERTENSION	140 – 159	or	90 – 99
HIGH: STAGE 2 HYPERTENSION	≥160	or	≥100

What stage of hypertension is Osman?
Stage 1

Osman is diabetic, what are the target BP values for Osman?
< 130/80 mmHg for diabetic patients

Osman has no history of hypertension- target organ damage. Which organs are usually affected adversely by persistent high BP?
Heart(MI…) / Kidneys (kidney failure)/ Brain (stroke)/ Retina(blindness)

Osman is 95 kg big. Is this weight proper for his length (176 cm)?
No, he is overweight.

If Osman has to reduce his weight, what other lifestyle modification should he do?
Weight loss, Sodium reduction, Physical activity, Smoking cessation(smoking increases the stiffness of blood vessels) , DASH plan(Dietary Approaches to Stop Hypertension), Complete abstinence of alcohol (alcohol activates RAAS and reduces the release of NO, a vasodilator, thus increases the BP).

Osman was prescribed hydrochlorothiazide & Valsartan. What is the rationale for combining hydrochlorothiazide and Valsartan?
Hydrochlorothiazide is a diuretic thus it enhances Na and water excretion, so the body tries to compensate to maintain Na by releasing aldosterone leading to retention of Na, an increase in blood pressure and reducing anti HT effect. While when administering Valsartan it inhibits the release of aldosterone, thus enhancing the therapeutic effect of each other.
+Hydrochlorothiazide enhances the excretion of K while valsartan causes its retention, thus balancing the ADRs of each other.

Osman was prescribed Hydrochlorothiazide & Diltiazem. What is the benefit of combining Hydrochlorothiazide and Diltiazem?
Reduce peripheral edema caused by Diltiazem.

The BP did not change on standing. What is your conclusion?
No postural hypotension (not using alpha blockers).

The BP of Osman was almost the same in both arms.What does this imply?
Not suffering from arteriosclerosis.

Could the "White coat phenomenon" be the cause for Osman's high blood pressure readings? (In a Turkish study involving 438 patients, 43% were found to be white coat hypertensives (high pulse rate)
No, his HR is regular "70".

Is the concomitant prescribing of clonidine, diltiazem and metoprolol to Osman wise?
No, because they all depress the myocardium and decrease CO, so they can result in severe depression of myocardium and heart failure.

Could the failure of control of Osman BP be due to secondary drug-induced effects?
No, he wasn't using a drug that increases BP.

Which drugs elevate BP?
"The image"

Could Osman be misdiagnosed? And the high BP is due to secondary disease causes ? No (investigation)

Which secondary diseases cause elevation of BP?
Cushing syndrome/ Pheochromocytoma/ Coarctation of the Aorta/ Renal artery disease/ Pyelonephritis/ Primary hyperaldosteronism.

Why do we use a combination of drugs for treatment of HT?
1-Decrease individual dose from drug thus decreasing ADRs
2-Some drugs induce a compensatory mechanism
3-Moderate anti HT effect of some drugs so we use combination to get a stronger effect.

Could the somatic complaints (fatigue and dry mouth) indicate the adherence of the patient to medication regimen and which drugs cause these symptoms?
Yes this can strongly indicate the usage of the drugs, fatigue is caused by β-blockers and dryness of mouth is caused by diuretics.

What suggestions do you have for Osman's treatment modification in order to attain BP goals?
1-Control lifestyle (reduce weight, exercise, diet, reduce Na intake)
2-Consider chlorthalidone instead of hydrochlorothiazide. *"Twice as potent"*
3-Consider an aldosterone antagonist
4-Consider sustained release Nifedipine instead of diltiazem *"very potent anti HT"*

Compelling contraindications of antihypertensive drugs *"summary"*

	Heart Failure	Pregnancy	Hypokalemia	Bradycardia	Asthma	Hyperkalemia	Gout
Diuretics			+ "K losing"			+ "K sparing"	+ "Increase Uric acid level"
ACEI Angiotensin converting enzyme inhibitor		+				+ "Increases level of K"	
CCB Ca channel blockers				+ "Verapamil and Diltiazem"*			
ß-blockers				+	+		
ARB Angiotensin receptor blockers		+				+	

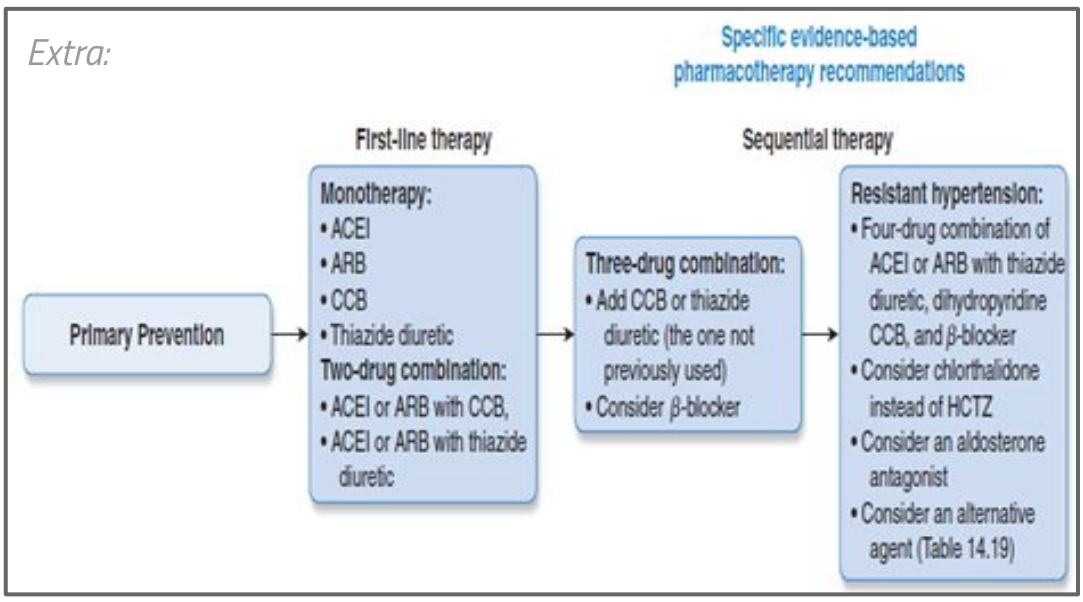
*They can cause heart failure, but Nifedipine can be used because it does not affect the myocardium.

Antihypertensive drugs in pregnancy 🤰 mnemonic "He Likes My Neonate":
Hydralazine, **L**abetalol, α-**M**ethyl Dopa, **N**ifedipine.
(Thank you Norah Alawlah !)

Antihypertensive drugs in emergency mnemonic "SEND *the patient to the ER*":
Sodium nitroprusside, **E**nalaprilat, **N**icardipine, **D**iazoxide.
(Thank you Abdullah Alyamani !)

ADRs of ACE inhibitors:
C : cough
A : angioneurotic edema
P : proteinuria
T : taste change (dysgeusia)
O : orthostatic hypotension
P : pregnancy (contraindicated)
R : rash
I : increased K+
L : leukopenia
(Thank you Norah Alawlah !)

Extra:



SAQs:

Q1: Which drugs can be used in the case of a hypertensive pregnant women?

Q2: What is the mechanism of action of Enalapril?

Click here!

A1:
Hydralazine, **L**abetalol, α-**M**ethyl Dopa, **N**ifedipine. (mnemonic: He Likes My Neonate)

A2:
It is an angiotensin converting enzyme inhibitor "ACEI" thus it decreases the level of angiotensin II (vasoconstrictor) and increase bradykinin levels (vasodilator).

Test yourself
From our amazing Qbank team

Good luck!

Pharmacology
TEAM 441

Team leaders

Alanoud Alhaider **Faisal Alhussaini**

Subleader

Leen Alhadlaq

NOTE TAKER

Arwa Almobeirek

TEAM MEMBERS

Ayah Sayed	Noyer Awad	Abdullah Alghamdi
Dania Alhudaithi	Raaoum Jabor	Abdullah Alyamani
Ghada Alharbi	Rahaf Alrayes	Ahmed Khoja
Ghadah Fahad	Rand Aldajany	Alwaleed Bin Shaya
Joud Alangari	Reema Alrashedi	Bassam Alhubaysh
Jumana Alqahtani	**Refal Manhi**	Mansour Aldhalaan
Norah Alqazlan	Sarah Alotaibi	Meshal Alqahtani
Nourah Alkhudiri	Shahad Almuqbil	Talal Alanazy

Contact us:
pharmateam441@gmail.com

MED441
KING SAUD UNIVERSITY