PHARMACOLOGY
TEAM 439

MED439
KING SAUD UNIVERSITY

Anti-hypertensive drugs

Objectives:

- Identify factors that control blood pressure.
- Outline the pharmacological classes of drug used in treatment of hypertension.
- Describe mechanism of action, therapeutic use and common adverse effects and contraindications of each class of drugs.
- Select the suitable antihypertensive drug to treat a specific patient according to efficacy, safety and cost.

Important

In male and female slides

Only in male slides

Only in female slides

Extra information

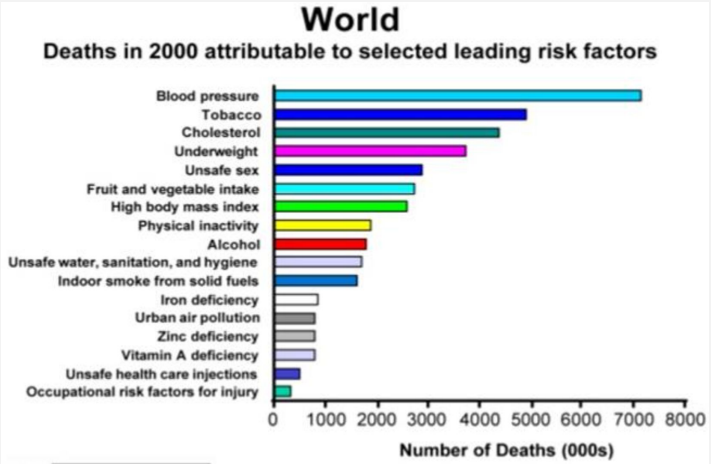
helpful video

Editing file

Hypertension

General information:

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



Summary of Robbins

- 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.

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 HT

Of them, 100 started treatment

Of them, only 50 are on correct drug

Of them, only 25 attained the goal BP

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

Classification of Antihypertensive drugs

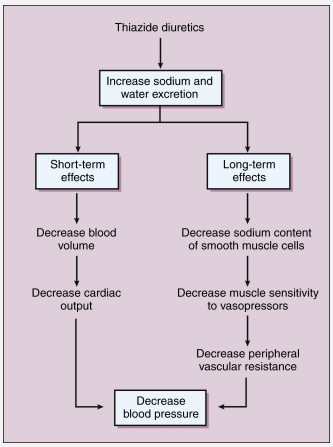
- Diuretics
- Drugs acting of the Sympathetic NS
- RAAS (Drugs acting on the renin-angiotensin-aldosterone system)
- Calcium channel blockers
- Vasodilators

Diuretics

Drug	Thiazides	Loop Diuretics	Potassium-sparing Diuretics
Example	Hydrochlorothiazide Chlorothiazide chlorthalidone	Furosemide more potent diuresis but a smaller decrease in PVR (Pulse volume Recording).	Spironolactone
Uses	Their action may differ between the short and long use (see the figure at the corner)	-Hypertension with **renal impairment** -Manage symptoms of **heart failure** and edema.	Minimal effect on lowering BP but used in combination with loop diuretics and thiazides to reduce potassium loss induced by these diuretics (438 Pharmacology team)
	Mild to moderate Hypertension		
M.O.A	The initial diuresis lasts 4-6 weeks and then replaced by a decrease in the PVR (Peripheral vascular resistance).		

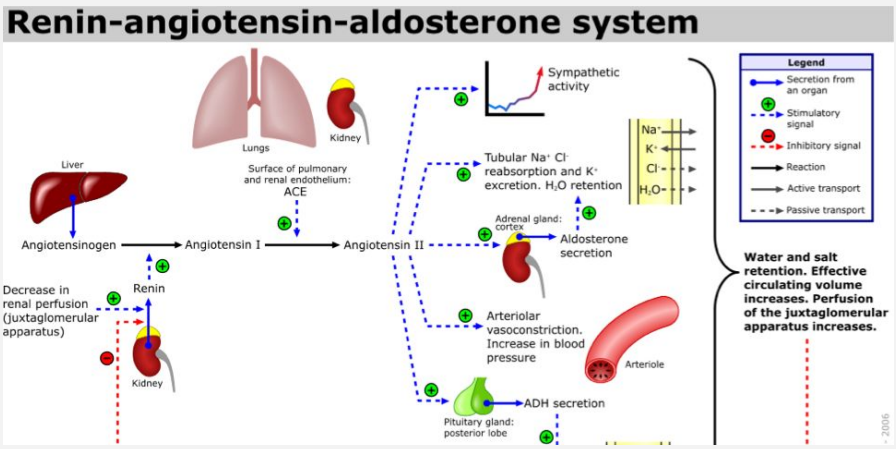
Extra information:

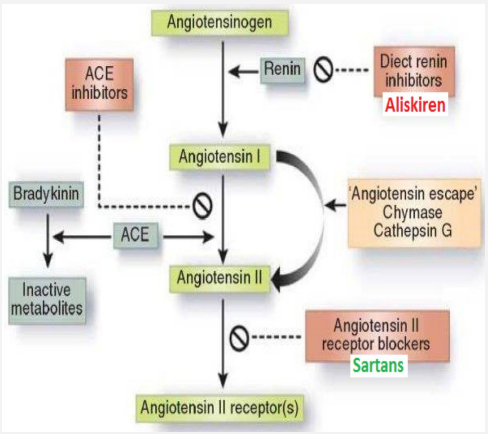
For all classes of diuretics, the initial mechanism of action is based upon **decreasing blood volume**, which ultimately leads to decreased blood pressure. Diuretics increase the volume of urine excreted. Most diuretic agents are inhibitors of renal ion transporters that decrease the reabsorption of Na+ at different sites in the nephron.
While diuretics are most commonly used for management of excessive fluid retention (edema), many agents within this class are prescribed for non-diuretic indications or for systemic effects in addition to their actions on the kidney. Examples, which are discussed above, include use of thiazides in hypertension



Physiological Mechanisms for Control of Blood Pressure (Extra from med438)

Renin angiotensin aldosterone (RAAS) system:





1- Juxtaglomerular cells in the kidney sense a decrease in blood perfusion "due to either decrease pressure or volume" and release **renin** (enzyme) into the circulation.
2- At the same time, the liver secretes **angiotensinogen** (hepatic hormone) into the circulation.
3- **Renin** cleaves angiotensinogen into **angiotensin I**, a precursor for **angiotensin II.**
4- Angiotensin I then reaches the lung through pulmonary circulation "through the pulmonary artery", where it is converted into **angiotensin II** by the action of **Angiotensin-Converting Enzyme "ACE"** (note that more than one enzyme can accomplish this conversion, but **ACE** is the most prominent).

Effects:
1- Angiotensin II acts on posterior pituitary gland to secrete ADH, increasing water retention.
2- Angiotensin II acts on the adrenal cortex and stimulates secretion of aldosterone, increasing sodium and water retention.
3- Angiotensin II causes constriction of the blood vessels, increasing preload and afterload.

Other important notes: ACE is responsible for the metabolism of **Bradykinin** (Causes vasodilation and potentially angioneurotic edema when increased, and has a cardioprotective effect by limiting the rate of myocardial remodeling, it is the reason why **ACE inhibitors** have this effect in treating heart failure)

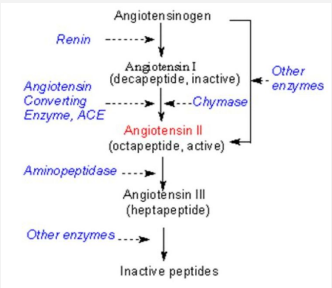
Baroreceptor Reflex:

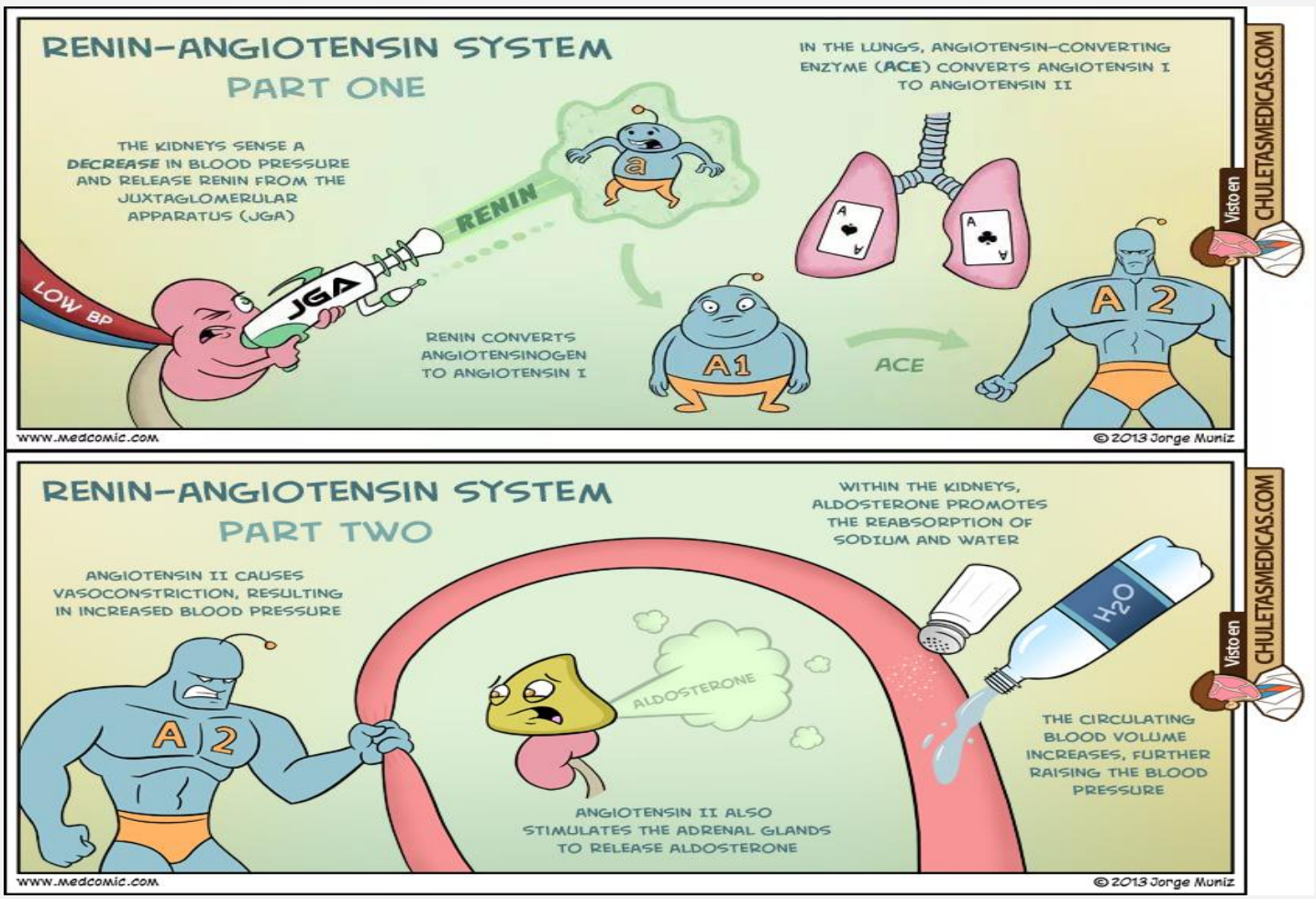
Mediated by:
1- Carotid and Aortic Baroreceptors (fire signals in response to stretch of vessels)
2- Sympathetic Neurons stretching from CNS
Increased blood pressure: When there is a stretching of the blood vessels (such as in an increased blood pressure), there is an increased firing rate through parasympathetic nerves from the baroreceptors to a regulatory region in the brain (NTS), NTS then responds to the baroreceptor signal by secretion of ACh to the heart, causing decreased heart rate (potential bradykardia), and a decreased cardiac output, blood pressure then returns to normal.
Decreased blood pressure: there is less stretch of vessels due to decreased blood pressure, therefore there will be less firing from baroreceptors, this will activate the NTS in the brain to send sympathetic signals to the heart to increase heart rate **(potential tachycardia)** and an increase cardiac output, this can happen when a person is in an upright posture, there will be pooling of the blood in the veins of the lower regions due to gravitational pull, and less venous return and vessels of the heart will be less stretched as a result. Orthostatic hypotension occurs when this reflex fails.

Drug acting on the renin angiotensin aldosterone (RAAS) system:

1-Angiotensin Converting enzyme inhibitors (ACEIs)	
Drugs	Captopril, Lisinopril, Enalapril, **Ramipril** you should know that **Ramipril** is ACE **inhibitor**.
M.O.A	● Particularly effective when hypertension results from **excess renin production** (renovascular hypertension, white & young) ● 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.
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. -**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 **chronic renal disease, ischemic heart disease , diabetes.** -Treatment of **Heart failure.**
ADRs	**-Dry Cough** **-Acute renal failure, especially in patients with renal artery stenosis.** **-Severe hypotension in hypovolemic patients** **-Renal angensia/ failure in the fetus resulting in oligohydramnios.** **-Angioneurotic edema** (swelling in nose, tongue, throat & larynx) -caused by inhibition of bradykinin metabolism which accumulate in bronchial mucosa. **-First dose effect (severe hypotension)** (Given at bed time - start with small dose and increase the dose gradually) **-Adverse effects Specific to captopril** ➔ skin rash, fever, dysgeusia (loss of taste),Proteinuria and neutropenia. These effects are due to a **sulfhydryl group** in the molecule of captopril.
Contraindication	-During the second and third trimesters of **Pregnancy** due to the risk of; fetal hypotension, anuria, renal failure & malformations. -**Renal artery stenosis.** -**Potassium-sparing diuretics.** -Patients using **NSAIDs** . (because NSAIDs reduce their hypotensive effects by blocking bradykinin-mediated vasodilatation)

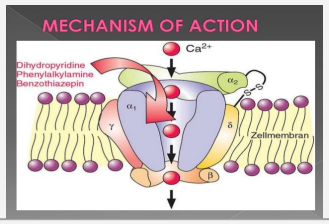
2-Angiotensin receptors blockers (ARBs)

Drugs	Losartan	Valsartan	Candesartan Telmisartan
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. - 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.		
Contrain dication	Same contraindications as ACEI .		



Very Nice Drugs

Calcium channel blockers

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.		
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	peripheral edema (ankle edema) - **constipation**	Tachycardia	Peripheral edema (ankle edema)
	Headache , Flushing , Hypotension		

Vasodilator

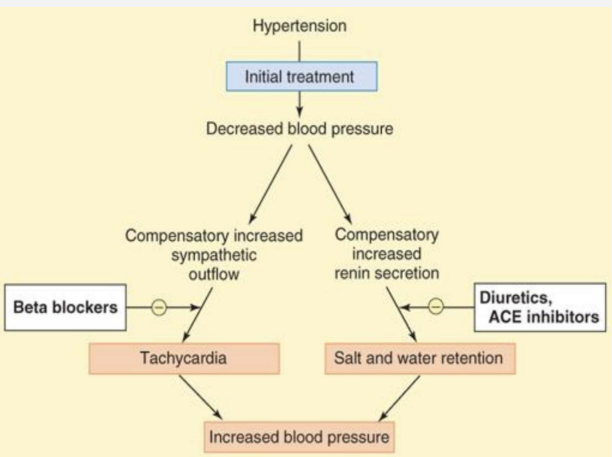
- **Classified into arterial, venous or mixed vasodilators**
- Once Vasodilator are administered,fall in BP produced will activate the sympathetic system & the RAAS

Extra:

Vasodilators

- Direct-acting smooth muscle relaxants: hydralazine ,minoxidil.
- Vasodilators produce relaxation of vascular smooth muscle, which decreases resistance and therefore decreases blood pressure.
- These agents produce reflex stimulation of the heart, resulting in the competing symptoms of increased myocardial contractility, heart rate, and oxygen consumption. These actions may prompt angina pectoris, myocardial infarction, or cardiac failure in predisposed individuals.
- Vasodilators also increase plasma renin concentration, resulting in sodium and water retention. These undesirable side effects can be blocked by concomitant use of a diuretic and a beta-blocker.

Dr Khaled M Hasan



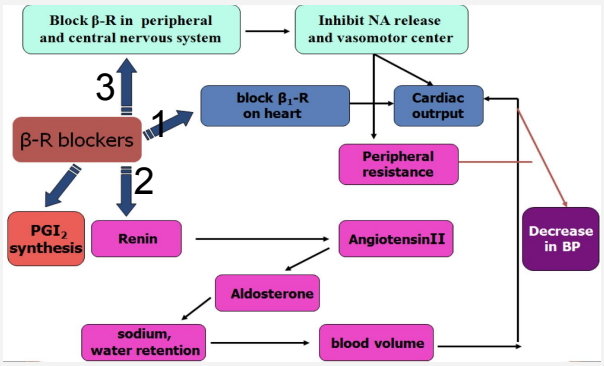
Vasodilators

Drug	Hydralazine	Minoxidil	Diazoxide	Sodium nitroprusside
Site of action	Artiodilator			Arterio & venodilator
M.O.A	Direct (Opening of potassium channels)	Opening of potassium channels in smooth muscle membranes by minoxidil sulfate (Active metabolite)	Opening of potassium channels.	Release of nitric oxide (NO)
Administration	Oral		**Rapid I.V**	**I.V infusion**
Uses	Moderate-severe hypertension		Hypertensive emergency	
Uses In combination with a diuretic & first-line. β-blockers	Hypertensive pregnant woman But not the first-line.	Correction of baldness, since it causes Hypertrichosis (the growth of body hair)	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).			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)

Team438: Sodium nitroprusside ADR mechanism: enters RBCs and steals an electron from Hb, resulting in Methemoglobin (Fe +3), the reduced drug then becomes unstable and disintegrates into cyanide, which is metabolized into thiocyanate.

Sympatholytic drugs

B-adrenoceptor blockers

Drugs	propranolol	atenolol	metoprolol
Type	Non selective	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 Because it cause bradycardia -when discontinued should be withdrawn gradually		
M.O.A	1- **decrease cardiac output** 2- **inhibit renin release** 3- Centrally mechanism by inhibition of NE release from adrenergic nerves -presynaptic inhibition		
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		

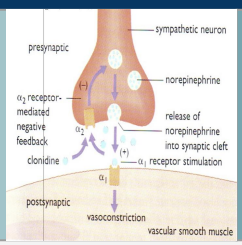
Contraindication with asthma patients

Sympatholytic drugs

α- adrenoceptor blockers

Drugs	prazosin	doxazosin
P.K	Short acting	Prefered for its long half life
M.O.A	-blocks alpha 1 receptors in arterioles and venules - reducing blood pressure by decreasing preload and afterload	
Clinical uses	treatment of hypertension in patients with benign prostatic hypertrophy	
ADRs	causes first dose hypotension (given in gradual dose),and postural hypotension ممكن تجيب في الخيارات prazosin or **α- adrenoceptor blockers**	-

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.	-

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.

Osman's medications

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- abnormalities in hormones e.g aldosterone
2- smoking
3-obesity
4- pheochromocytoma
5-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

What are the classes of HT?

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?

-Kidney -Brain -Heart

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

If Osman has to reduce his weight, what other lifestyle modification should he do?

Weight loss, Sodium reduction, Physical activity, Smoking cessation, DASH plan

Dietary Approaches to Stop Hypertension (DASH) is an eating plan to lower or control high blood pressure.

The BP was the same on both arms, what does this imply?

No vascular disease

The BP did not change while standing, what is your conclusion?

Is the concomitant prescribing of clonidine, diltiazem and metoprolol to Osman wise?

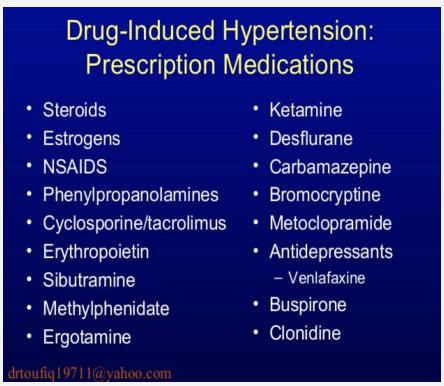
Osman was prescribed Thiazide & Diltiazem. What is the benefit of combining Thiazide and Diltiazem?

Reduce peripheral edema

Osman was prescribed hydrochlorthiazide & Valsartan. What is the rational for combining hydrochlorthiazide and Valsartan?

Hydrochlorothiazide induce the loss of K , which oppose the Hyperkalemia caused by valsartan

Which drugs elevate BP?



Could the failure of control of Osman BP be due to secondary drug-induced effects? (inappropriate combination)

Yes

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))

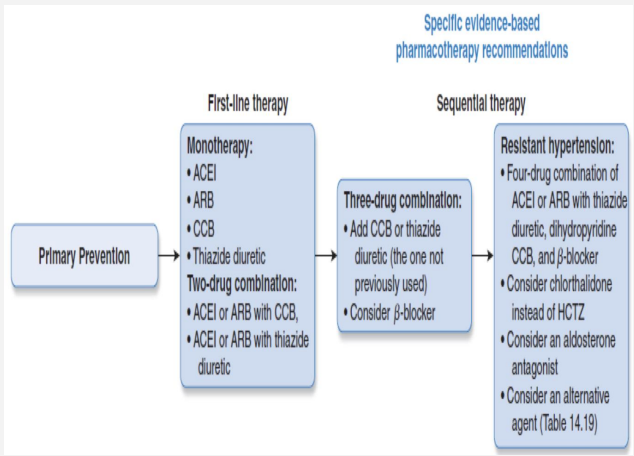
No. Pulse rate is normal.

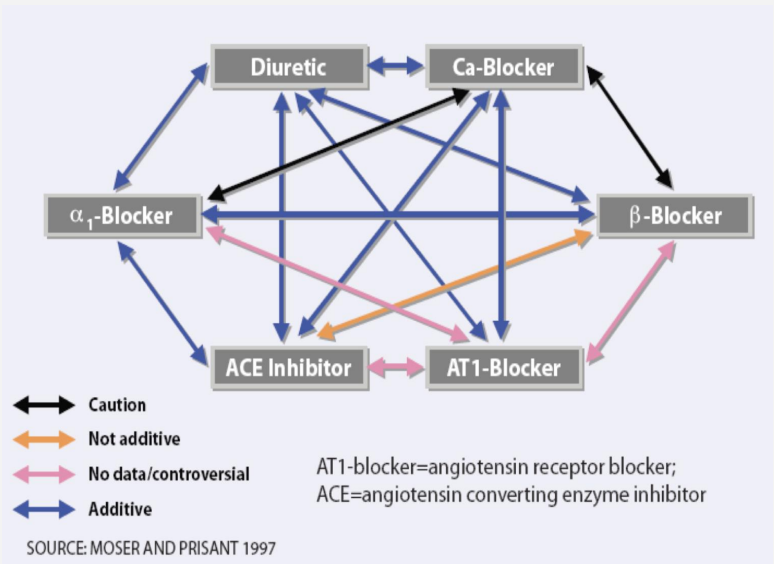
Thanks to 438 Pharmacology team

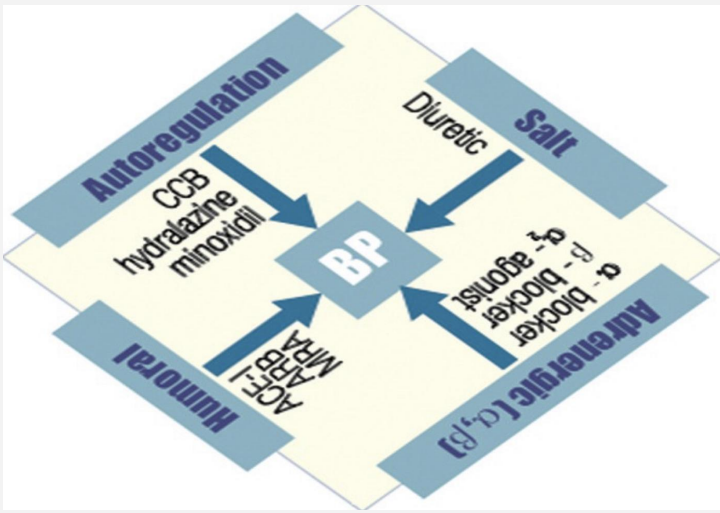
Compelling contraindications of antihypertensive drugs

	HF	Pregnancy	Hypokalemia	Bradycardia	Asthma	Hyperkalemia	Gout
Diuretics	+					+	
ACEI	+	+	+				
CCB	+						
ß-blockers	Selective			+	+		
ARB	+	+	+				

HF: Heart failure
ACEI:Angiotensin converting enzyme inhibitor
ARB:Angiotensin receptor blockers
CCP: Cyclic citrullinated peptide







MCQ

1-Which one of these drugs has ADR lupus erythematosus			
A- Minoxidil	**B- Hydralazine**	**C-Diazoxide**	**D-**Sodium nitroprusside

2-Which one of these drugs contraindicated in diabetics patients			
A-Hydralazine	**B-Verapamil**	**C-Diltiazem**	**D-Diazoxide**

3- Which one of the following drugs it's effective particularly when hypertension results from excess renin production			
A- Diazoxide	**B- Sodium nitroprusside**	**C- Ramipril**	**D-Verapamil**

4- How would Diuretics decrease blood pressure?			
A- Act on the CNS	**B- Decrease blood volume**	**C- Block beta receptors**	**D- Causes vasodilation**

5-which one of the following drugs first dose can causes hypotension?			
A-doxazosin	**B-prazosin**	**C-**α-methyldopa	**D-atenolol**

6-Which one of these drugs contraindicated in patients using NSAIDs			
A-losartan	**B-minoxidil**	**C-verapamil**	**D-captopril**

Answers

1	2	3	4	5	6	7	8
B	D	C	B	B	D		

SAQ

Q1) what is the mechanism of action of minoxidil?

Q2)List the ADRS of calcium channel blockers?

Q3) What is the result of block of calcium influx through calcium channel?

Q4) What is the mechanism of action of Losartan?

Q5) Enumerate the three classes of Diuretics and mention one example of each.

Q6) what is the Adverse effects of selective beta 1 blocker ?

Answers

A1) opening of potassium channels in smooth muscle membrane by minoxidil sulfate?

A2) Headache,flushing,hypotension

A3) -Peripheral vasodilatation-Decrease cardiac contractility

A4) It is Angiotensin receptors blockers and it is selective block of AT1 receptors.

A5) 1) Thiazides: Ch;orothiazide, 2) Loop Diuretics: Furosemide, 3) Potassium-sparing Diuretics: Spironolactone

A6) bradycardia , hypotension , mask hypoglycemia symptoms in diabetics , fatigue

GOOD LUCK!

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