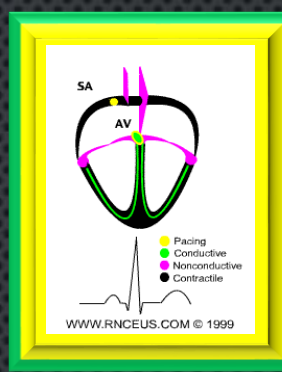


# ANTIHYPERTENSIVE DRUGS

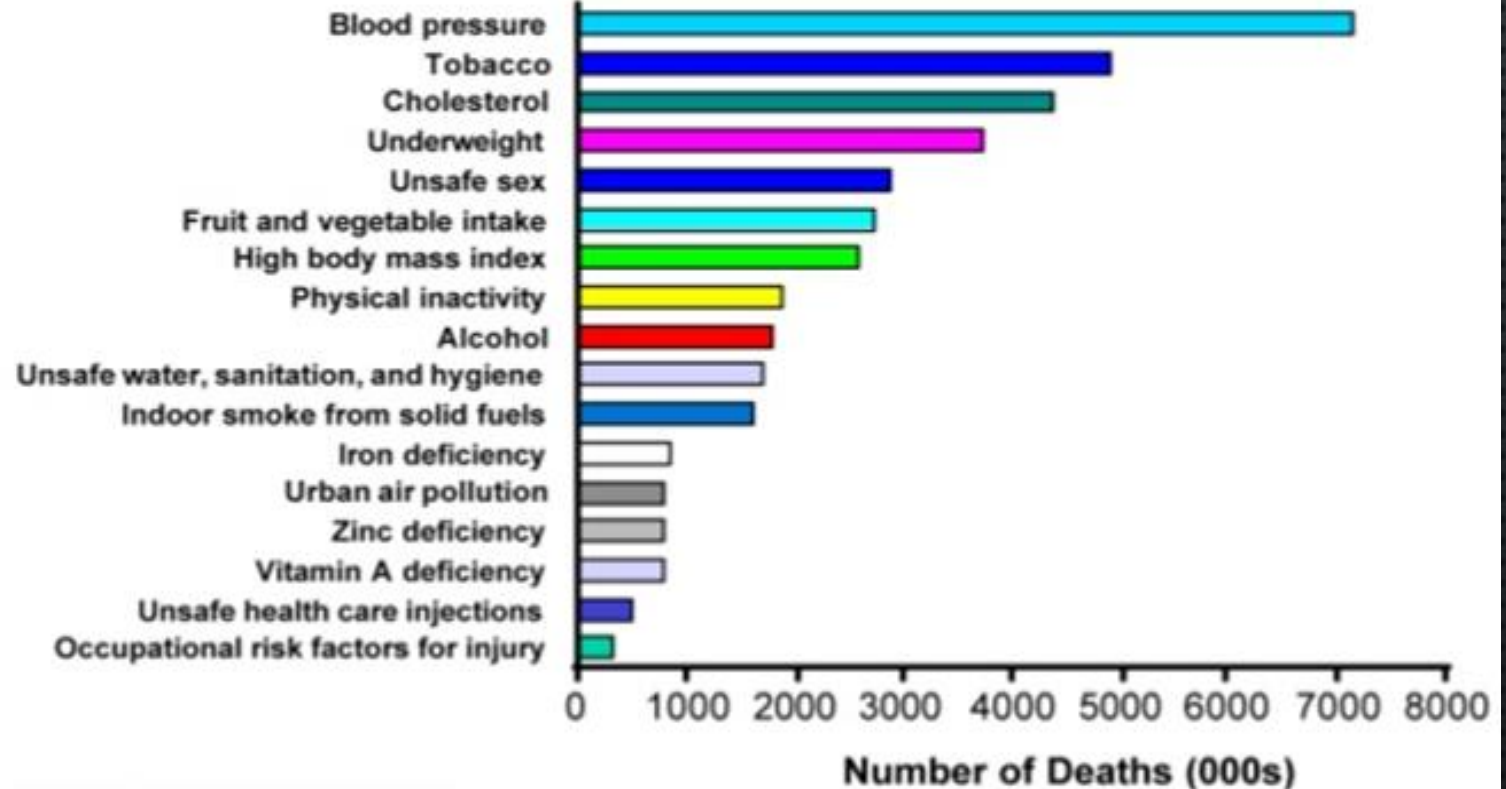


Prevalence 25-30%

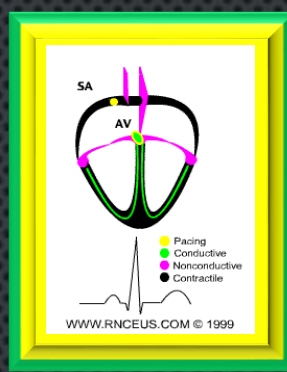
In majority of cases, it is symptomless "Silent Killer"

Number One cause of death

## World Deaths in 2000 attributable to selected leading risk factors



# THE RULE OF HALVES OF HYPERTENSION



- For every 800 adults in the community
- 400 are hypertensive (either  $\uparrow$  SBP or  $\uparrow$  DBP or both)
- Of them only 200 are diagnosed HT
- Of them only 100 are started on treatment
- Of them only 50 are on correct drug
- Of them in only 25 the goal B.P. is attained
- Means  $25 \div 400 = 6\%$  only have goal BP

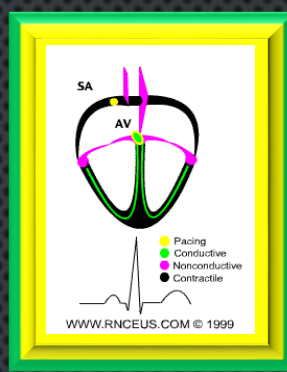
# ANTIHYPERTENSIVE DRUGS

## ILOS

Outline the pharmacologic classes of drugs used in treatment of hypertension

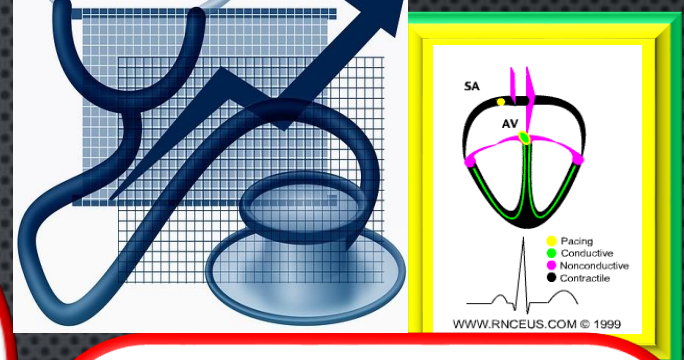
Describe the mechanism of action , therapeutic uses & common adverse effects of each class of drugs

Select an antihypertensive drug to treat a specific patient according to efficacy, safety, suitability & cost



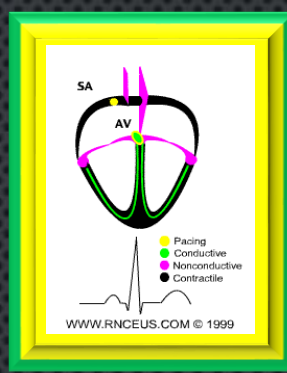
# CLINICAL CASE

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.

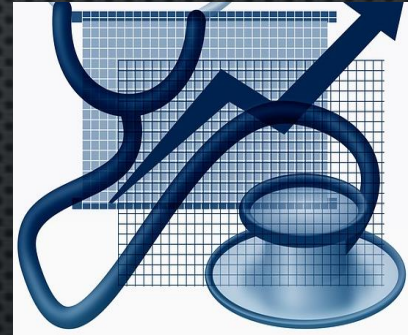


Name	Dose	Frequency
Hydrochlorothiazide	25mg	Daily
Valsartan	160mg	Daily
Diltiazem, long-acting	300mg	Daily
Clonidine	0.2mg	Twice daily
Metoprolol, long acting	100mg	daily
Simvastatin	40mg	Daily
Fenofibrate	145mg	Daily
Metformin	1g	Twice daily

## CLINICAL CASE



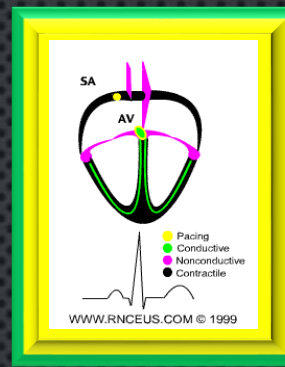
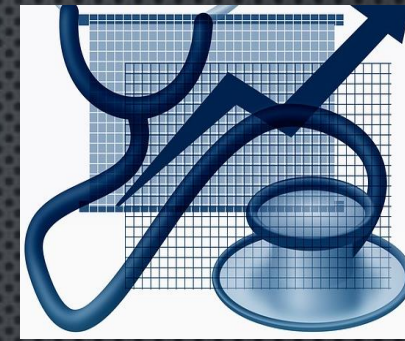
LIST AS MANY REASONS AS YOU CAN, WHY  
OSMAN FAILED TO RESPOND TO  
ANTIHYPERTENSIVE THERAPY?



# CLINICAL CASE

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

What stage of hypertension is Osman?



Target BP

<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

Osman is diabetic, what are the target BP values for Osman?

Diabetes melitus

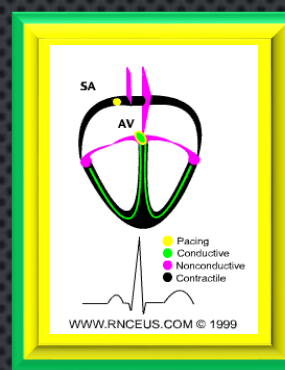
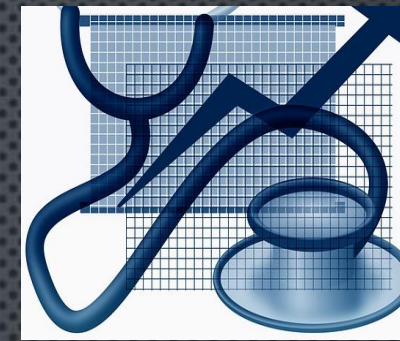
<130/80 mm Hg

# CLINICAL CASE

Osman has no history of hypertension-target organ damage. What are organs affected adversely by persistent high BP?

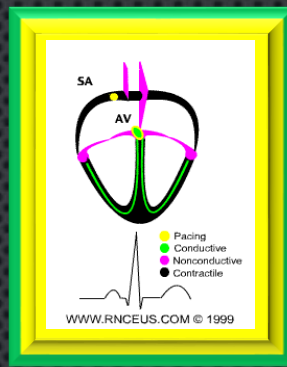
Osman is 95kg big. Is this weight proper for his length(176cm)?

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



Medscape®		www.medscape.com
Modification	Reoommendation	Approx SBP (mmHg) Reduotion
Weight loss	BMI 18.5–24.9	5–20 mmHg/10-kg weight loss
DASH plan	<ul style="list-style-type: none"> <li>• Increase fruit, vegetables</li> <li>• Consume low-fat dairy with reduced saturated and total fat</li> </ul>	8–14 mmHg
Sodium reduction	Limit to 2.4 g/day	2–8 mmHg
Physical activity	Aerobic exercise or brisk walking at least 30 min/day 5 times weekly	4–9 mmHg
Moderation of alcohol intake	Limit to no more than 2 drinks/day for men. Two drinks = <ul style="list-style-type: none"> <li>• 1-oz or 30-mL ethanol</li> <li>• 24-oz beer</li> <li>• 10-oz wine</li> <li>• 3-oz 80 proof whiskey</li> </ul> Limit to no more than 1 drink/day for women and lighter persons	2–4 mmHg
Smoking cessation		

# ANTIHYPERTENSIVE DRUGS



## CLASSIFICATION

1-Diuretics

2-Drugs acting on the renin-angiotensin-aldosterone system

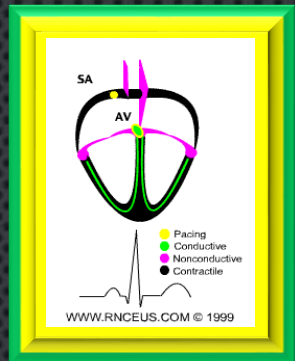
3-Calcium channel blockers

4-Vasodilators

5-Drugs acting on sympathetic nervous system



# ANTIHYPERTENSIVE DRUGS



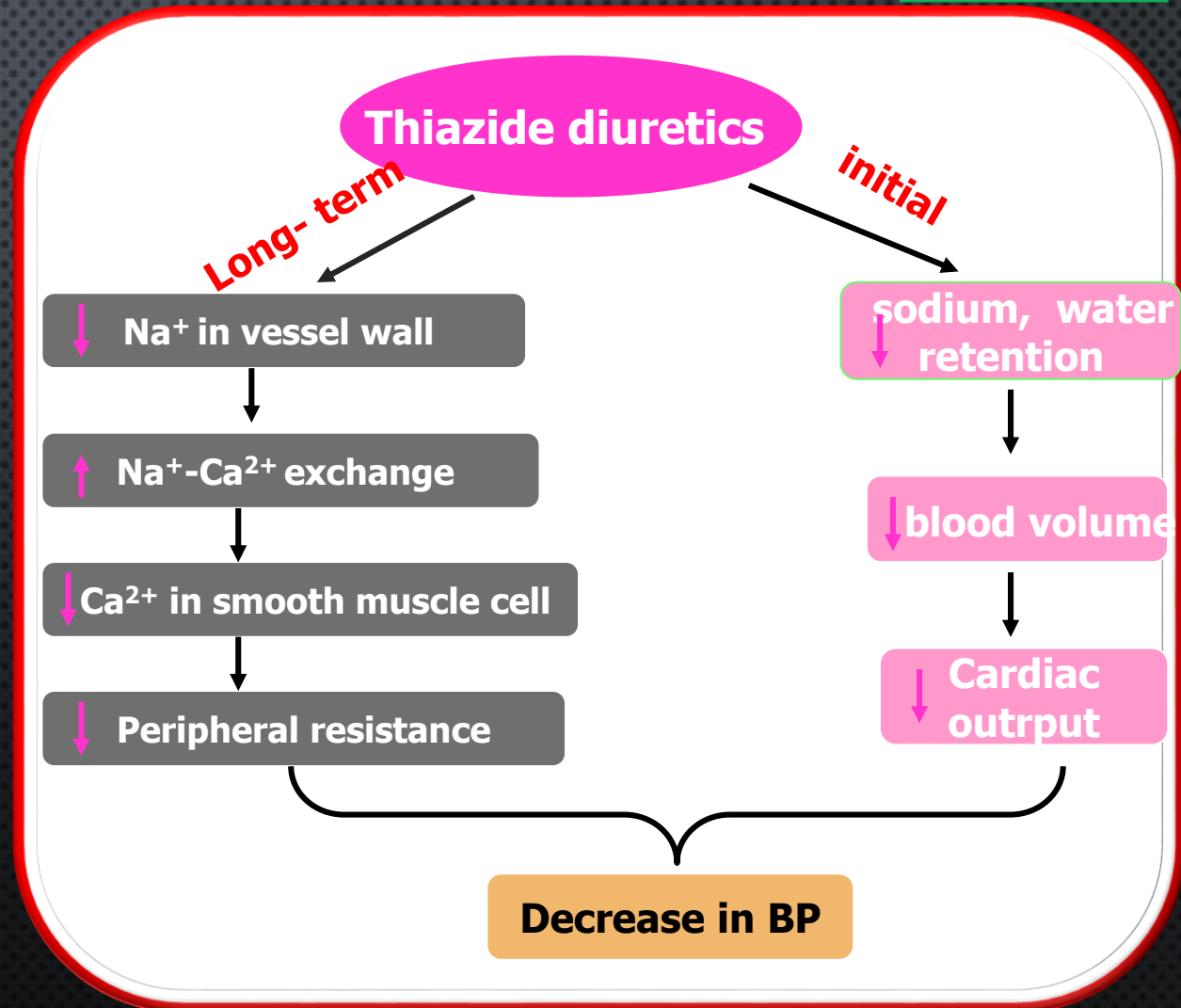
## DIURETICS



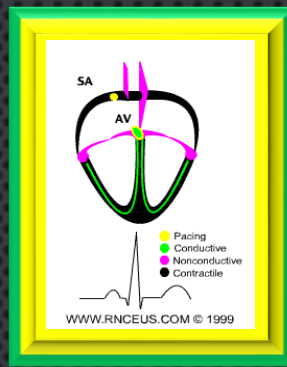
Hydrochlorothiazide , chlorthalidone & furosemide

## MECHANISM OF ACTION

The initial diuresis lasts 4-6 weeks and then replaced by a decrease in PVR



# ANTIHYPERTENSIVE DRUGS



Loop diuretics produce more potent diuresis but a smaller decrease in PVR

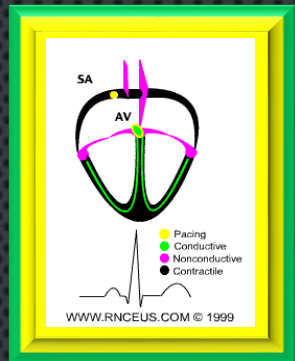
Loop diuretics are useful in hypertensive patients with either renal impairment, or heart failure

Potassium- sparing diuretics have minimal effect on lowering BP

Diuretics may be adequate in mild to moderate hypertension

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 CVD events.

# ANTIHYPERTENSIVE DRUGS



ii- Drugs acting on the renin- angiotensin - aldosterone system

## 1- ANGIOTENSIN-CONVERTING ENZYME INHIBITORS (ACEI)

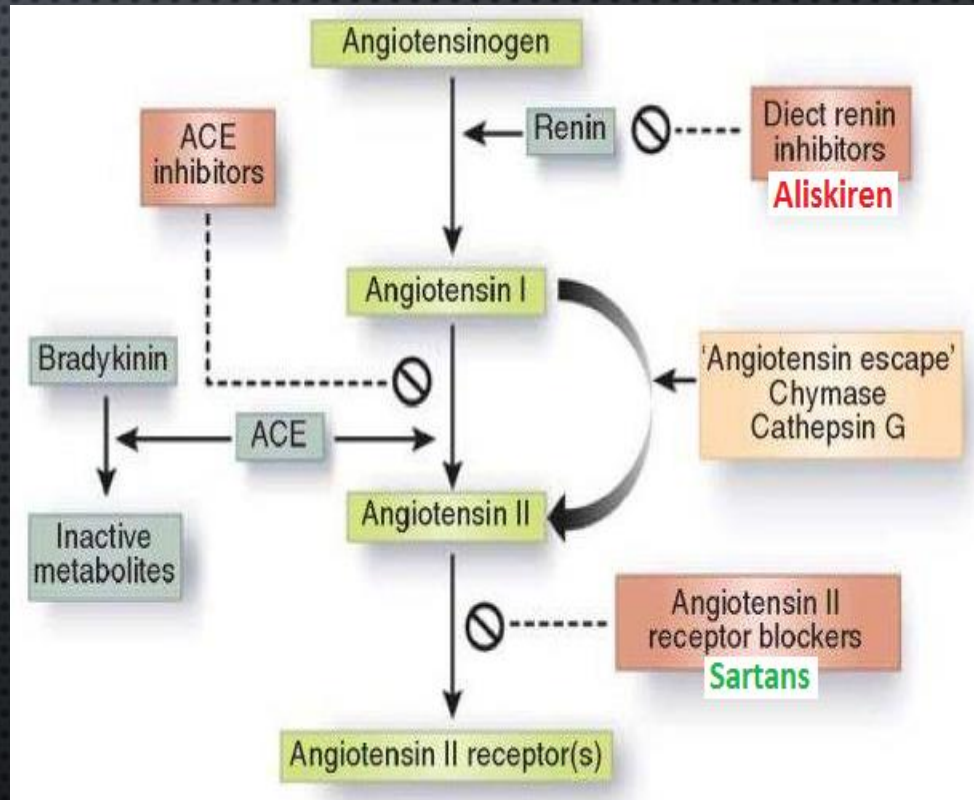
Captopril

Lisinopril

Enalapril

Ramipril

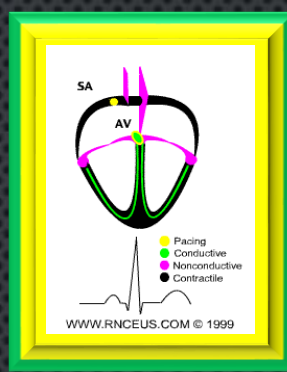
## 2- ANGIOTENSIN RECEPTORS BLOCKERS



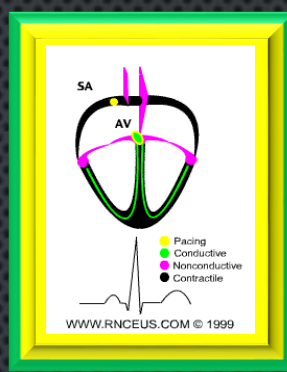
# ANTIHYPERTENSIVE DRUGS

## 1- ANGIOTENSIN-CONVERTING ENZYME INHIBITORS (ACEI)

Particularly effective when hypertension results from excess renin production (renovascular hypertension, white & young)



# 1- ANGIOTENSIN-CONVERTING ENZYME INHIBITORS



## PHARMACOKINETICS

Polar, excreted in urine

Do not cross BBB

Have a long half-life & given once daily

Enalapril & ramipril are prodrugs

Rapidly absorbed from GIT after oral administration

Food reduces their bioavailability

It takes 2-4 weeks to see the full antihypertensive effect of ACEIs

Enalaprilat is the active metabolite of enalapril given by i.v. route in hypertensive emergency

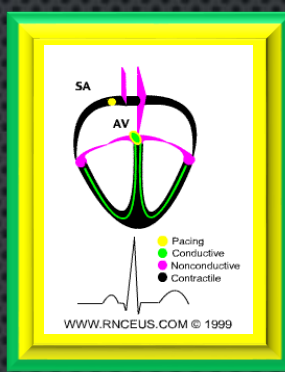
# 1- ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

## CLINICAL USES

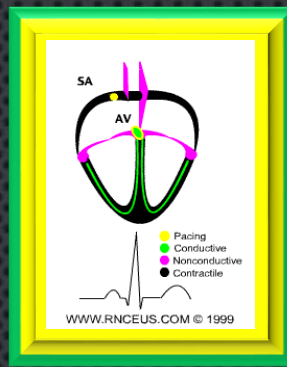
1-Treatment of essential hypertension

2-Hypertension in patients with chronic renal disease, ischemic heart disease, diabetes

3-Treatment of heart failure



# 1- ANGIOTENSIN-CONVERTING ENZYME INHIBITORS



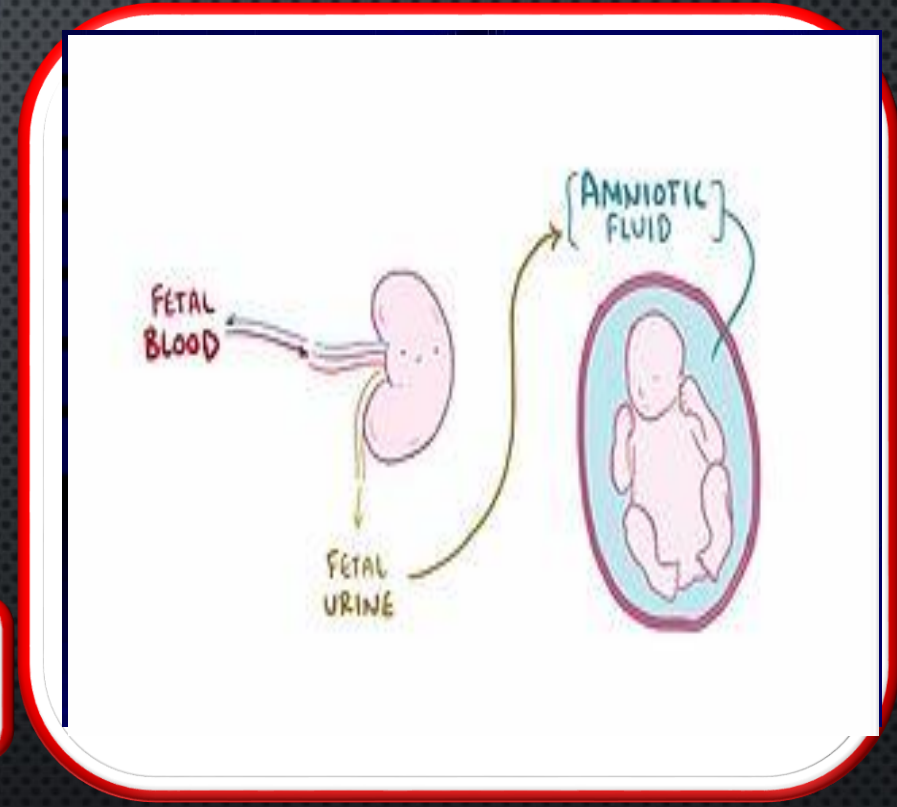
**ADRS**

Dry cough

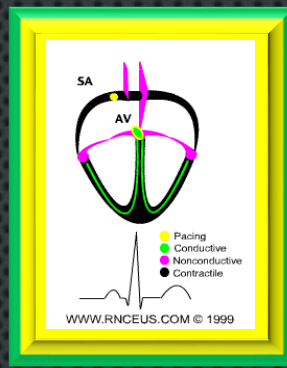
Acute renal failure, especially in patients with renal artery stenosis

Severe hypotension in hypovolemic patients

Cause renal agenesis/failure in the fetus, resulting in oligohydramnios



# 1- ANGIOTENSIN-CONVERTING ENZYME INHIBITORS



## ADRS

Angioneurotic edema, swelling in the nose, throat, tongue, larynx

First dose effect

## ADRS SPECIFIC TO CAPTOPRIL

Skin rash, fever

Dysgeusia

Proteinuria and neutropenia





# 1- ANGIOTENSIN-CONVERTING ENZYME INHIBITORS

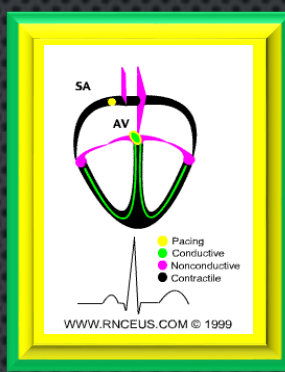
## CONTRAINDICATIONS

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

NSAIDs



# 2-ANGIOTENSIN RECEPTORS BLOCKERS

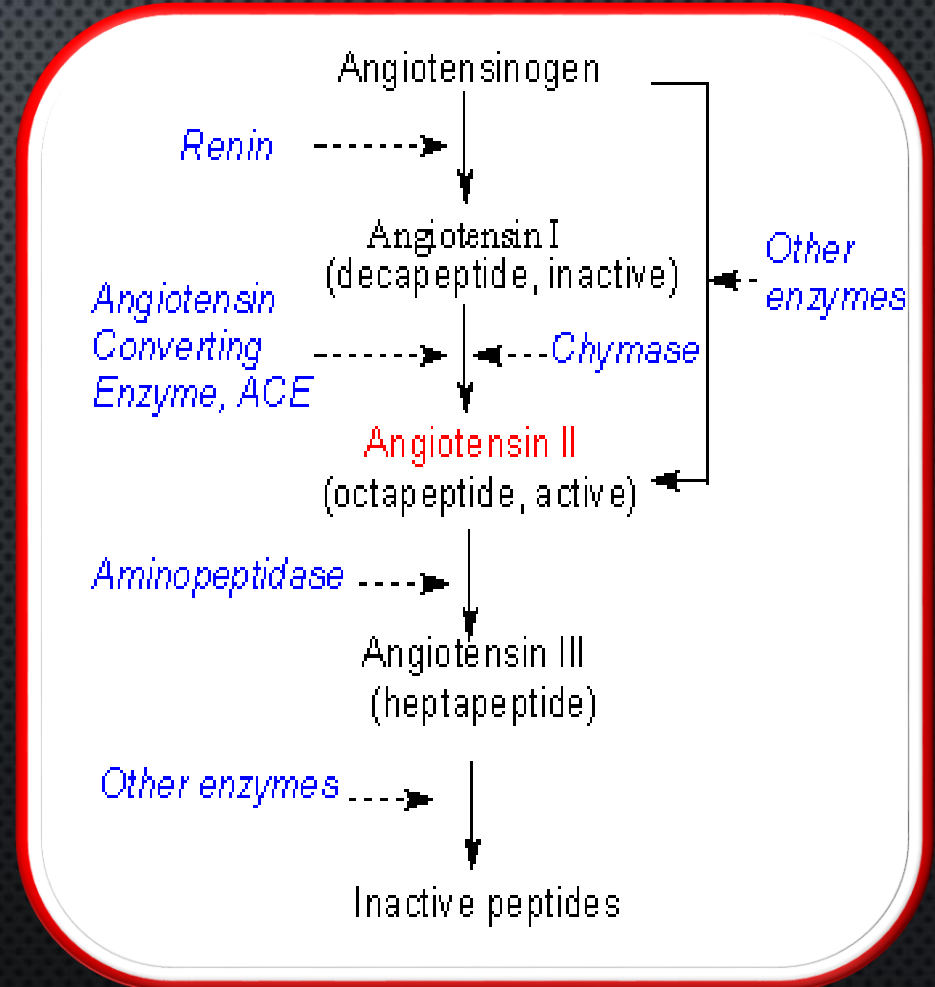
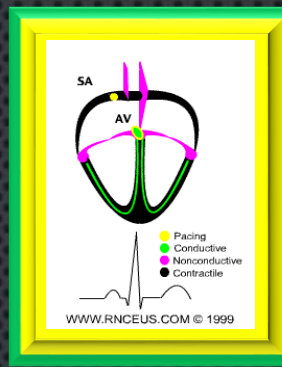
Losartan

Valsartan

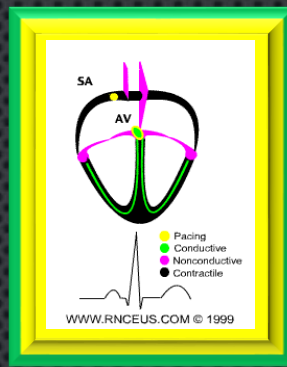
Cause selective block of AT1 receptors

No effect on bradykinin, no cough, no angioedema

Produce more complete inhibition of angiotensin



# 2-ANGIOTENSIN RECEPTORS BLOCKERS



## LOSARTAN

Has a potent active metabolite

Orally effective

Long half-life, taken once daily

Do not cross BBB

## VALSARTAN

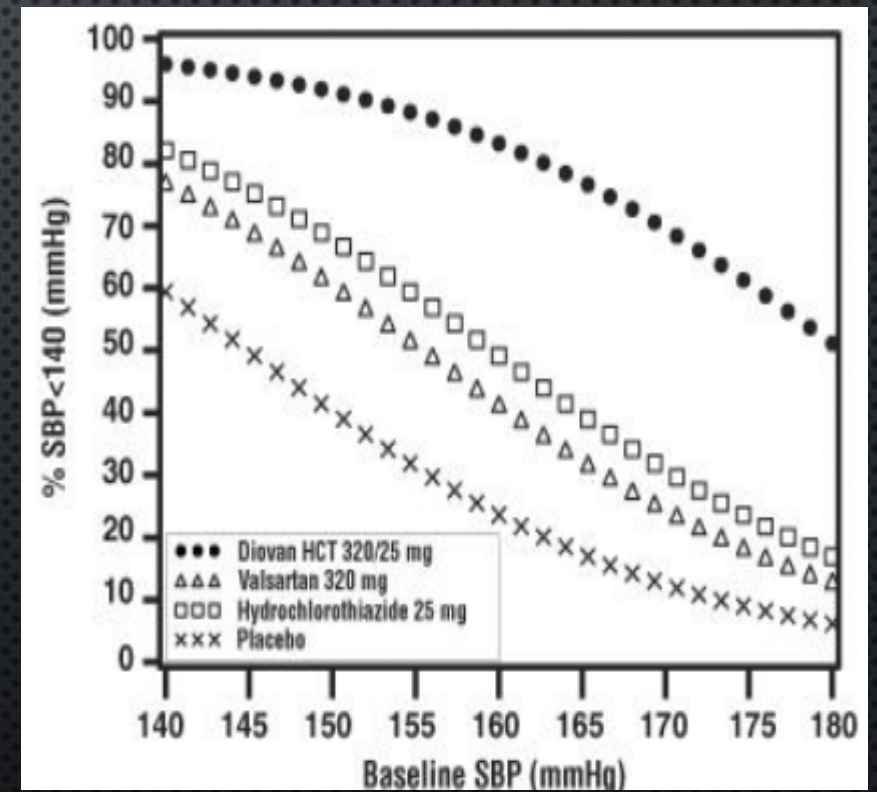
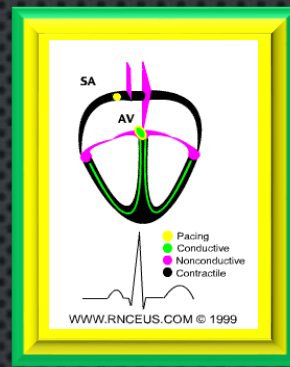
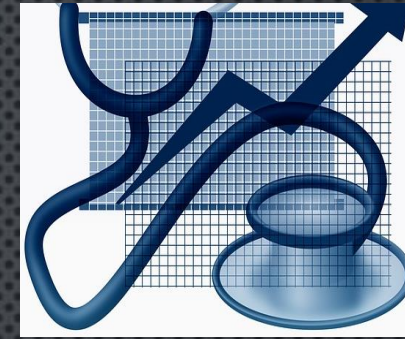
No active metabolites

Same contraindications as ACEI

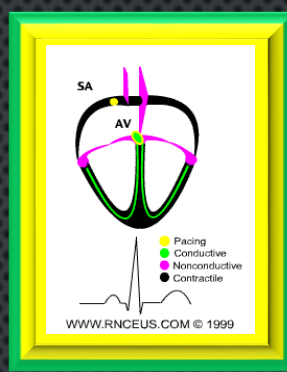
Same ADRs, except for dry cough & angioneurotic edema

# CLINICAL CASE

Osman was prescribed hydrochlorothiazide & valsartan. What is the rationale for combining hydrochlorothiazide and valsartan?



## THINK-PAIR-SHARE



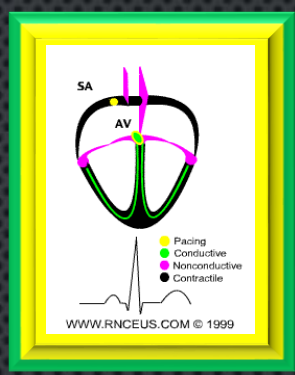
63-year-old hypertensive woman had been receiving an antihypertensive drug for 15 days. The following serum values were obtained from the patient before and after drug therapy:-

Plasma level	Before	After
Aldosterone	High	Low
Potassium (mEq/l)	3.5	4.3
Renin	Normal	High
Angiotensin II	High	Low

Which drug the woman has been receiving?

Plasma Levels Before After  
Aldosterone High Low  
Potassium (mEq/L) 3.5 4.3  
Renin Normal High  
Angiotensin II High Low

# THINK-PAIR-SHARE



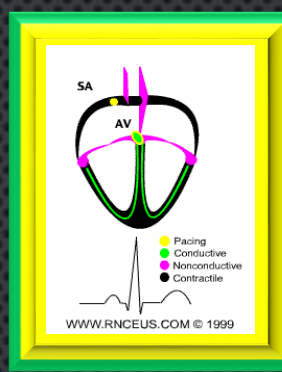
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Which drug the woman has been receiving?



# ANTIHYPERTENSIVE DRUGS

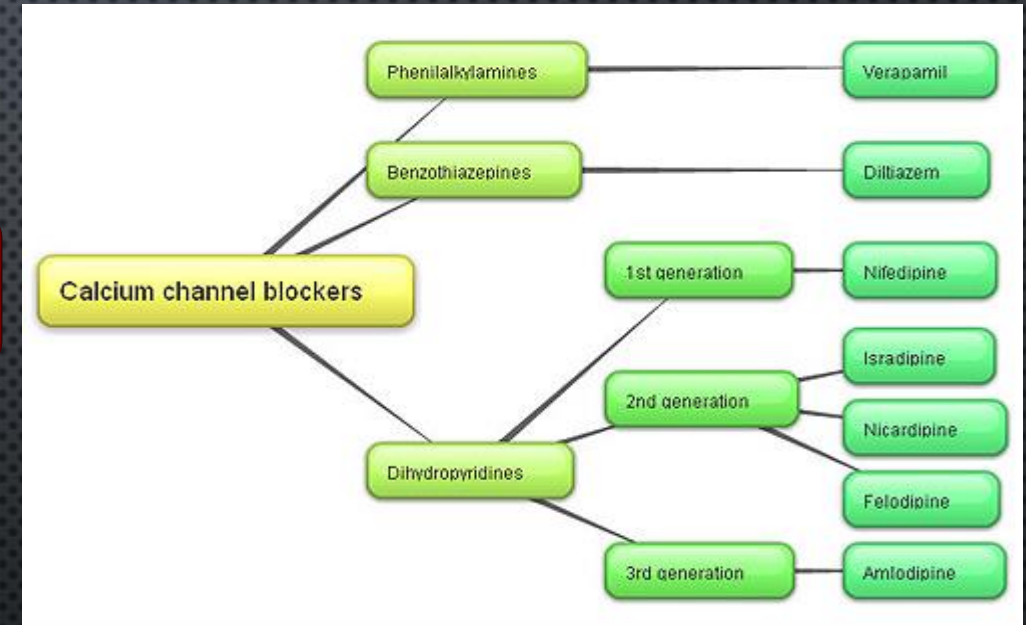


## 3-CALCIUM CHANNEL BLOCKERS

Verapamil act more on the myocardium

Dihydropyridine group act mainly on smooth muscle, **Nifedipine**

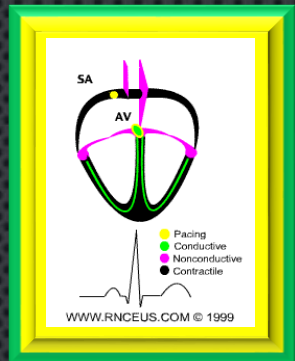
Diltiazem has intermediate effect



Very  
Nice  
Drugs

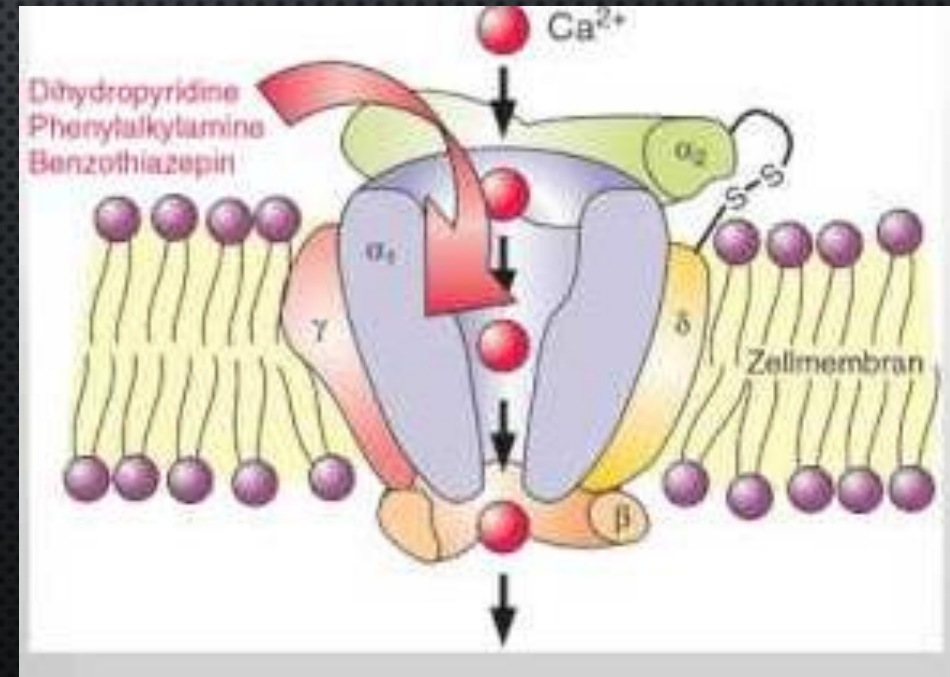
# CALCIUM CHANNEL BLOCKERS

## MECHANISM



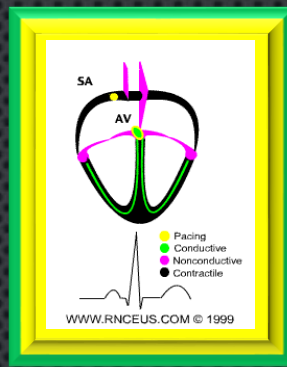
Block the influx of calcium through calcium channels resulting in:-

- 1- Peripheral vasodilatation
- 2- Decrease cardiac contractility





# CALCIUM CHANNEL BLOCKERS



## PHARMACOKINETICS

Given orally or IV

Onset 1-3 min after IV, 0.5-2hr after oral

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

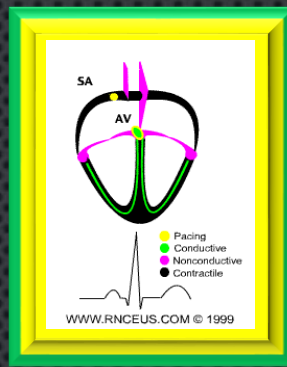
# CALCIUM CHANNEL BLOCKERS

## CLINICAL USES

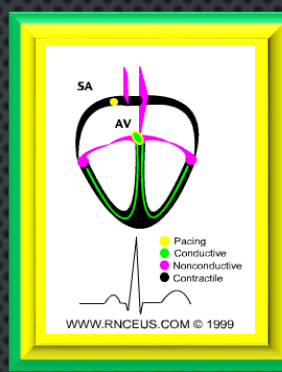
Treatment of chronic hypertension

Nicardipine can be given by I.V. route in hypertensive emergency

Sustained- release formulations are preferred for the treatment of hypertension due to the short half- life of CCBs



# ANTIHYPERTENSIVE DRUGS



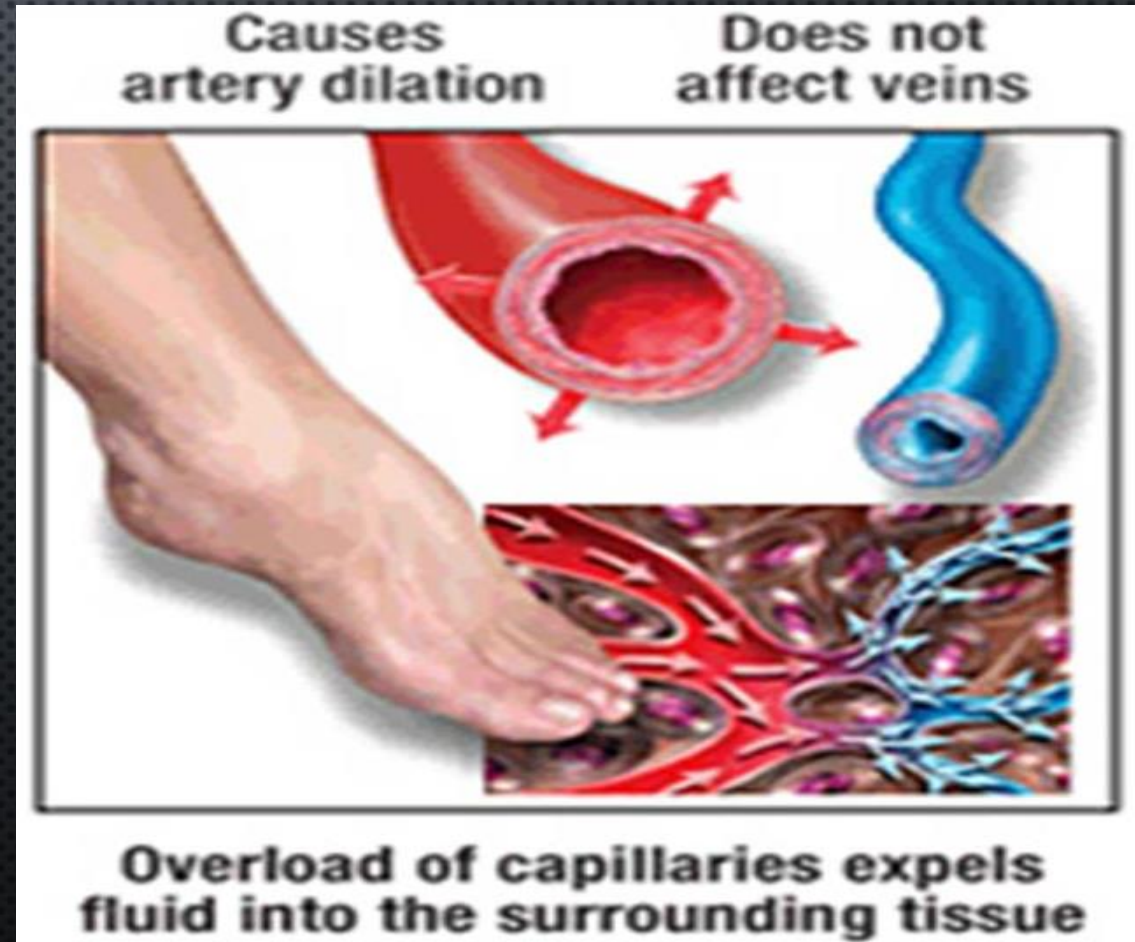
## ADRS

Headache , Flushing , Hypotension

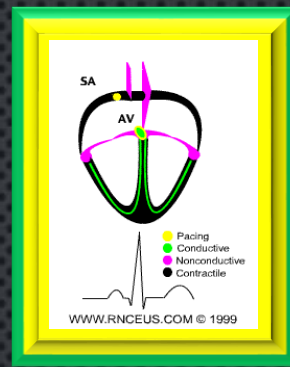
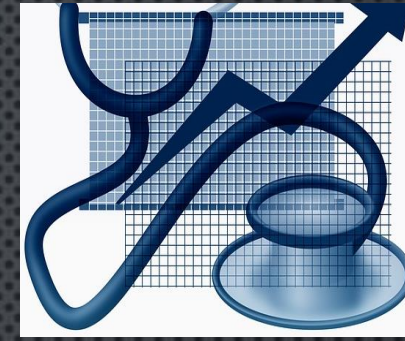
Nifedipine:-Tachycardia

Verapamil & Diltiazem:- peripheral edema (ankle edema)

Verapamil:- constipation

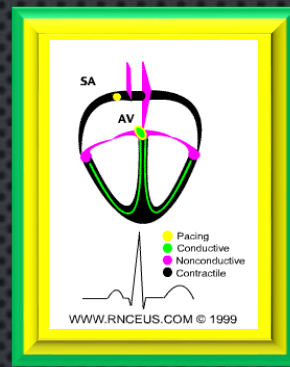
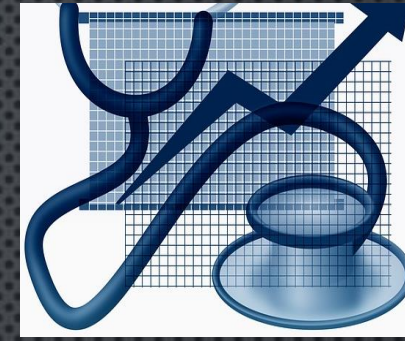


# CLINICAL CASE



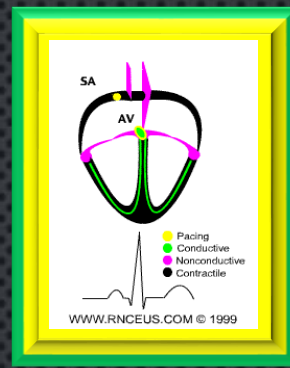
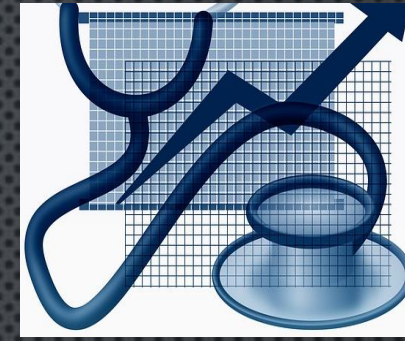
Osman was prescribed hydrochlorothiazide & diltiazem. What is the benefit of combining hydrochlorothiazide and diltiazem?

# CLINICAL CASE



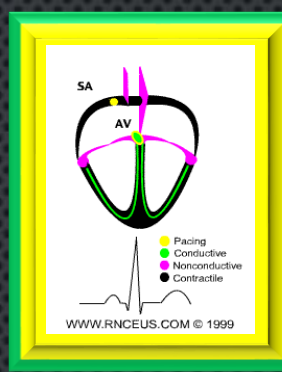
The BP of Osman did not change on standing.  
What is your conclusion?

# CLINICAL CASE



The BP of Osman was almost the same in both arms. What does that imply?

# TASK- SELECTION OF A P-DRUG



Instructions:

- 1- Select a leader for your group
- 2- Discuss the case according to the steps shown in the sheet
- 3- Use your mobile & internet access to obtain evidence for efficacy, toxicity, convenience & cost.
- 4- Due to time constrains divide yourself into 4 groups, each doing one search e.g. evidence for efficacy.
- 5- You have 10 minutes to do this and 1 minute to report to the class.

## The Many Faces of HT Therapy Today

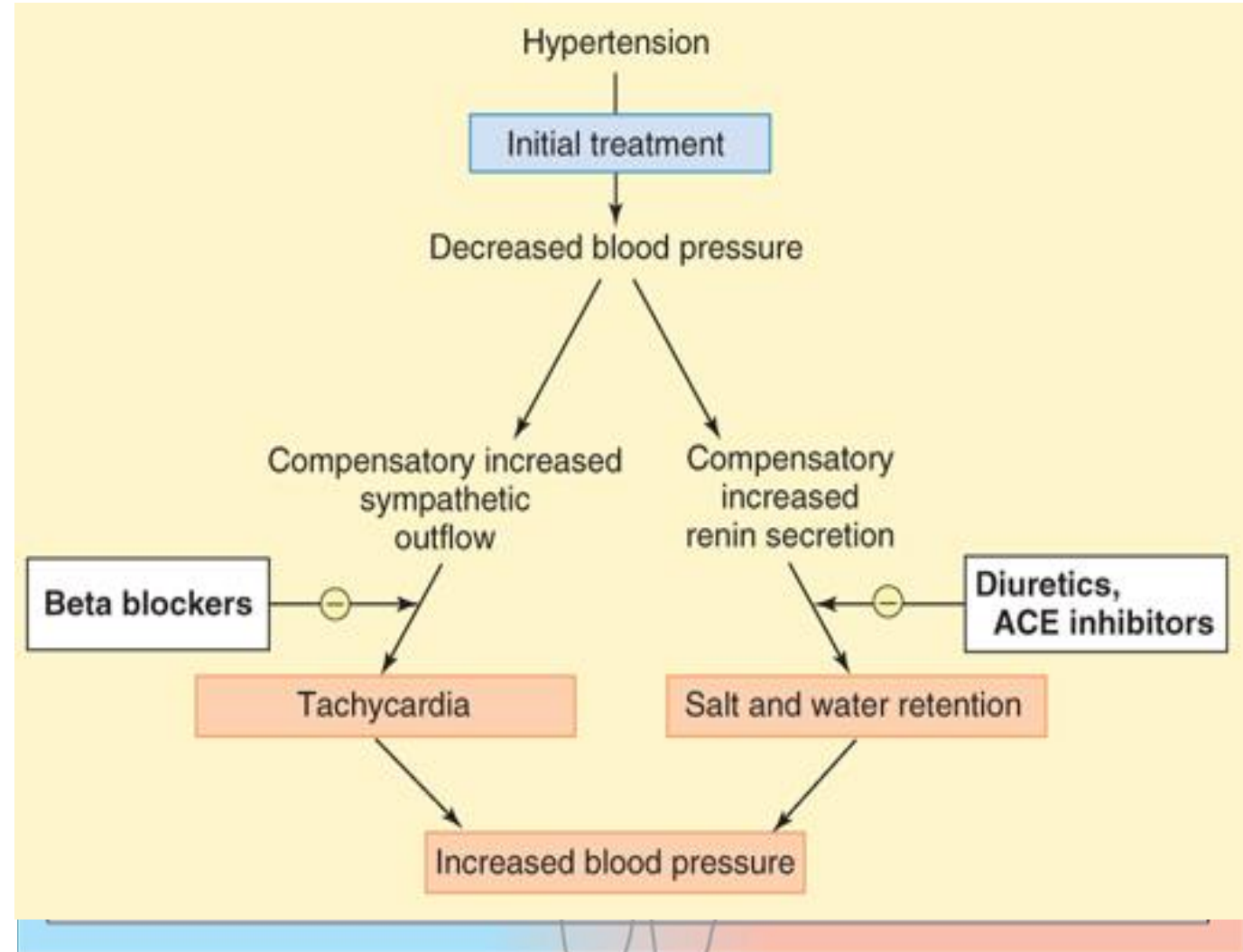
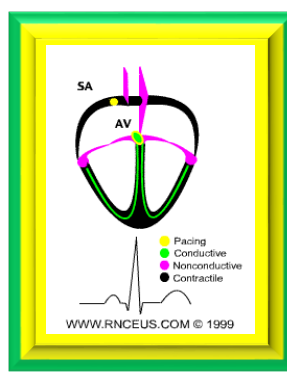


# ANTIHYPERTENSIVE DRUGS

## 4- VASODILATORS

Classified into arterial, venous or mixed vasodilators

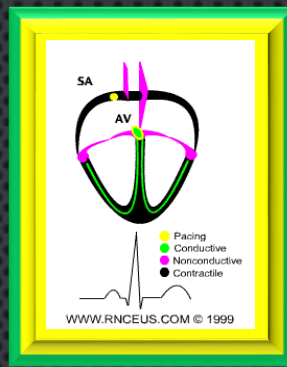
Once vasodilators are administered, fall in BP produced will activate the sympathetic system & the RAAS





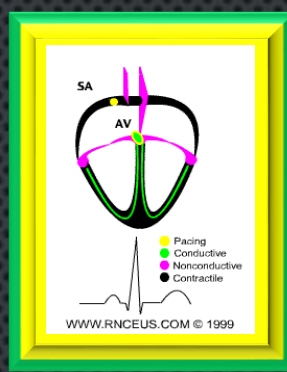
# ANTIHYPERTENSIVE DRUGS

## VASODILATORS



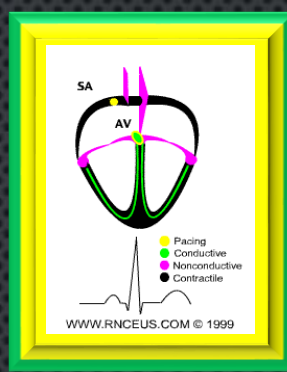
	<b>Hydralazine</b>	<b>Minoxidil</b>	<b>Diazoxide</b>	<b>Sodium nitropruside</b>
<b>Site of action</b>	Arteriodilator	Arteriodilator	Arteriodilator	Arterio & venodilator
<b>Mechanism of action</b>	Opening of potassium channels	Opening of potassium channels in smooth muscle membranes by minoxidil sulfate ( active metabolite )	Opening of potassium channels	Release of nitric oxide ( NO)
<b>Route of admin.</b>	Oral	Oral	Rapid intravenous	Intravenous infusion

# VASODILATORS



Continue Vasodilators	Hydralazine	Minoxidil	Diazoxide	Sodium nitropruside
	1.Moderate - severe hypertension.	1.Moderate – severe hypertension	1.Hypertensive emergency	1.Hypertensive emergency
Therapeutic uses	<b>In combination with diuretic &amp; <math>\beta</math>-blockers</b>			
	2.Hypertensive pregnant woman	2. baldness	2.Treatment of hypoglycemia due to insulinoma	2.Severe heart failure

# VASODILATORS



Continue Vasodilators	Hydralazine	Minoxidil	Diazoxide	Sodium nitropruside
<b>Adverse effects</b>	Hypotension, reflex tachycardia, palpitation, angina, salt and water retention ( edema)			Severe hypotension
<b>Specific adverse effects</b>	lupus erythematosus like syndrome	Hypertrichosis.  Contraindicated in females	Inhibit insulin release from $\beta$ cells of the pancreas causing hyperglycemia  Contraindicated in diabetics	1.Methemoglobin during infusion 2. Cyanide toxicity 3. Thiocyanate toxicity

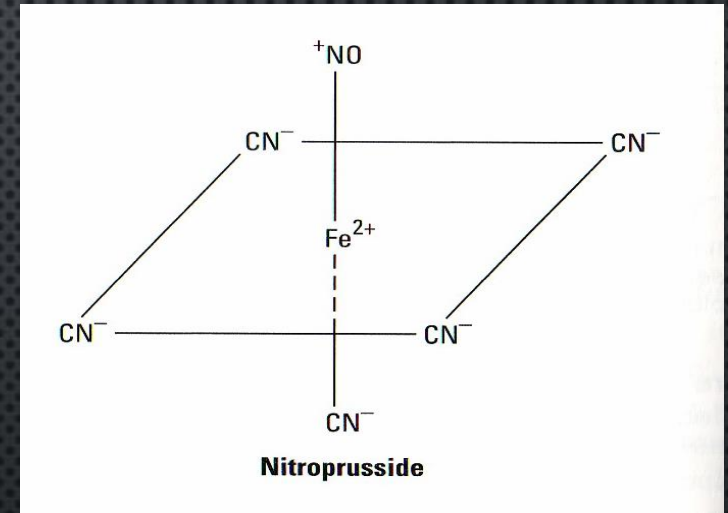
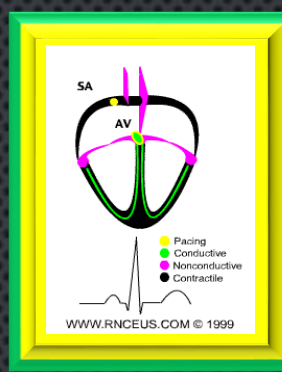
# VASODILATORS

## SODIUM NITROPRUSSIDE

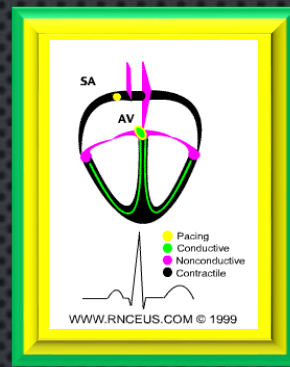
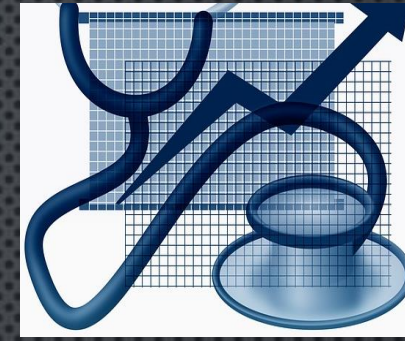
### ADRS

Headache, palpitations which disappear when infusion is stopped

Cyanide accumulation cause cyanide poisoning (metabolic acidosis, arrhythmias, severe hypotension and death)

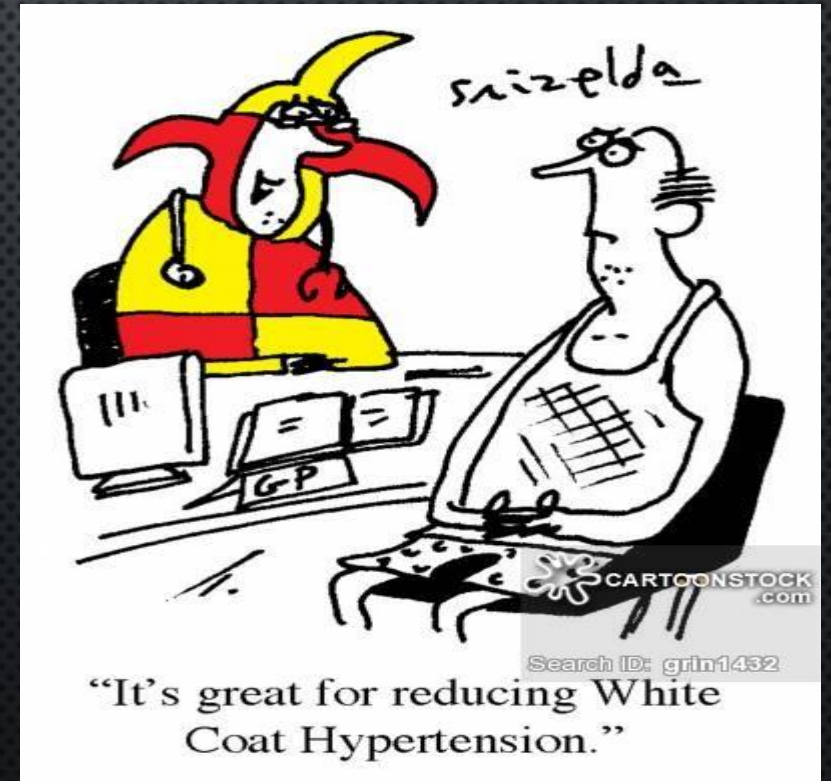


# CLINICAL CASE



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



# 5-SYMPATHOLYTIC DRUGS

$\beta$ -Adrenoceptor blockers

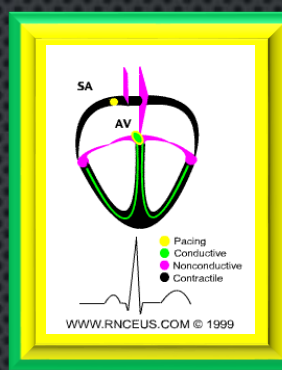
Propranolol, atenolol, metoprolol

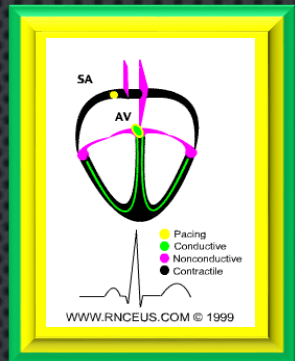
They should not be the primary agent for primary prevention but are effective as add-on therapy

May take two weeks for optimal therapeutic response

Evidence support the use of  $\beta$ -blockers in patients with concomitant coronary artery disease

When discontinued,  $\beta$ - blockers should be withdrawn gradually



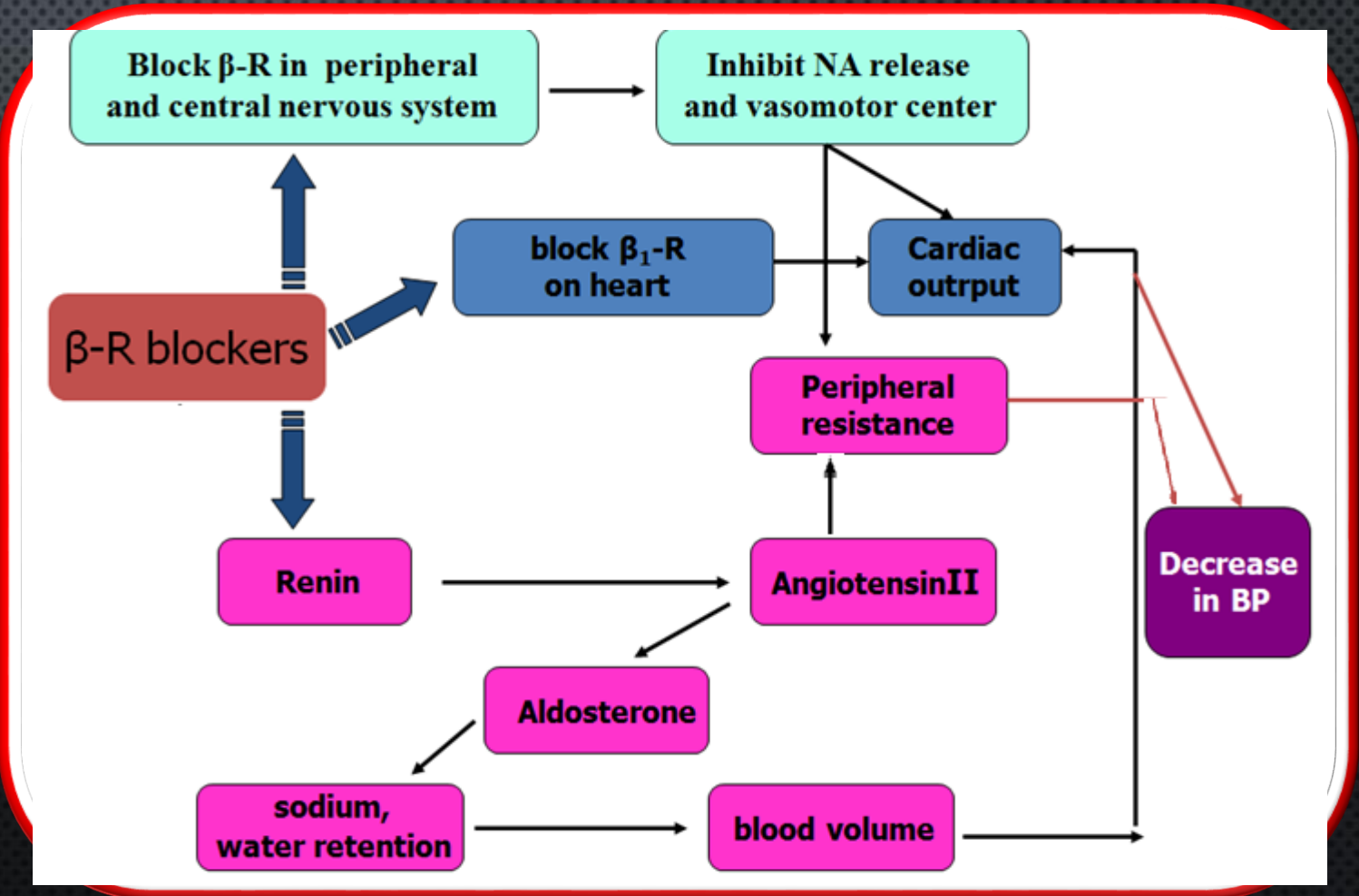


# β- Adrenoceptor blockers

## MECHANISM

They lower blood pressure by :

- i- Decreasing cardiac output.
- ii- Inhibiting the release of renin
- iii- Central mechanism
- vi- presynaptic inhibition



# $\beta$ - Adrenoceptor blockers

**ADRS**

Hypoglycemia

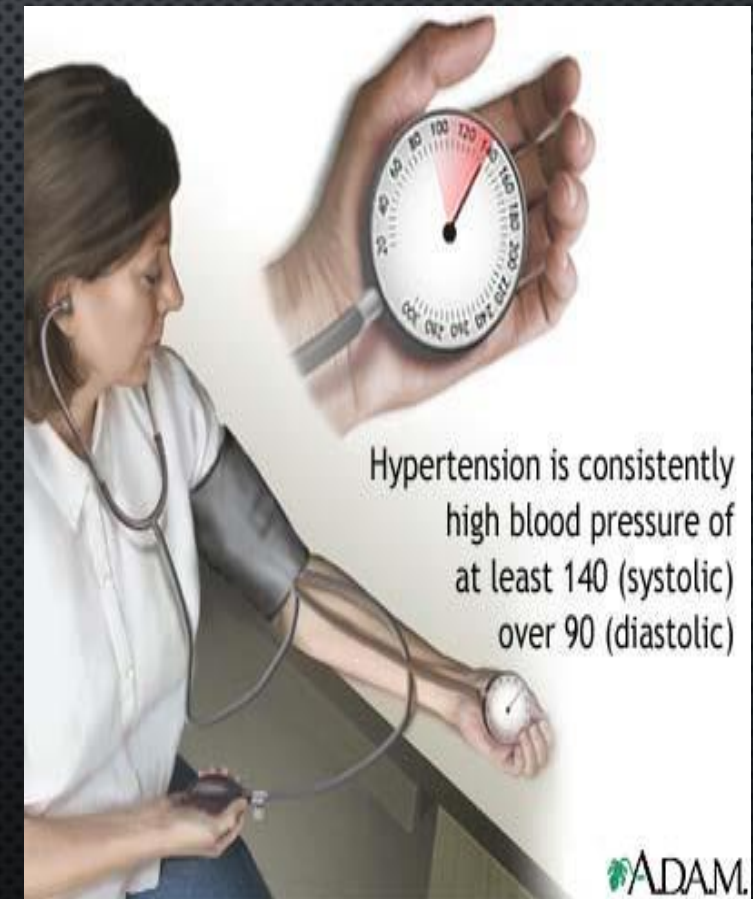
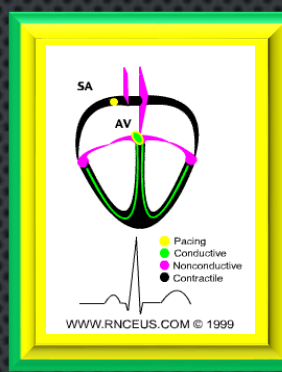
Fatigue

Mask the symptoms of hypoglycemia in diabetics

Increased triglycerides

Aggravate peripheral arterial disease

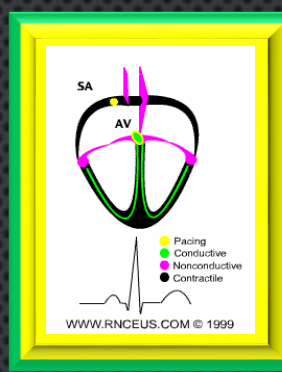
Erectile dysfunction





# MEMORY MATRIX

ENTER + OR - IN THE CELLS TO INDICATE THE PRESENCE OR ABSENCE OF A FEATURE



## COMPELLING INDICATIONS OF ANTIHYPERTENSIVE DRUGS

	HF	Pregnancy	Diabetes	CKD	IHD	Black patient	Resistant HT
Diuretics							
ACEI/ARB							
CCB							
$\beta$ -blockers							
Hydralazine							
Clonidine							

# SYMPATHOLYTIC DRUGS

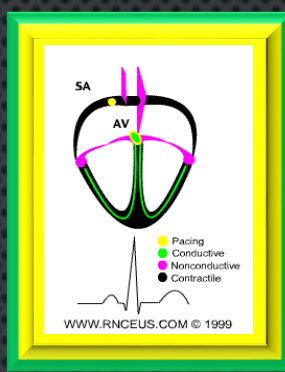
ii-  $\alpha$ - Adrenoceptor blockers

Block  $\alpha$ - receptors in arterioles and venules

Reduce blood pressure by decreasing both afterload & preload

Prazosin, short- acting causes first dose hypotension & postural hypotension

Doxazosin is preferred, long half- life



# III- CENTRALLY- ACTING

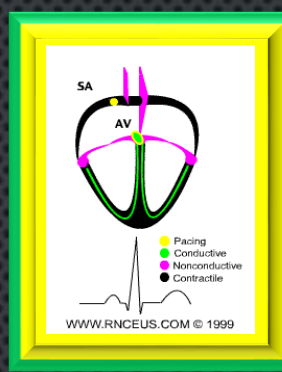
## A- Clonidine

$\alpha_2$ -agonist, diminishes central adrenergic outflow &  $\uparrow$  parasympathetic outflow

Abrupt withdrawal may lead to rebound hypertension

Does not decrease renal blood flow or glomerular filtration

Useful in the treatment of hypertension complicated by renal disease and resistant hypertension



pres

$\alpha_2$  rece  
mediate  
negative  
feedbac

cloni

posts

CNS  
sympathomimetic

$\alpha_2$  receptor  
stimulation

decrease in efferent  
sympathetic activity

decrease in arterial  
blood pressure

# SYMPATHOLYTIC DRUGS

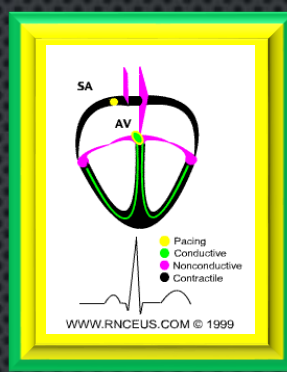
## CENTRALLY- ACTING

B-  $\alpha$ - methyl dopa

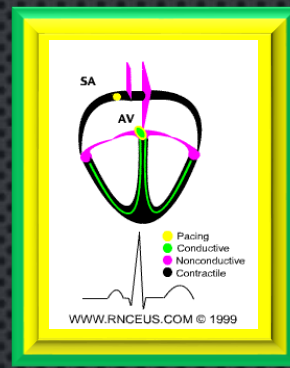
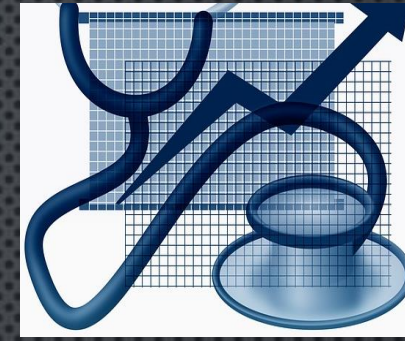
An  $\alpha$ - 2 agonist, is converted to methyl noradrenaline centrally to diminish the adrenergic outflow from the C.N.S

Lead to reduced total peripheral resistance, and a decreased in blood pressure

$\alpha$  -Methyl dopa is the first line treatment of hypertension in pregnancy



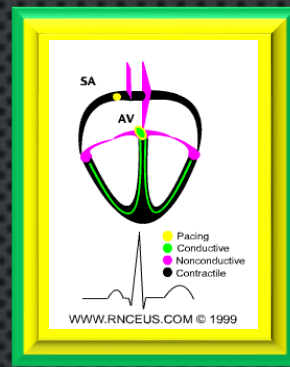
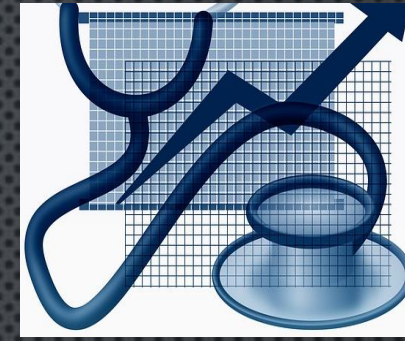
# CLINICAL CASE



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



# CLINICAL CASE



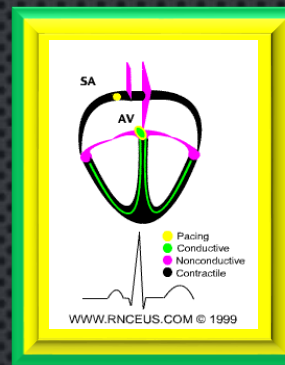
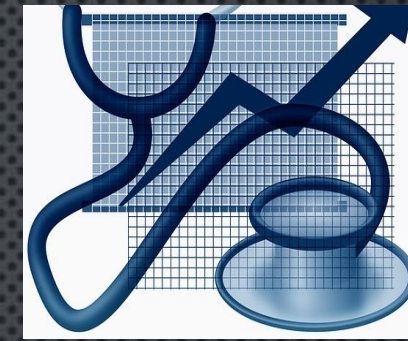
Could the failure of control of Osman's BP be due to secondary drug – induced effects?

Which drugs elevate blood pressure?

## Drug-Induced Hypertension: Prescription Medications

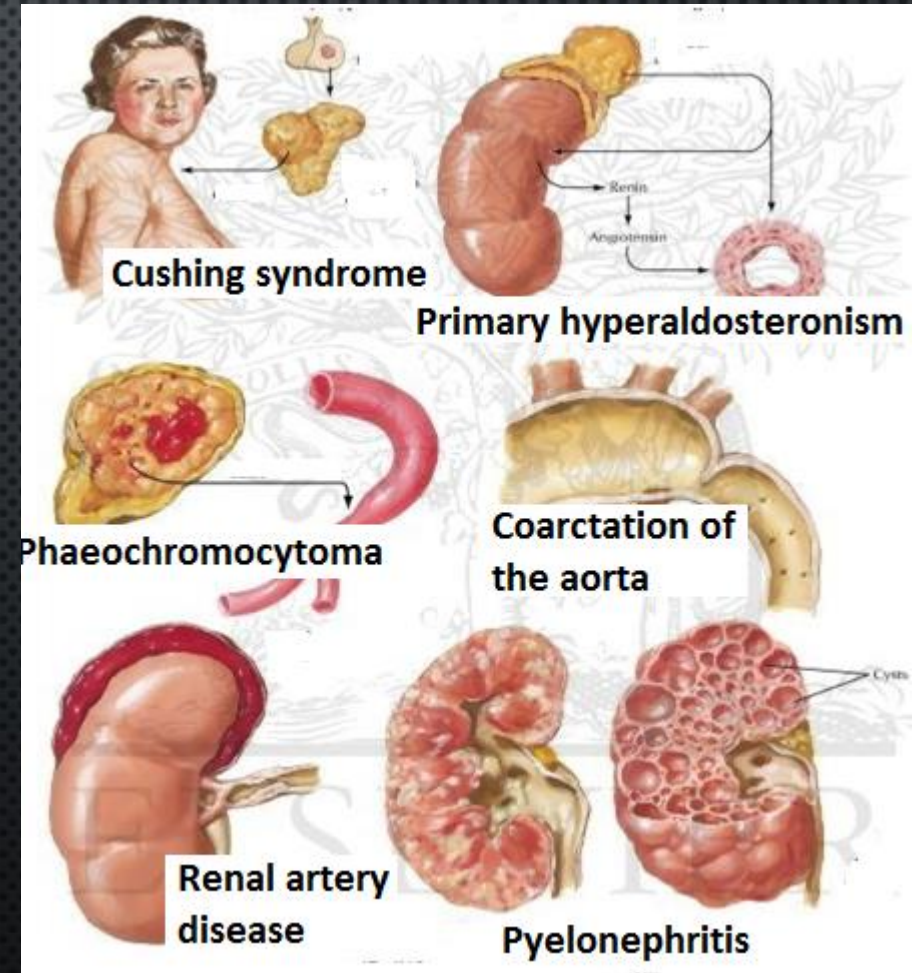
- Steroids
- Estrogens
- NSAIDS
- Phenylpropanolamines
- Cyclosporine/tacrolimus
- Erythropoietin
- Sibutramine
- Methylphenidate
- Ergotamine
- Ketamine
- Desflurane
- Carbamazepine
- Bromocryptine
- Metoclopramide
- Antidepressants  
– Venlafaxine
- Buspirone
- Clonidine

# CLINICAL CASE

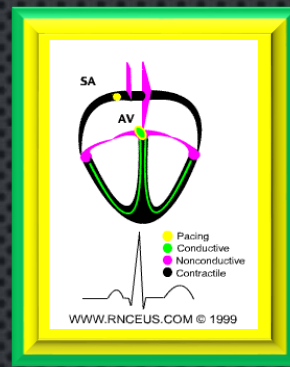
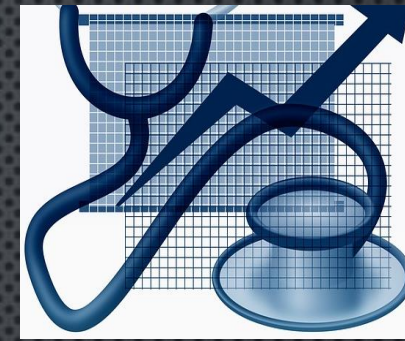


Could Osman be misdiagnosed? And the high BP is due to secondary disease causes?

Which secondary diseases cause elevation of BP?



# CLINICAL CASE

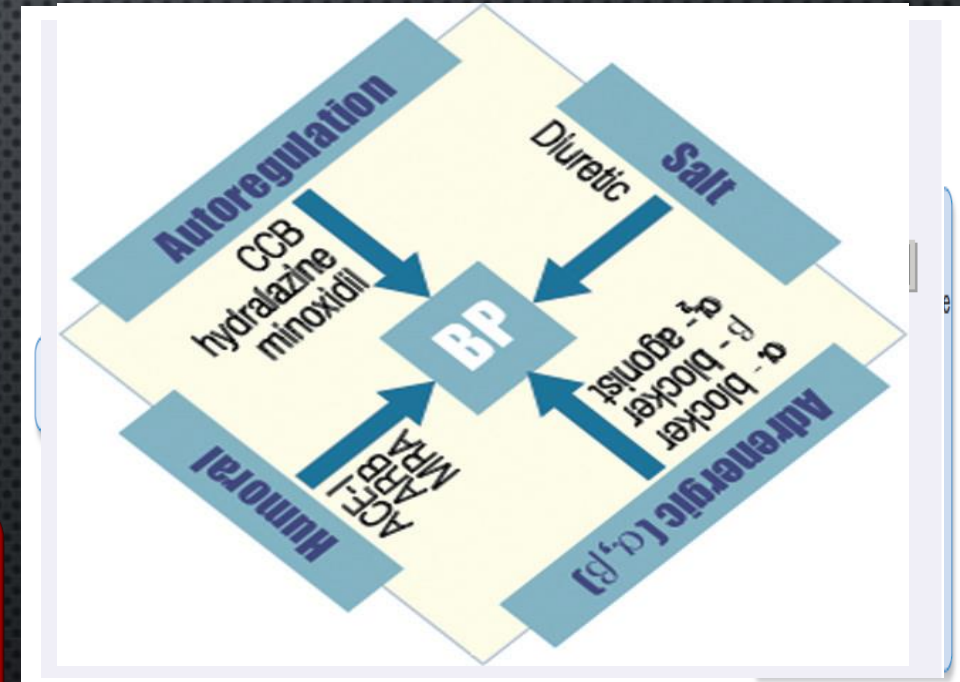


Could the failure of Osman control of BP be due to the use of inappropriate combinations of drugs?

Use of combinations  $\rightarrow$   $\downarrow$  individual dose  $\rightarrow$   $\downarrow$  ADRs

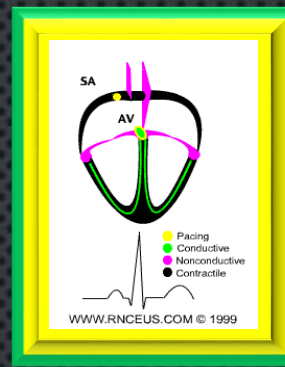
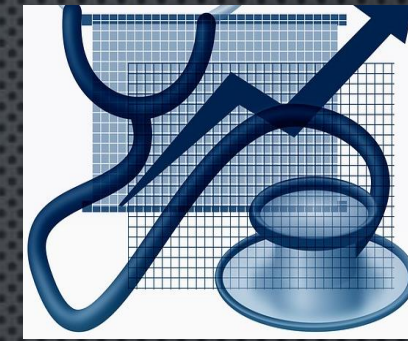
Select a drug that  $\downarrow$  the ADR of another, e.g. thiazides versus ACEI

Select a drugs that act by different mechanisms



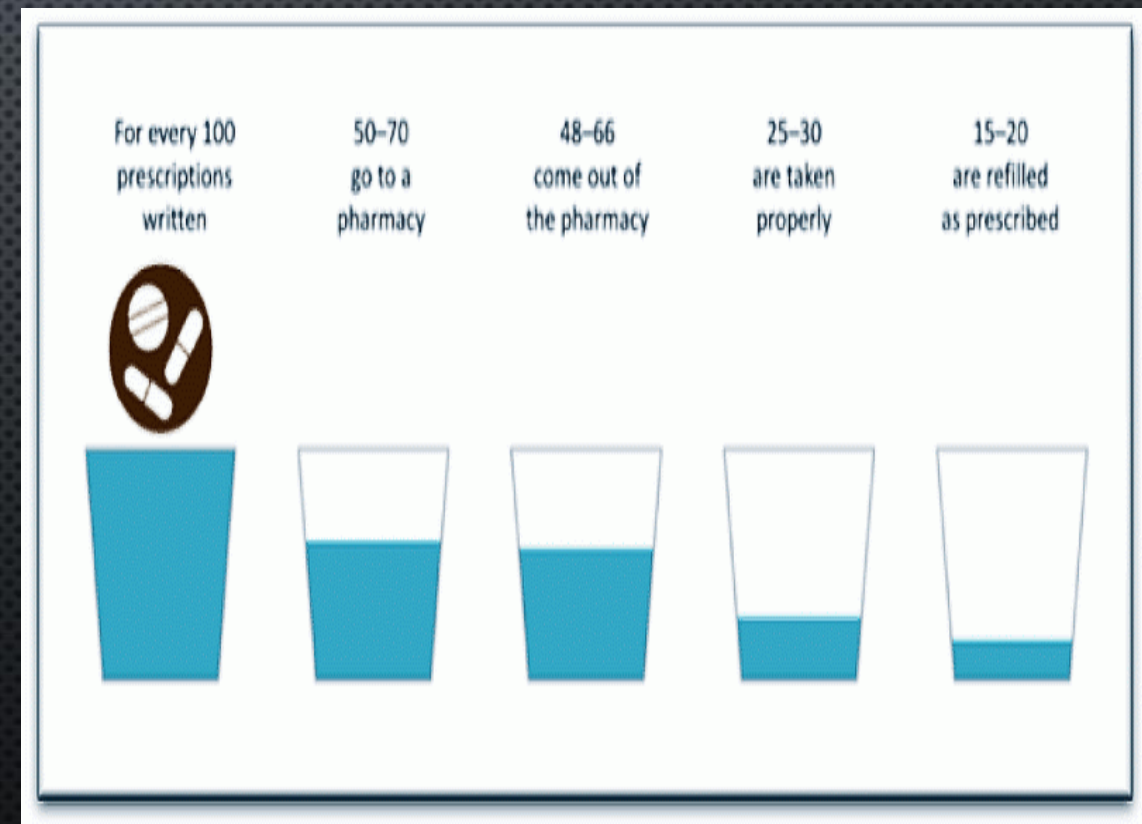


# CLINICAL CASE

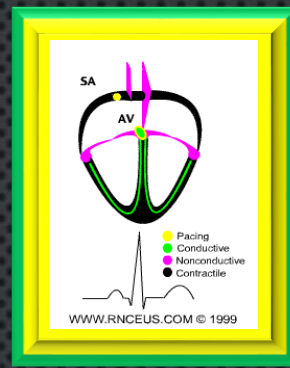
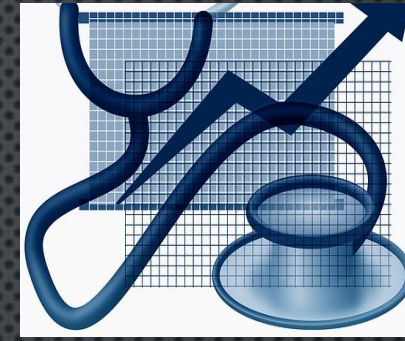


Could the failure of control of Osman's BP be attributed to non adherence?

Could the somatic complaints (fatigue and dry mouth) indicate the adherence of the patient to medication regimen and which drugs cause these symptoms?



# CLINICAL CASE



What suggestions do you have for Osnman's treatment modification in order to attain BP goals?