8) Centrally Acting Sympathetic Inhibitors

Clonidine (Catapres®)

- **Clonidine is an α2 agonist (centrally and peripherally) that is used for the treatment of Hypertension.**
- **It decreases blood pressure by;**
  - **1) Stimulate presynaptic a2 receptors:**
    - **Decrease Presynaptic Ca 2+ decrease NE release** decrease **blood pressure.**
  - **2) Stimulate central α2 receptors:**
    - **Decrease Sympathetic vasomotor centers decrease Sympathetic outflow decrease NE release** decrease **renin release** decrease **blood pressure.**
  - **3) Stimulate I1 (Imidazoline) receptor:**
    - **Sympatho-inhibitory action** decrease **blood pressure.**
- **Adult dose;**
  - **Oral preparation (Catapres®) → Must be given twice a day.**
    - **Initial dose; 0.1 mg tablet twice daily (morning and bedtime).**
    - **Maintenance dose; 0.2-0.6 mg per day given in divided doses.**
  - **Transdermal preparation (Catapres-TTS®) given once every 7 days.**
- **The most frequent adverse effects (dose-related) are:**
  - **Dry mouth, drowsiness, dizziness, constipation and sedation.**
- **Clonidine therapy should be gradually tapered off;**
  - **Clonidine suppresses sympathetic outflow resulting in lower blood pressure, but sudden discontinuation can cause rebound hypertension (life-threating hypertensive crisis) due to a rebound in sympathetic outflow. (treated by α1 and ß blockers).**

α-Methyldopa (Aldomet®)

- **Methyldopa is an α2 agonist that has both central and peripheral effects.**

Methyldopa has a dual mechanism of action

1) Methyldopa is converted into the false transmitter (metabolite) called; alpha-methylnorepinephrine, in the CNS by dopamine beta-hydroxylase (DBH) enzyme The false transmitter is central α2-agonist decrease sympathetic out flow decrease NE release decrease renin release decrease blood pressure.
2) It is a competitive inhibitor of dopa-decarboxylase enzyme which converts L-dopa into dopamine. Dopamine is a precursor for norepinephrine and subsequently epinephrine.

- **It is mainly used for management of hypertension in pregnancy (FDA pregnancy category B).**
- **Used with caution in lactating women (appears in breast milk).**
- **Adult dose;**
  - **Initial dose; 250 mg orally 2-3 times a day in the first 48 hours.**
  - **Maintenance dose; 500 mg to 2 g orally divided in 2 to 4 doses, up to a maximum of 3 g/day.**
  - **Hypertensive emergency; 250 to 500 mg IV over 30 to 60 minutes every 6 hours up to a maximum of 1 g every 6 hours or 4 g/day.**

Selective Imidazoline Receptors Agonists

Rilmenidine (Hyperium®)	Moxonidine (Cynt®)

- **Used in mild to moderate essential hypertension.**
- **Moxonidine may also promote sodium excretion, improve insulin resistance and glucose tolerance & protect against hypertensive target organ damage, such as kidney disease and cardiac hypertrophy.**

9) Peripherally Acting Sympathetic Inhibitors

Guanethidine (Ismelin®)

- Guanethidine is an antihypertensive drug that reduces the release of catecholamines, such as norepinephrine.
- It acts by blocking the release of stored norepinephrine (NE) (replacing NE in these vesicles) gradual depletion of NE stores in the nerve endings gradual decrease in BP and HR.
- It is used in the treatment of moderate and severe hypertension and renal hypertension.
- Side effects: Bradycardia, orthostatic hypotension, failure of ejaculation and nasal congestion.

Reserpine (Hypoten®)

- Reserpine is a plant alkaloid from dried root of Rauwolfia serpentina.
- It acts by irreversibly blocks vesicular monoamine transporter (VMAT) (block Mg2-/adenosine triphosphate-dependent transport) of monoamine neurotransmitters (norepinephrine, dopamine, and serotonin) from storage vesicles in the adrenergic nerve terminals in all body tissues.
- It has a slow onset, a long duration of action.
- After discontinuation The effects persist for many days.
- It is used in the treatment of mild hypertension.
- Most common side effects: diarrhea, hyperacidity, bradycardia and nasal congestion.

10) Ganglionic Blockers

Trimethaphan (Arfonad®)	Mecamylamine (Inversine®)
- Mono sulfonium (S+).	- Secondary amine.
- Don't pass BBB.	- Pass BBB.
- Ultra short duration of action (10 to 15 min.).	- Longer duration of action.
- Not given orally (IV).	- Given orally.
- Treatment emergency hypertension.	- Treatment moderate hypertension.
- Cause histamine release Flushing.	- Not cause histamine release.

11) Vasodilators

- Vasodilators, are drugs or substances that cause vasodilation.
- Classification of vasodilators drugs according to mechanism of action;
    1) Release of NO from drug or endothelium;
        - Sodium nitroprusside and Nitrates.
    2) Reduction of Ca2+ influx;
        - Verapamil, Diltiazem and Nifedipine (and other dihydropyridines).
    3) Hyperpolarization of smooth muscle membrane through opening K+ channels;
        - Hydralazine, Minoxidil and Diazoxide.
    4) Activation of dopamine receptors;
        - Fenoldopam.
- All the vasodilators that are useful in hypertension relax smooth muscle of arterioles.
- Sodium nitroprusside and the nitrates also relax veins.
- Nitrates are used mainly in angina.

Hydralazine (Apresoline®)

- Hydralazine is a direct vasodilator, it dilates arterioles but not veins.

Mechanism Of action	**- The exact mechanism of action is not fully understood:** - Hydralazine altering cellular calcium metabolism, i.e. hydralazine causes smooth muscle hyperpolarization quite likely through the opening of K-channels. It also may inhibit IP3-induced release of calcium from the smooth muscle sarcoplasmic reticulum. - It also ↑ plasma renin concentration sodium and water retention.
Therapeutic uses	- In Severe essential hypertension when the drug cannot be given orally or when there is an urgent need to lower blood pressure. - Commonly used in combination with nitrates for the treatment of CHF in self-identified African American populations. - Oral hydralazine is effective as monotherapy or as add-on therapy to methyldopa in the long term management of chronic hypertension in pregnancy. - Adult dose; - Oral dose. 10 mg orally 4 times a day for the first 2 to 4 days. Increase to 25 mg orally 4 times a day for the balance of the first week. For the second and subsequent weeks, increase dosage to 50 mg orally 4 times a day. - Hypertensive emergency, Usual dose: 20 to 40 mg IV or IM, repeated as necessary (patients with marked renal damage may require a lower dose).
Side effects	- Most common; Headache, nausea, anorexia, palpitation, sweating and flushing. - Up to 20% of patients (how slowly acetylate the drug) who receive 400 mg/day or more mainly develop a systemic lupus erythematosus syndrome.

Minoxidil (Loniten®)

- Minoxidil is a very efficacious orally active vasodilator.
- Like hydralazine, minoxidil dilates arterioles but not veins.
- Because of its greater potential antihypertensive effect, minoxidil should replace hydralazine when maximal dose of the hydralazine is not effective.
- Minoxidil and hydralazine is almost always (should be) administered in combination with a β-blockers (to balance the reflex tachycardia) and a loop diuretics (to decrease sodium retention).
- Uses;
- Oral minoxidil; Treatment of severe hypertension.
- Adult dose; 5 mg as a single daily dose, may be increased to 10, 20 and then to 40 mg. The effective dosage range is usually 10 to 40 mg per day. The maximum recommended dosage is 100 mg/day.
- Topical minoxidil (Rogaine®); used in topical treatment (regrowth) of androgenic alopecia in males and females and stabilisation of hair loss in patients with androgenic alopecia.
- Vasodilator mechanism of action; Minoxidil is a potassium channel opener, act by opening K+-channels in smooth muscle membrane which closes voltage-gated calcium channels and decreases intracellular calcium.
- Most common side effects; Tachycardia, angina and edema are observed when doses of B-blockers and diuretics are inadequate.
- Headache, sweating and hypertrichosis.

Sodium Nitroprusside (Nipride®)

- Sodium Nitroprusside, is a powerful short acting parenterally vasodilator that is used in treating hypertensive emergencies as well as sever heart failure.

- It is dilates both arterial and venous vessels.
- Pharmacokinetics;
  - Chemically, is an inorganic compound with the formula Na2[Fe(CN)5NO], It is rapidly metabolized by uptake into red blood cells, with liberation of cyanide. Cyanide in turn is metabolized by the mitochondrial enzyme in the presence of sulfur donor to the less toxic thiocyanate. Thiocyanate is slowly eliminated by the kidney.
  - Duration of action; 1-10 minutes after infusion is stopped.
  - Dose; 0.5 mcg/kg/min, may be increased up to 10 mcg/kg/min.
- Mechanism of action; Sodium nitroprusside breaks down in circulation to release nitric oxide (NO), NO activates guanylate cyclase in vascular smooth muscle and increases intracellular production of cGMP, the end result is vascular smooth muscle relaxation.
- Toxicity; The most serious toxicity is related to accumulation of cyanide and may cause death. Administration of sodium thiosulfate (sulfur donor) facilitates cyanide metabolism. Hydroxocobalamin (vit. B12) combined with cyanide to form the non-toxic cyanocobalamin.

Diazoxide (Proglycem®)

- Diazoxide is a long acting arteriolar dilator that is used to treat hypertensive emergencies.
- It is a potassium channel activator, which causes vascular smooth muscle relaxation.
- It is also inhibits the secretion of insulin from the pancreas, thus it is used to counter hypoglycemia in disease states such as insulinoma (a tumor producing insulin) or congenital hyperinsulinism.
- FDA warning (2015) pulmonary hypertension has been reported in infants and newborns treated with diazoxide.

Fenoldopam (Corlopam®)

- Fenoldopam is an agonist peripheral dopamine D1 receptors.
- It is a racemic mixture and the R-isomer is the active component.
- Routes of administration: for continuous IV infusion only due to extensive first-pass metabolism and short half-life elimination (10 minutes).
- Period of administration: up to 48 hours in adults up to 4 hours in pediatric.
- Mechanism of action: rapid-acting vasodilator agonist of peripheral dopamine D1 receptors VD of renal blood vessels diuresis.
- Uses: treat severe hypertension in hospitalized patients.
- Dose: initial; 0.1 mcg/kg/min, the dose is titrated upward every 15 or 20 min. to a maximum dose 1.6 mcg/kg/min.
- Adverse effects: Headache, flushing, dizziness, nausea and tachycardia (due to vasodilation).

12) Natural Antihypertensive Agents

- The following agents were identified: coenzyme Q10 (CoQ10), ubiquinone, garlic, arginine, fish oil, hawthorn, olive oil, vitamin C, vitamin E, skallcap, barberry, betel nut, bishop's weed, bitter melon, cat's claw, celery, Eleutherococcus, gotu kola, guar gum, herbal diuretics, hibiscus, holly, jiaogulan, procaine, lemongrass, mistletoe, morinda, Nigella sativa, oil of evening primrose, passion flower, periwinkle, reishi mushroom, rhubarb, saffron, stevia, veratrum, white hellebore, willard water, withania, yellow root, yohimbine, and yucca.

- **The degree of antihypertensive efficacy is rarely impressive when compared with the blood Pressure reduction that can be documented with the incorporation of lifestyle modifications (include DASH).**

Hibiscus Tea (Hibiscus sabdariffa)

- Hibiscus tea is a herbal tea made as an infusion from crimson or deep magenta-coloured calyces (sepals) of the roselle (Hibiscus sabdariffa) flower (in Egypt called Karkade).
- Studies has shown that drinking hibiscus tea may lower blood pressure in people with type 2 diabetes, prehypertension or mild hypertension. However, there is no reliable support recommending evidence hibiscus tea in the treatment of primary hypertension.
- Drinking 3 cups of hibiscus tea daily for 6 weeks reduced systolic blood pressure by 7 mm Hg in prehypertensive and mildly hypertensive.
- Hibiscus flowers contain anthocyanins, which are believed to be the active antihypertensive compounds, acting as ACE inhibitors.
- A study compared the effectiveness of hibiscus to the ACE-inhibiting drug captopril (9.6 mg of total anthocyanins and captopril 50 mg/day); hibiscus worked as well as the drug captopril and not show significant differences relative to hypotensive effect, antihypertensive effectiveness, and tolerability.
- There is no difference between drinking hibiscus cold or hot.

Co-Enzyme Q10

- Coenzyme Q-10 (CoQ-10) is a natural antioxidant (is a vitamin-like substance) synthesized by the body, found in many foods & available as a supplement, found in small amounts in meats & seafood.
- COQ10 may play a role in treating heart and blood vessel conditions such as CHF, angina and hypertension.
- COQ10 may play a role in reducing the number and severity of migraine headaches, and improving sperm motility in men.
- There is no official daily value recommendation, but suggests at least 90 to 120 mg/day of supplemental COQ10 for any adult with a family history of heart problems, or who is at increased risk for cardiovascular disease.
- Researchers concluded that COQ10 has the potential to lower systolic blood pressure by up to 17 mm Hg and diastolic blood pressure by 10 mm Hg, without significant side effects.
- Statins (class of lipid lowering drugs) are well-tolerated by most people, they do have side effects, including muscle and joint aches and a rare condition that causes muscle cells to break down. Some researchers have proposed that taking a CoQ10 might reduce the risk of these side effects.
- Some research has indicated therapeutic value in high doses to slow the progression of Parkinson's disease.

✔ Hypertensive Crises :-

- **Hypertensive crisis;** patients with blood pressures (BP) ≥ 180/110 mm Hg.
- This condition has been classified as hypertensive emergencies and hypertensive urgencies:
    - **Hypertensive urgency;**
        - Elevations in BP (≥ 180/110 mm Hg) without progressive target-organ damage.
        - May or may not experience one or more of these symptoms: severe headache, shortness of breath, nosebleeds and severe anxiety.
    - **Hypertensive emergency,**
        - Severe elevations in BP (≥ 180/110 mm Hg) with the presence of acute or ongoing

target organ damage.
- Acute target-organ damage can include; hypertensive encephalopathy, intracranial hemorrhage, acute myocardial infarction, acute heart failure, pulmonary edema (shortness of breath), aortic dissection, retinopathy or papilledema, decreased urine output or acute renal failure and eclampsia.

Goals and treatment options;

Hypertensive Urgency	Hypertensive Emergency
- Managed by using oral antihypertensive agents. - Treatment is initiated with very low doses of oral agents using incremental doses as needed and avoiding large starting doses that may result in excessive blood pressure reduction. - The initial goal is to reduce blood pressure to 160/110 mm Hg over several hours to 2 days. - Mean arterial pressure (MAP) should reduced by no more than 25% within the first 24 hours. - All patients with hypertensive urgency should be reevaluated within 7 days. **- Specific agents;** - Captopril; 25 mg oral initially, followed by 50- 100 mg time 90-120 minutes later, until the target BP is achieved. - Nicardipine; 30 mg oral initially, repeated every 8 hours until the target is achieved. - Labetalol; 200 mg orally, repeated every 3-4 hours until the target is achieved - Clonidine; 0.1-0.2 mg orally, followed by 0.05- 0.1 mg every 1 hour until target is achieved (max dose of 0.7mg) - Nifedipine; 10-20 mg repeated every 6 to 8 hours until target is achieved.	- Managed by using IV antihypertensive agents. - Patients are usually admitted for intensive care unit (ICU) care and close follow-up. - Reducing the mean arterial pressure (MAP) by no more than 25% or diastolic BP to 100-110 mm Hg within 30-60 minutes. - Specific agents (Agents are chosen on the basis of patient characteristics); - Sodium Nitroprusside; 0.25-10 mcg/kg/min., maximum 3 mcg/kg/min. - Fenoldopam; 0.1 mcg/kg/min., maximum 1.6 mcg/kg/min. - Nitroglycerin; 5-10 mcg/min., maximum 100 - Enalaprilat; 0.625-125 mg every 4-6 hours, maximum 5 mg every 6 hours, - Hydralazine; 5-10 mg every 4-6 hours. - Nicardipine; 5-15 mg/hour, max. 15 mg/hour. - Esmolol; 250-400-mcg/kg IV Bolus, then a 50- 100-mcg/kg/min. infusion, maximum 300 mcg/kg/minute. - Labetalol; 20-80 mg IV Bolus every 15 minutes or 0.5-2 mg/min., max 300 mg/24 h. - Phentolamine; 5-15 mg IV bolus.

- ***Preferred agents in treatment of specific types of hypertensive emergencies;***

Types of emergency	Preferred agents
Hypertensive encephalopathy	Nitroprusside, Labetalol, Fenoldopam, Nicardipine
Subarachnoid hemorrhage	Nimodipine, Labetalol, Nicardipine
Cerebrovascular accident (CVA)	Labetalol , Nitroprusside, Enalaprilat
Acute renal failure	Fenoldopam, Nicardipine
Acute aortic dissection	Labetalol, Esmolol (B-Blocker; must precede other agents) alone or in combination with Nicardipine, Clevidipine or nitroprusside
Acute pulmonary edema	Nitroglycerin or {Nitroprusside ±ACE inhibitor}

Acute myocardial infarction	Nitroglycerin + B-Blocker
Pheochromocytoma	{Nitroprusside + Labetalol} or Phentolamine
Eclampsia	Methyldopa, Magnesium sulfate (do not use with CCBS), Hydralazine

- **Special Populations:-**

Population or Disease State	Preferred Agents	Avoid Agents
- African Americans and Elderly	Thiazide, CCB	
- Pregnancy	α-Methyldopa, CCB, Labetalol	ACEI, ARB, Aliskiren and others
- Coronary Diseases (Angina & MI)	β-blocker, CCB, ACEI, ARB	
- Asthma and COPD	CCB	β-blockers, ACEI, ARB
- Benign Prostatic Hyperplasia	α-blocker	
- Depression	CCB, ACEI, ARB	Centrally acting inhibitors, β-blockers, Reserpine
- Diabetes Mellitus	CCB, ACEI, ARB	β-blockers
- Gout	CCB, ACEI, ARB	Diuretics
- Heart Failure	ACEI, ARB, B-blocker	
- Hyperlipidemia	CCB, ACEI, ARB	β-blockers, Diuretics
- Migraine	B-blocker, CCB	
- Osteoporosis	Thiazide	Loop diuretics
- Peripheral Vascular Diseases	α-blockers, Dihydropyridines CCB	β-blockers
- Renal Diseases	Loop diuretics	Thiazide diuretics