Anti-hypertensive Drugs

**Hypertension** is defined as blood pressure $\geq 140/90$ mmHg, measured in three separate different occasions.

N.B.

- **Isolated Systolic Hypertension**: SBP = $140 – 160$ mmHg with normal DBP. It usually found above age of 60.
- **White Coat Hypertension**: hypertension only when visiting doctors. Ambulatory 24 hours recording of blood pressure may be needed to establish the diagnosis.

**Classification and Etiology:**

1. **Primary (essential) hypertension**: of unknown cause, but many risk factors can contribute e.g. Smoking, obesity, excess salt intake, hypercholesterolemia and diabetes mellitus. Constitute about 85-95% of cases.

2. **Secondary hypertension**: of a known cause. Constitute only 10-15% of cases and may be due to:
   - Renal diseases: Renal artery stenosis and glomerulonephritis.
   - Endocrine diseases: Pheochromocytoma, primary hyperaldosteronism and Cushing’s syndrome.
   - Vascular diseases: coarctation of aorta.
   - Drug induced (Iatrogenic): corticosteroids, oral contraceptives, carbenoxolone and sympathomimetics with predominant $\alpha$ effect.

**Symptoms and complications:**

Essential hypertension may remain symptomless until appearance of complications (end organ damage), which may be fatal (**SILENT KILLER**).

**Symptoms**: headache, blurred vision, nausea, palpitation and fatigue.

**Complications**:

1. **CVS**: left ventricular hypertrophy, angina pectoris, myocardial infarction and congestive heart failure.
2. **Cerebral**: cerebral atherosclerosis, thrombosis and hemorrhage (cerebral stroke).
3. **Renal**: chronic renal failure.
4. **Retinal**: Retinal hemorrhage and papilledema (edema of optic disc) $\rightarrow$ impaired vision.
**Regulation of blood pressure:**

* Arterial blood pressure is directly proportional to product of cardiac output (COP) and total peripheral resistance (TPR).
  
  \[ \text{B.P.} = \text{CO} \times \text{TPR} \]

* It is maintained by regulation of COP, TPR exerted at the arterioles, post-capillary venules (capacitance vessels), and heart.
* Kidney contributes by regulating the volume of blood, also baroreceptors coordinate with these sites to maintain B.P. Thus decreased blood pressure will reflexly increase the sympathetic tone to increase peripheral resistance and COP (by stimulating the heart and constriction of venules).
* Local hormones released from vascular endothelium affect vascular resistance e.g. nitric oxide dilates and endothelin-1 constricts B.V
* Decreased renal perfusion pressure causes intrarenal redistribution of blood and increases salt and water reabsorption. Also increased sympathetic supply via \( \beta_1 \) receptor will increase renin release resulting in angiotensin II and aldosterone formation.
Anti-hypertensive Drugs

1-Sympathetic depressants (Sympatholytics): include

*Adrenergic receptor blockers which include α and β blockers.

*Adrenergic neurone blockers: these drugs rarely used nowadays in treatment of essential hypertension not due to their ineffectiveness but due to marked adverse effects associated with them. They include:

-Guanethidine and Guanadrel: ↓ norepinephrine release → ↓ sympathetic tone so guanethidine can produce all of the toxicities expected from "pharmacologic sympathectomy," including marked postural hypotension, diarrhea, and impaired ejaculation. Because of these adverse effects, guanethidine is now rarely used.

-Reserpine: ↓ stores of norepinephrine, dopamine, and serotonin throughout the body (both central and peripheral neurons). These effects if lowers BP but also leads to psychic depression and extrapyramidal manifestations.

-Metyrosine: ↓ norepinephrine synthesis.

*Ganglion Blockers: Trimethaphan (I.V. infusion) was used in emergency hypertension and to produce controlled hypotension.

*Centrally acting sympatholytics
-α₂ agonists: α methyl dopa and clonidine.
-β₁ agonists: Relminidine and moxonidine. They are similar to clonidine but without sedation.
2-Diuretics:
- Thiazide diuretics.
- Loop diuretics.
- K-sparing diuretics.

3-Angiotensin Antagonists (Drugs inhibiting Renin-Angiotensin-Aldosteron System).

4-Vasodilators:
- Venodilators
- Arteriolar dilators.
- Balanced dilators (dilate both arterioles and venules).

α blockers
- non-selective α blockers e.g. phentolamine is not used in treatment of essential hypertension as they block both presynaptic (α2) and postsynaptic (α1) receptors, with the result that reflex activation of sympathetic neurons produces greater release of Norepinephrine onto α + β receptors and correspondingly blood pressure elevation and cardio-acceleration.

- Selective α1 blockers as prazosin, trimazosin, doxazocin and tamsulosin (selective α-1A blocker). They reduce arterial pressure by dilating both resistance and capacitance vessels. As expected, blood pressure is reduced more in the upright than in the supine position (postural hypotension). Although long-term treatment with these α blockers causes relatively little postural hypotension, a steep drop in standing blood pressure develops in some patients shortly after the first dose is absorbed. For this reason, the first dose should be small and should be administered at bedtime. Retention of salt and water occurs when these drugs are administered without a diuretic. The drugs are more effective when used in combination with other agents, such as a β blocker and a diuretic, than when used alone.

β Blockers:
Include non-selective blockers (propranolol, nadolol, timolol, pindolol…etc) ,cardioselective blockers (atenolol, metoprolol, celiprolol, bisoprolol…etc) and combined β + α blockers (labetalol and carvedilol)

Mechanism of anti-hypertensive action:
a-Inhibition of renin release.
b-Reduction in COP (initially).
c-Resetting of baroreceptor mechanism.
d-Block of peripheral presynaptic β-receptors so decrease norepinephrine release and ↓ sympathetic outflow.
e-Decrease TPR (late, although they may increase it initially).
f-Others (not with all β blockers):
- Partial agonist on β₂ (Celiprolol)
- ↑ synthesis of prostacyclin (PGI₂).
- ↑ release of endogenous nitric oxide e.g. Nebivolol.
- Calcium channel blocking effect.
- Potassium channel activators.

**Common adverse effects:**
1-Sudden cessation of therapy after chronic use may be followed by sympathetic over-activity (angina, infarction or arrhythmia). This may be due to up-regulation of beta receptors.
2-Precipitation of heart failure when COP is dependent on sympathetic drive in patient with abnormal myocardial function.
3-Heart block and severe bradycardia (treated with atropine).
4-Bronchospasm particularly with non-selective β-blockers in asthmatic patient.
5-Hypotension.
6-Cold extremities (due to reduced peripheral blood flow).
7-Fatigue, depression and sleep disturbances.
8-Enhance the hypoglycemic effect of insulin in diabetic patient.
9-Sexual dysfunction.
10-Increased VLDL and decrease HDL (not with β blockers with ISA).

**α-Methyl dopa**

**Mechanism of action:**
- Central mechanism through stimulation of α₂ receptors by α-methyl norepinephrine (false neurotransmitter). So ↓ V.M.C. and ↓ sympathetic tone and ↓ renin.

**Uses:** Hypertension especially if accompanied by renal impairment and in pregnancy. Minimal or no postural hypotension occurs.

**Adverse effects:**
- Sedation, depression, vertigo, night mares and parkinsonism.
- Hypersensitivity reaction: fever, hepatitis, bone marrow depression and hemolytic anemia and positive Coomb’s test.
- Gynecomastia.
- Salt and water retention.

**Clonidine**: stimulates $\alpha_2$, and partial agonist on $\alpha_1$. It may act on imidazoline receptors and increase parasympathetic tone. It decreases COP, H.R., relaxes capacitance vessels and reduces peripheral resistance.

**Uses**:
- Essential Hypertension.
- Prophylaxis of migraine headache and control of menopausal flushes (in small dose).
- To relieve withdrawal symptoms of opioids and tobacco.

**Adverse effects**:
- Dry mouth (xerostomia), sedation.
- Sudden withdrawal may result in hypertensive crisis, nervousness, headache and tachycardia (which can be controlled by readministration of clonidine or by $\alpha$ blocker or $\alpha + \beta$-blocker), so it is stopped gradually.

**Diuretics**
They include:

* **Thiazide** and thiazide like as **chlorothiazide, hydrochlorothiazide, chlorothalidone**. their antihypertensive effect is mainly due to ↓ peripheral resistance and not due to ↓ blood volume. This effect usually appears 1-2 months after starting treatment. Better used in mild to moderate cases of hypertension especially if accompanied with edema (due to CHF, liver cirrhosis with ascites or nephrotic syndrome). They produce hypokalemia, hyperuricemia, hyperglycemia & hyperlipidemia (↑ LDL). They are contraindicated in renal failure.

**N.B.:** **Indapamide is a non thiazide sulphonamide diuretic which has VD activity.**

- **Loop diuretics** as furosemide, ethacrynic acid, Trosemide and bumetanide. Their antihypertensive effect is mainly due to ↓ blood volume and not due to ↓ peripheral resistance. This is because they are short acting and most potent diuretics → rapid ↑ in urine volume → rapid ↓ in BP. Better used in emergency hypertension where rapid reduction of BP is needed within short period. Note that multiple use of loop diuretic/day → more side effects than more blood pressure control. They are used in hypertension with renal insufficiency, emergency hypertension, and when multiple drugs with salt retaining effect are used.

- **Potassium sparing diuretics** as spironolactone, triamterene and amiloride. They are useful to avoid hypokalemia induced by other diuretics and to enhance the effect of other diuretics. They are not used alone in treatment of hypertension.

**Drugs inhibiting renin angiotensin Aldosterone System (RAAS)**

A) Angiotensin converting enzyme inhibitors (ACE inhibitors):

```
Angiotensinogen \(\rightarrow\) renin

\[\text{Angiotensin I (inactive)} \rightarrow \text{ACE} \rightarrow \text{Kininogen} \rightarrow \text{Kininase II} \rightarrow \text{Bradykinin} \rightarrow \text{↑ PGs} \rightarrow \text{V.D.}\]
```
Angiotensin II, III          Inactive
- V.C. $\rightarrow$ ↑ TPR
- ↑ aldosterone $\rightarrow$ Na$^+$ retention, hypokalemia.
- ↑ sympathetic transmission & catecholamine release.
- Hypertrophy of cardiovascular system and remodeling.

**ACE inhibitors** include:
- Drugs: **Captopril, lisinopril**.
- Pro-drugs: **enalapril, fosinopril, benazepril, ramipril, prindopril**
  ....etc converted in liver into active enalaprilat, fosinoprilat, benazeprilat... etc

**Pharmcokinetics**
Given orally, eliminated by kidney but fosinopril and moexipril are eliminated also by liver.
**I.V. Enalaprilat** is available in emergency hypertension

**Actions:**
- They inhibit ACE, kininase II so decrease angiotensin II and increase bradykinin.
- They decrease TPR, aldosterone and sympathetic transmission and reduce both pre- and afterload and ↓ B.P. without postural hypotension.
  COP and H.R. are not significantly changed but renal flow is increased.

**Uses:**
1- Essential hypertension. They have no metabolic effects, reduce left ventricular hypertrophy in hypertensive patients and prevent hypertrophy in cardiovascular system.
2- Congestive Heart failure.
3- Myocardial infarction, they reduce remodeling after infarction.
4- Diabetic nephropathy (normo or hypertensive), they reduce proteinuria.

**Adverse Effects:**
- Hyperkalemia especially in renal insufficiency, with K-retaining diuretics or K$^+$ supplement or $\beta$-blockers or NSAIDs.
- Cough, angioneurotic edema (due to increased bradykinin level)
- Skin rash, neutropenia, hepatic toxicity (rare).
- Proteinuria, however, they improve proteinuria in diabetics.
- Hypotension especially in Na\(^+\) depleted patients.
- Acute renal failure in bilateral renal artery stenosis.
- Dysgeusia (decreased taste sensation).
- In pregnancy, they produce fetal growth retardation and oligohydramnios.

**Contraindications:**
- Pregnancy.
- Bilateral renal artery stenosis.

**Interactions:**
- Antacids ↓ absorption.
- NSAIDs ↓ the effect.
- Hyperkalemia (with K-retaining diuretics).

**B) Angiotensin receptor antagonists:**

Losartan, candesartan, telmisartan, irbesartan and valsartan are nonpeptide angiotensin receptor antagonists selective for AT\(_1\) receptors so block the pressor response, stimulatory effect on sympathetic system, release of catecholamines, action on kidney, secretion of aldosterone and growth promoting action.
- They are used in hypertension and congestive heart failure (as ACE inhibitors).

**Side effects** are similar to ACE inhibitors but with much less cough and angioneurotic edema.

**Vasodilators**

**Classified into:**

A. **Arteriolar:** hydralazine (oral & I.V.), minoxidil (oral), diazoxide (I.V.) and fenoldopam (I.V. drip)

B. **Veinodilators:** Nitrates (SEE ANTI-ANGINAL DRUGS).

C. **Balanced (Mixed) dilators:** sodium nitroprusside (I.V. drip).

D. **Calcium Channel blockers.**

The relaxation of vascular smooth muscles of arterioles will ↓ systemic vascular resistance and mean arterial pressure, thus eliciting compensatory
mechanism mediated through baroreceptors, sympathetic nervous system and renin angiotensin system which elevates B.P. again. The addition of a β blocker prevents the tachycardia; addition of a diuretic (e.g. hydrochlorothiazide) prevents the salt and water retention. In effect, all three drugs increase the sensitivity of the cardiovascular system to each other's actions.

1) **Hydralazine**:

**Uses:**
- Hypertension especially with renal insufficiency.
  It is given oral or I.V. in emergencies.

**Adverse effects:**
- Headache, flushing, tachycardia, palpitation, arrhythmia, anginal pains, sweating, anorexia, nausea and salt retention.
- Peripheral neuritis and pyridoxine-responsive polyneuropathy.
- With large doses especially in slow acetylators it may produce reversible lupus like syndrome (arthralgia, myalgia, skin rash, fever, vasculitis and glomerulonephritis, renal damage).

**Contraindications:**
- Angina pectoris.
- Cardiac arrhythmia.

2) **Minoxidil**

Very effective potent oral vasodilator affecting arterioles, it may act by opening of K^+ channels. **It is a prodrug.**

**Uses:**
* Essential Hypertension. It should be combined with diuretic and beta-blocker.
* Topical in alopecia or baldness.

**Adverse effects:** Tachycardia, palpitation, angina pectoris, salt retention, headache, sweating and hypertrichosis.

3) **Diazoxide**

**Uses:**
* Emergency hypertension given I.V. starting by small doses then gradually increased.
**Adverse effects:** Excessive hypotensive, salt retention, tachycardia, hypokalemia, hyperglycemia, hyperuricemia, hypersensitivity reaction, thrombophlebitis and relaxes uterus.

4) Sodium nitroprusside (Nipride):

**Pharmacokinetics:** It is rapidly metabolized by uptake into RBCs liberating cyanide which is then metabolized by rhodanase enzyme to thiocyanate. Thiocyanate is distributed extracellularly and is eliminated by kidney.

* It is given by I.V. drip and should be freshly prepared and protected from light.

**Uses:**

* Hypertensive emergencies.
* To produce controlled hypotension.
* In acute heart failure.
* In acute dissecting aortic aneurysm (combined with β-blocker).

**Advantages:** Rapid onset, potent and flexible control.

**Adverse effects:**

- Excessive hypotension, arrhythmia and accumulation of cyanide (so with large dose give sodium thiosulphate or hydroxocobalamin). Thiocyanate accumulation in renal impairment → weakness disorientation, psychosis, convulsions or rarely hypothyroidism (inhibit iodide uptake). It is removed by hemodialysis.
- Nitroprusside can worsen arterial hypoxia in chronic obstructive pulmonary disease. Also rebound hypertension may occur after sudden cessation.

5) Fenoldopam: is a D₁ agonist which dilates peripheral arterioles with t₁/₂ 10 minutes. It is given by I.V drip in emergency hypertension. It produces tachycardia, headache, flushing and increases IOP.

**Ca++ channel blockers**

**Classification:**

* **Dihydropyridines:** nifedipine, amlodipine, nitrendipine, nimodipine, nicardipine …etc
* **Non-Dihydropyridines:** verapamil, diltiazem and bepridil.
Verapamil diltiazem and bepridil affect heart more than vessels while nifedipine, nimodipine and nicardipine affect vessels more than heart.

**Mechanism of action:**
- These drugs are bound to membrane structures responsible for slow inward current of calcium and so smooth and cardiac muscles are affected. They block voltage gated Ca\(^{++}\) channels (L-type).
- They act from the inner side of the membrane.
- They relax smooth muscles but vascular smooth muscles are the most sensitive and arterioles are more affected than veins. So they decrease peripheral and coronary resistance especially nifedipine.
- The rate of S.A. node and A.V. conduction are reduced by verapamil and diltiazem. Both verapamil and diltiazem block tachycardia in calcium dependent cells while nifedipine has less depressant cardiac effects.

1) **Verapamil:**
   - **Uses:**
     a- Antiarrhythmic in supraventricular arrhythmia (class IV).
     b- Prophylactic treatment of all types of angina.
     c- Essential Hypertension.
     d- Prophylaxis of migraine headache, hypertrophic cardiomyopathy, peripheral vascular diseases and premature labour.
   - **Adverse effects:** Bradycardia, heart block, heart failure, hypotension, headache, dizziness, flushing, ankle edema and constipation.
   - **Interactions:**
     - With beta-blocker severe cardiac depression may occur.

2) **Diltiazem:** Is similar to verapamil but less potent, less effect on contraction.

3) **Nifedipine:**
   - **Uses:**
     a- Essential Hypertension, Raynaud's disease, cardiomyopathy, migraine.
     b- Angina pectoris.
   - **Adverse effects:** Hypotension, headache, flushing, nausea, vomiting, constipation and ankle edema.
4) **Nitrendipine**: Is similar to nifedipine but more potent and has a longer duration.

5) **Nimodipine** is used to reduce morbidity following subarachnoid haemorrhage probably by preventing vasospasm.

**Treatment of Hypertension**

**Aim of Treatment:**
1-To reduce morbidity (control of risk factors) and to reduce mortality (control of complications).
2-Exclude secondary causes of hypertension that might be treated by definitive surgical procedures.
3- Being a chronic illness try to use the least effective dose and consider side effects of the drug, cost effectiveness and improve compliance by simplifying dosing regimens and having the patient monitor blood pressure at home.
3- Follow-up visits should be frequent enough to convince the patient that his illness is serious. With each follow-up visit, the importance of treatment should be reinforced and questions concerning dosing or side effects of medication encouraged.

**Lines of Treatment:**

A- **Non-pharmacological Treatment:**
1-Dietary sodium restriction to 2 gm Na+/day.
2-Weight reduction in obese patients. Weight reduction even without sodium restriction has been shown to normalize blood pressure in up to 75% of overweight patients with mild to moderate hypertension.
3-Regular exercise has been shown in some but not all studies to lower blood pressure in hypertensive patients.
4-Alcohol restriction.
5- Cessation of smoking.
6- Proper control of Diabetes Mellitus and hypercholesterolemia.
7-Relaxation and biofeedback therapy.

B- **Pharmacological Treatment**

**Choice of Drugs in Therapy of Hypertension (Stepped Care Approach)**

A. **Mild or Moderate Hypertension:**
1) Start with a single drug (monotherapy) using one of the following: thiazide diuretic or β-blocker or ACE inhibitor or Ca²⁺ channel blocker. Choice of first line therapy should be based on the type of patient and the presence of concomitant disease (see table below).
However, the preferred drugs for initial therapy of mild or moderate hypertension are **thiazide diuretics or β-blockers** which were shown to reduce cardiovascular morbidity and mortality in large clinical trials.

2) The selected drug should be started at a low dose to avoid side effects. If blood pressure remains uncontrolled, the dose is increased.

3) If blood pressure is not controlled either change to a single drug of a different group or **ADD** a second drug with a different site of action e.g. **thiazide diuretic + β-blocker or thiazide diuretic + ACE inhibitor.**

**Fixed-dose drug combinations containing a β blocker, an ACE inhibitor, or an angiotensin receptor blocker plus a thiazide, and a calcium channel blocker plus an ACE inhibitor are available. Fixed-dose combinations have the drawback of not allowing for titration of individual drug doses but have the advantage of allowing fewer pills to be taken, potentially enhancing compliance and decreasing incidence of adverse drug effects.**

4) If hypertension still is **not** controlled by the "two-drug regimen", **ADD** a 3rd drug e.g. **thiazide diuretic + β-blocker + vasodilator** (ACE inhibitor or Ca²⁺ channel blocker; or Hydralazine or Prazosin).

**B. Severe Hypertension:**
Start by "triple therapy" using a combination of three drugs e.g. **thiazide diuretic + β-blocker + vasodilator** (see above).

**Alternative Choices:**
• In patients with renal impairment, thiazide diuretics are contra-indicated and loop diuretics (e.g. frusemide) are recommended instead.
• β-blocker can be substituted with a central α2-agonist (e.g. clonidine, methyldopa) when β-blockers are contraindicated or are poorly tolerated.

C. Hypertension Resistant to Triple Therapy:
Patients resistant to triple therapy described above may respond to:
• Minoxidil + β-blocker + loop diuretic (e.g. frusemide) or
• ACE inhibitor + loop diuretic + Ca2+ channel blocker.

D. Hypertensive Emergencies:
Drugs for Use in Hypertensive Emergencies (see table below)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Action</th>
<th>Route</th>
<th>Onset</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium Nitroprusside</td>
<td>Arteriolo- &amp; veno-dilator</td>
<td>IV infusion</td>
<td>&lt; 1 min</td>
</tr>
<tr>
<td>Nitroglycerin</td>
<td>Venodilator &amp; to a less extent arteriolar dilator.</td>
<td>IV infusion</td>
<td>2-5 min</td>
</tr>
<tr>
<td>Trimethaphan</td>
<td>Ganglion blocker.</td>
<td>IV infusion</td>
<td>1-3 min</td>
</tr>
<tr>
<td>Nicardipine</td>
<td>Ca channel blocker</td>
<td>IV</td>
<td>1-5 min</td>
</tr>
<tr>
<td>Diazoxide</td>
<td>Arteriolo-dilator</td>
<td>IV</td>
<td>1-2 min</td>
</tr>
<tr>
<td>Labetalol</td>
<td>β-and α-Blocker</td>
<td>IV</td>
<td>5-10 min</td>
</tr>
<tr>
<td>Hydralazine</td>
<td>Arteriolar dilator</td>
<td>IV</td>
<td>10-30 min</td>
</tr>
<tr>
<td>Frusemide</td>
<td>Loop diuretic</td>
<td>IV</td>
<td>15 min</td>
</tr>
<tr>
<td>Enalaprilat</td>
<td>ACE inhibitor</td>
<td>IV</td>
<td>15 min</td>
</tr>
</tbody>
</table>

• Hypertensive emergencies are defined as diastolic blood pressure >130 mmHg associated with progressive end-organ damage e.g. papilledema, hypertensive encephalopathy, pulmonary edema or acute renal insufficiency.
• The patient should be hospitalized for rapid but careful and controlled reduction of blood pressure.
• Avoid excessively rapid lowering of blood pressure since it can result in stroke or myocardial infarction.
• As soon as reasonable blood pressure control is achieved, oral antihypertensive therapy should be substituted, because this allows smoother long-term management of hypertension. Rather, blood pressure should be lowered maintaining diastolic blood pressure at no
less than 100-110 mm Hg. Subsequently, blood pressure can be reduced to normal levels using oral medications over several weeks.

**Choice of Antihypertensive Drugs in Special situation of Hypertension**

Usually hypertension is accompanied by other diseases which restrict the use of some antihypertensives and favors the use of others. The following are the best choices of drugs if hypertension is associated with:

1. Heart Failure: Thiazides, ACE inhibitors and.
2. Heart Block: Thiazides, ACE inhibitors, ARBs and Nifedipine.
3. Angina Pectoris: β blockers and Ca\(^{2+}\) channel blockers.
4. Bronchial asthma: Ca\(^{2+}\) channel blockers.
5. Diabetes Mellitus: ACE inhibitors, ARBs and Ca\(^{2+}\) channel blockers.
6. Gout: ACE inhibitors and Ca\(^{2+}\) channel blockers.
7. Peptic Ulcer: all classes except reserpine.
9. Renal Failure: α2 agonists, loop diuretics and Ca\(^{2+}\) channel blockers.
10. Hyperlipidemia: ACEIs and Ca\(^{2+}\) channel blockers (avoid diuretics and β blockers).

**Common Causes of Treatment Failure in Hypertension**

1. Non-compliance with drug therapy.
2. Inadequate drug dosage.
3. Incorrect choice of drugs e.g. thiazides in advanced renal insufficiency.
4. Excess salt intake.
5. Concomitant use of antagonistic drugs e.g. NSAIDs, cold remedies, sympathomimetics, oral contraceptives and adrenal steroids.
6. Failure to recognize a cause for hypertension e.g. pheochromocytoma or renal artery stenosis.