



Interesting Cases in Hypertension

Useful Lessons on Management

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SECTION 2

Hypertension – Types

YP Munjal

CASE 1: Resistant Hypertension

A 55-year-old woman, known hypertensive since past 6 years, came to OPD with complaints of persistent headache. She denied any history of chest pain, dyspnea, or visual disturbance. On examination, the heart rate (HR) was 64 bpm and blood pressure was 180/100 mm Hg. Cardiovascular system (CVS) and respiratory system (RS) examinations were clinically normal. Electrocardiogram (ECG) showed left ventricular hypertrophy (LVH). She had been compliant with her medication which included 10 mg amlodipine, 100 mg atenolol, and 12.5 mg chlorthalidone.

- Q1. Resistant hypertension is defined as all these, as per Indian Guidelines on Hypertension IV recommendations, except**
- Not able to attain BP <140/90 mm Hg
 - 2 drugs + 1 diuretic at maximum tolerable dose
 - 3 drugs + 1 diuretic at maximum tolerable dose
 - Does not include newly detected case of systemic hypertension
- Q2. The prevalence of resistant hypertension is around:**
- <1%
 - 20–25%
 - 70–75%
 - 85–90%
- Q. 3. All these are termed as “pseudo-resistance”, except:**
- Suboptimal BP recording techniques
 - Thick walled arteries in elderly (Osler’s sign)
 - White coat effect
 - Poor adherence to antihypertensive drugs
- Q4. The risk factors associated with resistant hypertension:**
- Diabetes
 - Left ventricular hypertrophy
 - Black race
 - All
- Q5. Nonsteroidal anti-inflammatory drugs (NSAIDs) cause resistant hypertension due to which mechanism:**
- Inhibit prostacyclin synthesis
 - Decrease renal blood flow

- c. Sodium and water retention
- d. All of the above

Ans. 1-c, 2-b, 3-b, 4-d, 5-d

■ DISCUSSION

Resistant hypertension is defined as blood pressure that remains above goal of <140/90 mm Hg in spite of the use of three antihypertensive agents of different classes. One of the three agents should be a diuretic. All the agents should be prescribed in optimal doses. What constitutes an “optimal dose” of medication is a moderate dose but not necessarily a maximum dose.

■ PREVALENCE AND PROGNOSIS

The exact prevalence of resistant hypertension in the general population remains unknown. Data from different studies shows a wide variation from 10% to 30% in different populations.

“Uncontrolled hypertension” is not resistant hypertension. This includes patients who lack blood pressure control due to poor adherence and/or an inadequate treatment regimen. Patients with true resistant hypertension are part of it also.

The prognosis of resistant hypertension is worse than those with good blood pressure control. Patients with secondary hypertension often have resistant hypertension unless the underlying cause is treated. We should investigate patients with resistant hypertension more extensively for secondary causes. Also, they more often have associated cardiovascular risk factors such as diabetes, obstructive sleep apnea, left ventricular hypertrophy (LVH), and/or chronic kidney disease (CKD).

True and pseudo-resistant hypertension, it is important to determine whether the hypertension is truly resistant.

True resistant hypertension includes those who have uncontrolled clinic and home blood pressures despite being compliant with an antihypertensive regimen that includes three or more drugs.

Pseudo-resistant hypertension includes patients with uncontrolled blood pressure that is due to factors other than true resistance. This may be due to white-coat effect, suboptimal doses, lack of compliance, or concomitant use of drugs such as NSAIDs or alcohol.

Patient Characteristics Associated with Resistant Hypertension

- Older age
- High baseline blood pressure
- Obesity
- Excessive dietary salt ingestion
- Chronic kidney disease

- Diabetes
- Left ventricular hypertrophy
- Black race
- Female sex
- Residence in southeastern United States.

A variety of medications can raise the blood pressure and, in some cases, reduce the response to antihypertensive drugs. These include:

- *Non-narcotic analgesics:*
 - Nonsteroidal anti-inflammatory agents, including aspirin
 - Selective cyclooxygenase-2 (COX-2) inhibitors
- Sympathomimetic agents (decongestants, diet pills, and cocaine)
- Stimulants (dextroamphetamine, amphetamine, and modafinil)
- Alcohol
- Oral contraceptives
- Cyclosporine
- Erythropoietin
- Natural licorice
- Herbal compounds (ephedra)

Secondary causes: Patients with resistant hypertension are also much more likely to have an identifiable cause of hypertension.

Common:

- Obstructive sleep apnea
- Renal parenchymal disease
- Primary aldosteronism
- Renal artery stenosis

Uncommon:

- Pheochromocytoma
- Cushing's disease
- Hyperparathyroidism
- Aortic coarctation
- Intracranial tumor

■ EVALUATION

The evaluation should be directed toward confirmation of true resistance; identification of causes contributing to resistance, secondary causes of hypertension; and evaluation of target-organ damage. Blood pressure measurements should be done at home and in the clinic both. In some cases, ambulatory BP monitoring may be required.

Medical history for duration, severity and progression of the blood pressure; treatment adherence, response to prior medications, adverse effects of drugs, and current medications must be evaluated. History of use of herbal, over-the-counter medications, and other drugs known to increase BP such as cocaine,

amphetamines, cyclosporine, tacrolimus, tobacco, and some illicit drugs. History pointing toward secondary causes of hypertension should be taken. Drug compliance at times depends on cost factors, which needs to be looked at. At times patients miss drugs when they have other concomitant acute ailments.

Usual precautions for proper BP measurement technique should be adopted. This includes having the patient sit quietly in a chair with his or her back supported for 5 minutes before taking the measurement; use of the correct cuff size with the air bladder encircling at least 80% of the arm. The arm should be at heart level during the measurement. Minimum of 3 readings should be taken at intervals of at least 1 minute and the average of those readings should be taken.

The white coat effect can be assessed by comparing home blood pressure measurement (HBPM) with the office blood pressure values. Multiple readings should be undertaken in both settings. More recently automated office blood pressure (AOBP) can be used since it partly eliminated the white coat effect. AOBP readings are often less than physician/nurse measured manual blood pressure office readings although they are often somewhat higher than the HBPM readings. At times of 24-hour ambulatory blood pressure monitoring may be done.

Biochemical evaluation of resistant hypertensive should include routine metabolic profile (sodium, potassium, glucose, blood urea nitrogen, and creatinine) and urine analysis. Plasma aldosterone levels to look for primary aldosteronism should be done. Once biochemical parameters are suggestive of a secondary cause imaging can be used. Ultrasound abdomen and renal Doppler studies are cost effective and can be used initially. Computed tomography (CT) abdomen for adrenal masses or renal pathology and radio nuclear imaging are to be used where initial imaging studies or biochemistry raises suspicion of secondary causes.

■ TREATMENT RECOMMENDATIONS

- Maximize the drug adherence.
- Nonpharmacological recommendations should be emphasized. This includes weight loss, dietary salt restriction, moderation of alcohol intake, increased physical activity, and ingestion of a high-fiber and low-fat diet.
- Treatment of secondary causes of hypertension whenever diagnosed.

Better BP control is achieved by combining drugs from different classes rather than by increasing the dose of a single medication. Use multiple drugs in combination. Pill burden should be kept low by using fixed dose combinations.

Aldosterone-antagonist spironolactone should be added as the fourth agent once angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACE inhibitor/ARB) + calcium channel blocker (CCB) and thiazide like diuretic has been used. The PATHWAY 2 study showed that it is to be preferred over beta-blockers and doxazosin as an add on therapy. Therapy with mineralocorticoid receptor antagonist involves pharmacologic blockade of the mineralocorticoid receptor targeting the excess aldosterone commonly present in patients with

resistant hypertension (RH). Spironolactone is most frequently used. Eplerenone has fewer adverse effects but is a costlier and less potent alternative. Spironolactone may reduce systolic BP by 15–20 mm Hg in patients with hypertension that is resistant to 3 drugs.

Further add on agents for those in whom blood pressure is still uncontrolled can include vasodilating β -blocker (e.g., labetalol, carvedilol, and nebivolol), direct vasodilators (e.g., hydralazine or centrally acting agent such as clonidine) or alpha methyl dopa.

Recent technological advances, along with the growing need for effective management of RH, rekindled the concept of interventional management and made it one of the hottest research areas in hypertension. Interventional options available are carotid baroreceptor activation and renal denervation.

A small device, like a pacemaker, is used to constantly activate carotid baroreceptors. The effects of carotid baroreceptor activation are mediated by the attenuation of sympathetic nervous activity. Muscle sympathetic nervous activity (MSNA), a reliable and commonly used index of systemic SNA, has been shown to be reduced following baroreceptor activation. Long-term efficacy and outcome data from large randomized controlled trials (RCTs) are needed to establish baroreceptor activation as a viable alternative for the management of RH.

Renal denervation therapy using radiofrequency probes to ablate the sympathetic fibers along the renal artery showed great promise in initial studies. The SYMPPLICITY 1 and 2 studies showed reduction in BP with renal denervation. These results were better than the drug therapy. However, the subsequent larger and more meticulous study, the SYMPPLICITY 3 trial showed that there was no significant difference in patient outcome between renal denervation and a sham procedure among patients with drug resistant hypertension. After 6 months, office systolic blood pressure decreased from baseline to a similar extent in the renal-denervation and sham-procedure groups. These findings contradict most published data on renal denervation.

■ SUGGESTED READINGS

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CASE 2: Isolated Systolic Hypertension

A 72-year-old gentleman, retired government officer, presented in the OPD. He is in good health. There is no significant medical history in the past except for an uneventful inguinal hernia surgery 10 years back. He has no other cardiac risk factor such as diabetes, smoking, obesity, or dyslipidemia. A routine health check-up for senior citizen revealed a blood pressure (BP) of 180/80 mm Hg. He does "brisk walks" regularly in the morning for 30 minutes, at least 5 days a week. Clinical examination revealed short systolic murmur over the aortic area. Baseline biochemical investigations, including renal function were normal. Lipid profile was normal. Electrocardiogram (ECG) showed evidence of left ventricular hypertrophy. ECG showed aortic valve sclerosis with no hemodynamically significant transaortic gradient or regurgitation. A clinical diagnosis of isolated systolic hypertension (ISH) was made. Therapy was initiated with a combination of calcium channel blocker (CCB—amlodipine) with low dose diuretic (chlorthalidone).

- Q1. Individual with blood pressure recording of 172/84 mm Hg should be classified as?**
- High normal
 - Isolated systolic hypertension
 - Grade 1 hypertension
 - Grade 2 hypertension
- Q2. About ISH, which of the following statement is not true?**
- Raised systolic pressure with normal or low diastolic pressure is seen
 - Widened pulse pressure is observed
 - It is a disease of elderly
 - Need not to be treated with antihypertensive therapy
- Q3. Which of the following statements is wrong regarding management of ISH?**
- Lifestyle modification rarely helps
 - Thiazide diuretics can be used as first line drug
 - In patients with benign prostatic hyperplasia (BPH), one can use alpha blocking agents
 - All of the above statements are wrong
- Q4. All is true regarding lifestyle modifications for management, except:**
- Dietary sodium restriction
 - Physical exercise
 - Low fiber diet
 - Moderation of alcohol

Q5. Which of the following is/are risk factor for development of ISH?

- a. Cigarette smoking
- b. Alcohol abuse
- c. Diabetes
- d. All of the above

Ans. 1-b, 2-d, 3-a, 4-c, 5-d

■ DISCUSSION

Isolated systolic hypertension is seen more often in the elderly. Systolic blood pressure (SBP) is known to rise with advancing age; whereas diastolic BP usually levels off and does not change beyond 60 years. ISH is the most prevalent type of hypertension in those over 60 years of age and represents a substantial healthcare problem as the target BP is more difficult to attain. ISH is defined as systolic BP >140 mm Hg and diastolic BP <90 mm Hg.

■ CLASSIFICATION

ISH	Systolic (mm Hg)		Diastolic (mm Hg)
Stage 1	140–159	and	<90
Stage 2	>160	and	<90

■ ETIOLOGY AND PATHOPHYSIOLOGY

Besides increase with advancing age, ISH may be seen in young patients. ISH in young individuals is seen especially among those who are obese and smokers. Subjects with hyperthyroidism, hyperaldosteronism, renal insufficiency and failure, and renal artery stenosis also have predominant systolic BP elevation. Similarly drug-induced hypertension [nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2) inhibitors, corticosteroids, and cyclosporine], excess alcohol use, obstructive sleep apnea (OSA), anemia, beriberi, Paget's disease, and some cancers can cause a relative high output state resulting in greater systolic elevation.

Isolated systolic hypertension largely occurs due to progressive structural and functional changes in the arterial wall, involving endothelial dysfunction, atherosclerosis, aortic stiffness, increased wall stress, and pulse pressure. Vascular endothelial damage and mechanical strain from each stroke volume also play a role. Atherosclerosis progressively leads to the replacement of elastin by collagen and other structural proteins and the build of calcium in the arterial wall, and this in turn results in hypertrophy and fibrosis of arterial wall. All these factors lead to increased vascular stiffness and reduced compliance causing a decrease in the "Windkessel function" of the large arteries. Renin-angiotensin system also plays a role in the pathogenesis of arterial stiffness by decreasing elastin content and increasing collagen of arterial wall.

■ CLINICAL FEATURES

Isolated systolic hypertension is most often asymptomatic and diagnosed on routine examination. Severe hypertension or an abrupt rise of BP may cause headache, blurred vision, or dizziness. Epistaxis may be a presenting feature. Some patients may have concomitant end organ damage including symptoms of coronary artery disease (CAD), heart failure, arrhythmias, stroke, intermittent claudication due to peripheral arterial disease, aortic aneurysm, aortic dissection, features of hypertensive retinopathy, and renal insufficiency or failure.

■ EVALUATION

Evaluation should include assessment of other cardiovascular (CV) risk factors, potentially contributing lifestyle factors (diet, exercise, alcohol, smoking, body weight, and drugs), end organ damage and secondary causes of hypertension. Physical examination should include looking for all peripheral pulses, optic fundi, cardiac, and neurological system. Abdominal and carotid bruit should be looked for. Ambulatory BP Monitoring (ABPM) may be used in some elderly patients to identify white coat effect, nondippers, and to assess response to drugs. Home BP measurement (HBPM) should be advocated to all for monitoring the response to treatment. The devices are easily available and user friendly.

■ MANAGEMENT

The systolic BP is a stronger predictor of cerebrovascular and CV events than diastolic BP. Several intervention studies in ISH (such as SHEP, SYST-EUR, SYST-China, INSIGHT, and LIFE) have demonstrated beneficial effects of treatment of ISH. Effort should be made to bring down systolic BP below 140 mm Hg in all individuals. Patients with very low diastolic BP of below 60 mm Hg those who have known coronary artery disease one should keep in mind the J-curve phenomenon.

Lifestyle Changes

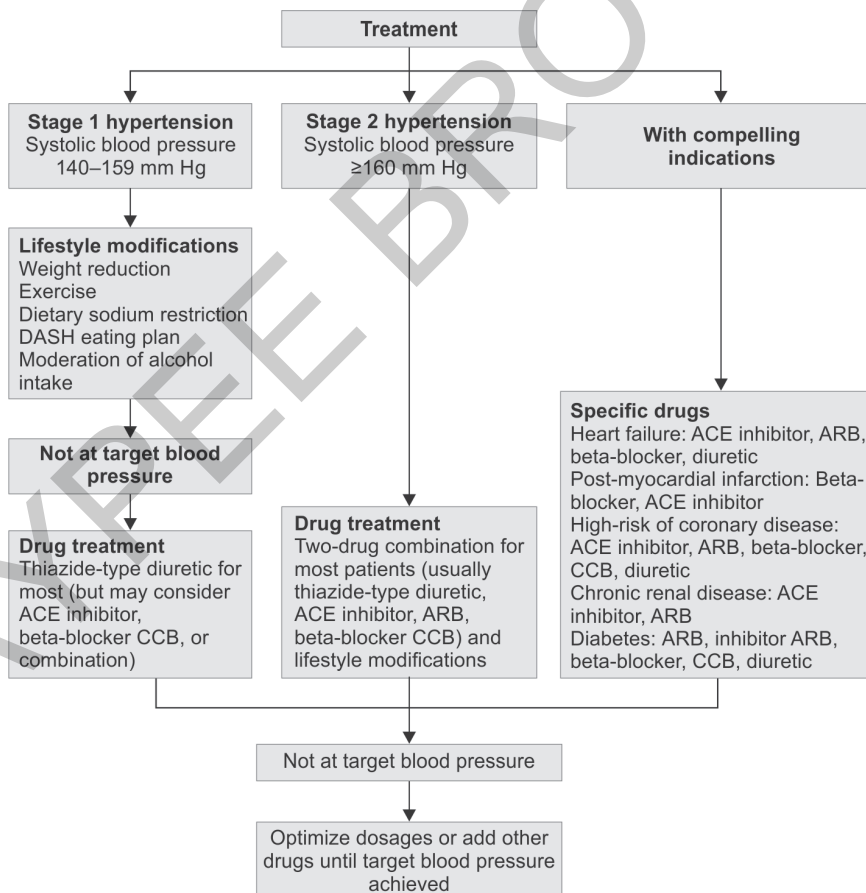
- *Weight reduction:* It improves insulin sensitivity, sleep apnea, and the response to drugs. It is advisable to maintain ideal body weight (BMI 18.5–24.9 kg/m²).
- *Dietary sodium restriction:* Moderate degrees of sodium restriction to 2.4 g/day results in SBP reduction by 2–8 mm Hg. Indian diet contains 8–12 g of salt and it should be reduced to 5 g.
- *Diet changes:* Diet should be rich in fruits, vegetables, low in saturated and total fat, and high in fiber content. Besides better BP control, it helps in reducing the risk of CAD and stroke.
- *Moderation of alcohol:* Excessive alcohol use is a common cause of reversible hypertension. Binge alcohol use can be particularly harmful. Abstinence can cause systolic BP reduction of 4–6 mm Hg.
- *Avoidance of tobacco:* Smoking in any form including chewable tobacco is a significant contributory factor for ISH. Smoking cessation results in significant BP reduction.

- **Physical exercise:** Regular aerobic physical activity such as brisk walking at least 45 minutes daily for most of the days of the week results in SBP reduction by 4–8 mm Hg.
- **Stress management:** Relaxation techniques, yoga, and meditation can reduce BP. We should discourage excessive consumption of coffee.

Drug Treatment

Four major classes of antihypertensive agents can be used as first line drugs. These are: (1) diuretics, (2) CCBs, (3) angiotensin-converting enzyme (ACE) inhibitors, and (4) angiotensin receptor blockers (ARBs). Usual approach of combining ACE inhibitor/ARB with a diuretic or a CCB would be second step. As a third step all these three agents can be combined. Spironolactone is the fourth add on agent. In patients with symptoms of benign prostatic hyperplasia, alpha-blockers like doxazosin or prazosin may be used early. Alpha-blockers can cause postural hypotension and so both lying and standing BP should be recorded.

The treatment algorithm for ISH can be as given below:



(ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blockers; CCB: calcium channel blocker)

Flowchart 1: Treatment algorithm for patients with isolated systolic hypertension.

Isolated Systolic Hypertension in the Young

Isolated systolic hypertension among young adults is increasing in prevalence. Some patients with increased sympathetic activity can have tachycardia, features of anxiety and ISH. Isolated systolic hypertension in the young patients is often successfully treated with lifestyle modification and long-acting beta-blockers.

Obesity and smoking are also associated with ISH among young adults. Body fat has been shown to be a strong predictor of aortic stiffness in both young and older adults, which may account for the isolated elevation in SBP among obese young adults.

CASE 3: Downregulation of Antihypertensive Treatment

A 42-year-old male was diagnosed to have hypertension 3 years back. His hypertension has been well controlled and he has been having regular visits every 3 months. Presently he is taking tab amlodipine 5 mg once daily and is also compliant with dietary sodium restriction. He also exercises regularly, has lost 28 kg since past 3 years and presently weighs 78 kg. There is no evidence of any end-organ damage.

- Q1. Among the following, all are the factors predicting successful withdrawal of antihypertensive drugs, except:
 - a. Multiple antihypertensive drugs
 - b. Lower doses of antihypertensive drugs
 - c. Dietary compliance with sodium restriction
 - d. Adherence to lifestyle modifications
- Q2. What percentage of well-controlled stage I hypertensives to remain normotensive even after drug withdrawal?
 - a. <15%
 - b. 30–50%
 - c. 50–80%
 - d. >80%
- Q3. Benefits of antihypertensive drug withdrawal include:
 - a. Less adverse effects
 - b. Better cognition, especially in elderly
 - c. Both
 - d. None
- Q4. Possible mechanisms that make drug withdrawal successful:
 - a. Blood pressure (BP) control may reverse hypertension-induced arteriolar hyperplasia
 - b. Initial mislabeling of white-coat hypertension
 - c. Failure to depend on lifestyle modifications initially
 - d. All of the above

Q5. Withdrawal syndrome is characterized by:

- a. Decreased sympathetic activity
- b. Rebound hypertension
- c. Relief of angina
- d. All of the above

Ans. 1-a, 2-a, 3-c, 4-d, 5-b

■ DISCUSSION

Some patients with stage 1 hypertension are well controlled, often on a single medication. After a period of years, the question arises as to whether antihypertensive therapy can be gradually reduced or even discontinued. The issue of discontinuation of therapy also arises in patients who develop symptoms related to low blood pressure.

Selecting Patients for Antihypertensive Drug Downregulation

Antihypertensive treatment may be gradually reduced or discontinued in those patients who have mild hypertension and are well-controlled for a minimum duration of 1 year. Once treatment has been discontinued, 5–55% of patients stay normotensive for minimum 1–2 years. With a reduction in the number and/or dosage of medications taken, a larger number of patients do well.

As an example, as per a review that included published series of planned withdrawal, it was noted that 42% of the selected patients with mild hypertension (140–149/90–95 mm Hg) were found to remain normotensive for 12 months or longer off medication. Only 18% patients remained normotensive following discontinuation of medications in a more heterogeneous group of patients with well-controlled hypertension.

Patients who had milder hypertension, were taking fewer and lower doses of antihypertensive therapy, and were adherent to modifications in lifestyle (such as weight reduction and restriction of sodium) more likely tolerated cessation of antihypertensive therapy. It is suggested by these findings that in patients who are on multiple drugs, full withdrawal of antihypertensive medications may not be possible; however, gradual tapering of doses and agents of antihypertensive therapy may be possible.

The benefit of discontinuing successful drug therapy is still not certain, though lower doses are related to a lesser incidence of side effects induced by antihypertensive drugs. Therefore in well-controlled patients, it appears to be reasonable to decrease the dose, and withdraw if tolerated, with close monitoring of BP.

Observational studies have suggested that withdrawal of antihypertensive therapy in older adults with cognitive decline may improve cognitive function and prevent progression to dementia. However, a randomized trial found that discontinuation of antihypertensive therapy in older adults did not improve

cognitive function. In this trial, 385 individuals who were 75 years or older with mild cognitive impairment, controlled hypertension (mean blood pressure 148/81 mm Hg), and no significant cardiovascular disease were assigned to have their antihypertensive therapy gradually discontinued or to have no changes made. At 16 weeks, blood pressure increased in the discontinuation group by 7/3 mm Hg, but there was no improvement in cognition or functional status.

Mechanism of Successful Drug Withdrawal

There is limited understanding of the mechanism of persistent normotension with less intensive drug treatment. Hypertension-induced arteriolar hyperplasia may be reversed with long-term BP control, thus decreasing vascular resistance directly as well as by decreasing the sensitivity to vasoconstrictors (e.g., angiotensin II and norepinephrine).

Medical Research Council trial studied this issue in a controlled fashion and gave an alternate explanation for this. The trial suggested that course of the disease may not be altered by effective therapy. But several patients being treated for mild hypertension are, in fact, normotensive or become normotensive by compliance with nonpharmacologic therapies. Many factors, specifically initial mislabeling and modifications in diet, can contribute to this effect. However, the ability to reduce drug dose in many patients may be because of the initial use of excessive dosage.

Mislabeleding

Several patients who are initially diagnosed with mild hypertension are in fact normotensive. The increase in BP represents an acute stress response that is induced by visiting the clinician. This phenomenon, called "white coat" hypertension, illustrates the importance of repeated blood pressure measurements over several months in the office or, preferably, by multiple home measurements before considering an asymptomatic patient with no end-organ damage to be truly hypertensive. Sequential studies have shown that the blood pressure drops by an average of 10–15 mm Hg between the first and third office visits in newly diagnosed patients with mild hypertension, with a stable value not being achieved until >6 visits in some cases.

Dietary Modification

With the modifications in diet alone, initially hypertensive patients can reduce their BP to the normal range. While considering the step-down therapy, the triad of restriction of dietary sodium, weight loss in the obese person, and avoiding excess intake of alcohol may be especially significant. Persistent normotension following drug withdrawal may be most likely among nonobese patients who restrict sodium, and overweight patients who lose weight.

Excessive Doses

Now it is clear that for many antihypertensive drugs, previous dosing recommendations were too high. This resulted in a rise in incidence of side effects while yielding little if any further decrease in BP.

Interesting Cases in Hypertension

Useful Lessons on Management

Key Features

- *Interesting Cases in Hypertension: Useful Lessons on Management* is a unique book covering around 50 cases scenarios specifically related to hypertension
- The book has 230 MCQ's on hypertension from various case scenarios which have been divided into 9 Sections of various aspects of hypertension with different modes of presentation of patients
- Each section of this book has been written by experts and professionals in their respective fields. Particular chapter in the book covers case scenario followed by a detailed discussion regarding the management and treatment strategies pertaining to that case; which is further followed by questions for self-assessment of doctors which can be accessed online
- Several books have been published regarding hypertension but none of the books exclusively discuss the various case scenarios in hypertension; therefore, this book is one of its kind and will be extremely helpful to medical professionals and practitioners.

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