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A REVIEW ON HYPERTENSION: ASSOCIATED RISK FACTORS AND DRUG-RELATED PROBLEMS IN HYPERTENSION MANAGEMENT

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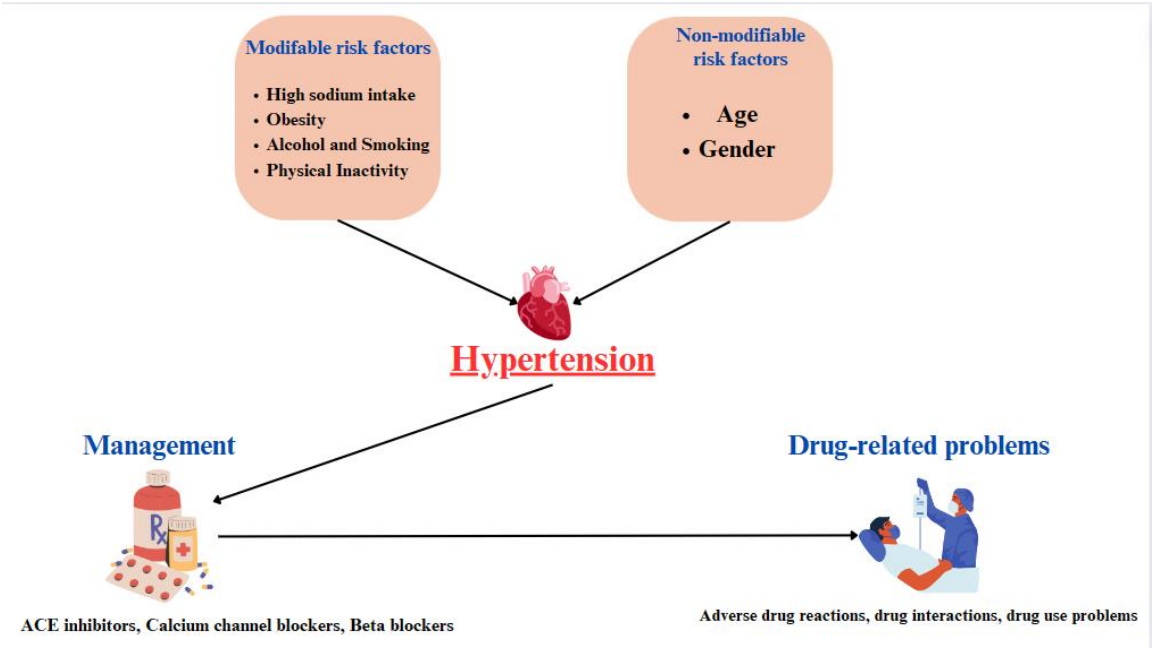
ABSTRACT

Objectives: Hypertension, is a significant contributor to cardiovascular disease-related morbidity and mortality worldwide. It affects a considerable number of adults, estimated to be around 1.28 billion people. The prognosis of hypertension is influenced by various risk factors, including modifiable ones such as high sodium intake, alcohol consumption, smoking, obesity, and physical inactivity, as well as non-modifiable ones like age and gender. However, managing hypertension can be challenging due to patients' co-existing conditions and multiple medications, leading to drug-related issues such as drug choice, dosing, and usage. **Methods:** The data was gathered from various databases including ScienceDirect, PubMed, and Google Scholar, utilizing keywords such as hypertension, risk factors, and drug-related problems. **Result/ Conclusion:** Various risk factors associated with hypertension were analyzed to assess their impact on the prevalence of the condition. Additionally, drug-related issues in the management of hypertension were identified, and categorized, and their prevalence rates were scrutinized.

KEYWORDS: Hypertension, risk factors, Drug-related problem (DRP's).

Graphical abstract



INTRODUCTION

Cardiovascular disease (CVD) encompasses a wide array of conditions that impact the heart muscle and circulatory system, resulting in compromised blood flow to crucial organs such as the brain. Among the varied CVD conditions are hypertension (HTN), coronary artery disease (CAD), congestive heart failure (CHF), arrhythmias, myocardial infarction (MI), angina pectoris, and numerous others. [1] CVD is a significant contributor to mortality worldwide, with a vast majority of fatalities (almost 80%) attributed to low- and middle-income countries.[2]

The most common illness condition among the aforementioned cardiovascular disorders is HTN, often known as increased BP. As per the guidelines from the American Heart Association (AHA) and the American College of Cardiology (ACC), a healthy blood pressure reading is indicated by a diastolic pressure below 80 mm Hg and a systolic pressure below 120 mm Hg. In case the systolic pressure exceeds 130 mmHg or the diastolic pressure is above 80 mmHg, it is categorized as HTN. When the systolic BP falls between 120-129 mmHg and the diastolic BP is below 80 mmHg, it is considered elevated blood pressure, which is a borderline condition.[3,4]

Based on the data provided by the World Health Organization (WHO), the global prevalence of HTN among individuals aged 30 to 79 is estimated to exceed 1.28 billion. Notably, the majority of those affected, which accounts for approximately two-thirds of the total, are residents of low- and middle-income countries.[5] According to a study, around 45.4% of US natives have HTN and in the Chinese population, the prevalence is around 46.4%.[6] In India, approximately 33% of individuals in urban areas and 25% in rural areas have HTN.[7] A study conducted in the urban slums of South India estimated that 34.8% of the population living in slums had HTN.[8]

The prognosis of HTN is influenced by several risk factors, which can be categorized as modifiable and non-modifiable. The patient's age and gender are examples of non-modifiable risk variables. Modifiable risk factors for HTN that can be changed to reduce the chance of developing HTN include high salt intake, alcohol use, smoking, stress, obesity, lack of physical activity, higher levels of triglycerides and total cholesterol, and decreased levels of HDL.[9,10]

The WHO and JNC8 guidelines recommend thiazide diuretics, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers as the first-line treatments for HTN management. These drug classes can also be considered for combination therapy.[11,12] Patients with HTN often require multiple medications and may also have other chronic conditions such as diabetes and chronic kidney disease. This can increase the risk of drug-related problems (DRPs). The most common DRPs experienced by hypertensive patients include adverse drug reactions, side effects, issues with drug selection, problems with dosage, drug misuse, and interactions between drugs and food. These issues can lead to poor adherence to medication, which can ultimately fail antihypertensive treatment.[13,14]

1. Risk factors associated with HTN

Two categories of risk factors determine the prognosis of HTN: modifiable and non-modifiable. The patient's age and gender fall under the non-modifiable risk factors category, whereas the modifiable risk factors include elevated levels of (LDL) and triglycerides, alcohol consumption, smoking, high intake of salt and potassium in food, and lack of physical exercise.[15]

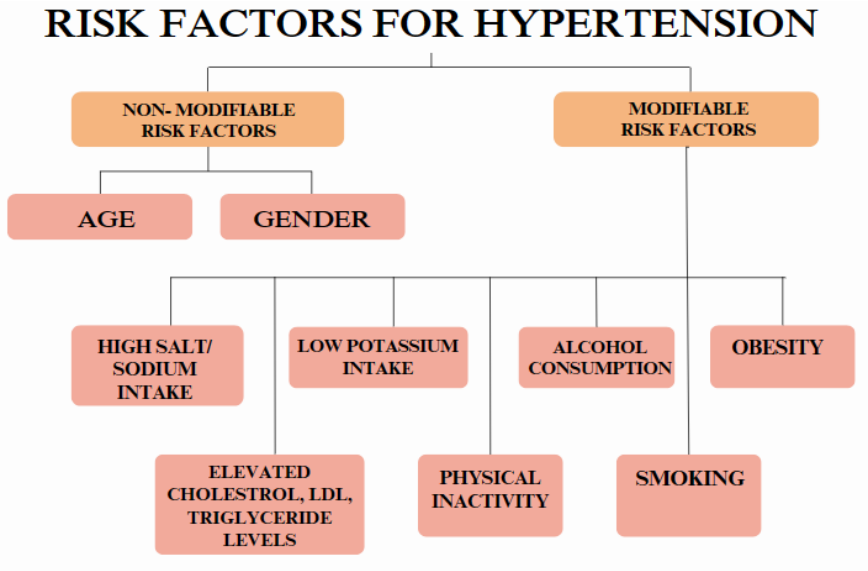


Figure 1: Risk factors for HTN.

1.1. Non-modifiable risk factors for HTN

1.1.1. Age

The prevalence of HTN increases with age, as it affects approximately 27% of young individuals and 74% of older patients. At the age of 60 years, 60% of the individuals are diagnosed with HTN, and it increases to 65% among men and 75% among women by the age of 70 years.[16] The increase in prevalence of HTN in adults is due to various pathophysiological mechanisms such as arterial stiffness, neurohormonal dysregulation, and kidney aging.[17] In older adults, the main cause of decreased diastolic blood pressure and increased systolic blood pressure in arterial stiffness.[18] Frailty also contributes to hypertension in older adults by causing age-related multi-organ dysfunction, which impairs kidney function and disturbs blood pressure regulation.[19] A study conducted on the Korean population reported that 37.4% of hypertensive patients in Korea were elderly patients over the age of 65 years, and both males and females experienced an increase in the prevalence of HTN as they aged.[20]

1.1.2. Gender

Blood pressure affects men and women differently in terms of prevalence and is a sexually dimorphic trait. HTN has been diagnosed in 31% of males and 25.3% of women.[21] For every 10 mmHg increase in SBP, the risk of CVD (coronary heart disease, ischemic heart disease, or MI) increases by 15% in men and 25% in women, respectively.[22] With age, blood pressure increases more in women as compared to men. By age 60, women generally have higher average blood pressure and a greater likelihood of hypertension compared to men.[6,23] Fluctuations influence the pathogenesis of hypertension in postmenopausal women in sex hormone levels. Estrogens regulate the sympathetic nervous system and RAAS, promoting vasodilation and preventing vascular remodeling, which diminishes after menopause, leading to increased hypertension risk.[24]

1.2. Modifiable risk factors for HTN

1.2.1. High intake of sodium and salt

According to WHO, excessive intake of sodium (>5g/day) leads to high blood pressure and HTN [25]. High intake of sodium leads to increased hypertension prevalence as it increases sympathetic activation, impairs vasodilation, and promotes arterial stiffness, all contributing to the development of hypertension.[26] A study conducted in China demonstrated that the population with high dietary salt/sodium intake was either at higher risk of developing HTN or was already diagnosed with HTN.[27]

In the management of HTN, salt/sodium reduction is an additive non-pharmacological intervention or lifestyle modification in lowering blood pressure levels.[28] DASH recommends a diet rich in fruits, vegetables, and low-fat dairy while limiting sodium to lower blood pressure. This can reduce HTN-related diseases. Adopting a DASH-style diet may improve overall health and reduce chronic disease risk.[29] According to a study conducted on the American population, individuals who followed the DASH-style diet and reduced their salt intake from 8g/day to 4g/day showed a reduction in blood pressure levels. Hypertensive patients experienced a reduction of 11.5/5.7mmHg, while normotensive individuals experienced a reduction of 7.1/3.7mmHg.[30]

1.2.2. Low Potassium intake

Potassium is a vital nutrient and the most common intracellular cation. It is essential for preserving cell function. The Institute of Medicine's Food and Nutrition Board suggests a daily intake of 4700 mg of potassium.[31] By decreasing intravascular volume and partially by boosting urine sodium excretion, potassium has an anti-hypertensive effect. For the benefits of lowering blood pressure, dietary potassium, and salt should be taken into account jointly.[32] The reduced intake of potassium causes disturbances in the sodium-potassium ratio and can lead to a significant rise in blood pressure levels. Various studies suggested that by increasing the potassium-sodium ratio, the blood pressure values in the general population decrease.[29,33] Few observational studies suggested that increasing the intake of potassium by 750-1000mg/ day lowers the BP by 2-3mmHg.[34] A systematic review and meta-analyses has shown that increased potassium intake lowers BP in hypertensive patients without any negative effects on blood lipid levels or adult renal function.[35]

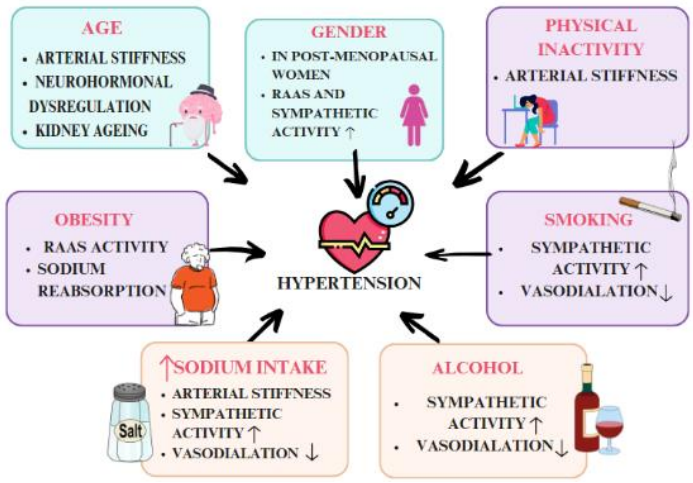


Figure 2: Mechanism of risk factors in the onset of HTN.

1.2.3. Alcohol consumption

Moderate alcohol consumption may confer health benefits, while excessive intake—defined as three or more drinks daily, each containing at least 12 grams of alcohol—can lead to hypertension and cardiovascular diseases. [36] Excessive alcohol consumption directly stimulates the sympathetic nervous system and inhibits vascular relaxing substances, and increases intracellular calcium in vascular smooth muscles, resulting in hypertensive effects.[37, 8] A meta-analysis study was conducted to determine the risk of HTN in individuals who consumed alcohol. It was found that men who consumed 31–40 grams of alcohol a day and women who consumed 21–30 grams per day had a greater risk of developing HTN.[39] Studies also reveal that reducing alcohol consumption can potentially lead to a reduction in blood pressure. A meta-analysis study that included a total of 2865 participants (2464 men and 401 women) revealed that those who consumed 3 or more drinks of alcohol per day earlier, experienced a decrease in SBP (mean value -5.50mmHg) and DBP (mean value -3.97mmHg) after reducing their alcohol intake.[40]

1.2.4. Smoking

Smoking is one of the major causes of the onset of chronic diseases, such as hypertension (HTN). However, the relationship between smoking and HTN is not completly understood. Some studies suggest that current smokers may exhibit lower blood pressure levels than those who have quit smoking. Additionally, other studies indicate that former smokers have a prevalence of HTN that is 2.36 times higher compared to current smokers.[41] Smoking products such as cigarettes and tobacco are known to have nicotine which produces hypertensive effects through endothelial dysfunction and sympathetic stimulation.[42] A study conducted on male MBBS students to identify the risk of smoking with HTN revealed that out of 63 smoker students, 31.75% of smokers were hypertensive and 61.9% of smoker students were in the pre-hypertensive phase.[43] Another study conducted to estimate the effects of cigarette smoking on HTN in young individuals stated that smoking accelerated the age-related decline of BP and led to increased arterial stiffness in young individuals.[44]. A research study was conducted in Indonesia to determine the impact of smoking on HTN in individuals aged between 15 and 60 years. The study found that the participants who smoked were 4.7 times more likely to develop HTN than those who didn't smoke.[45]

1.2.5. Physical Inactivity

Physical inactivity and a sedentary lifestyle are primary contributors to the development of HTN in individuals of all ages. Various studies have reported that individuals with physical inactivity and a sedentary lifestyle possess a greater risk of developing HTN than those who are physically active.[46] Physical activity is any movement that results from the contraction of skeletal muscles and raises an individual's energy consumption above resting levels.[47] Studies have suggested that participation in physical activities such as exercise and yoga, delays the onset of HTN. Regular exercise for a minimum of 30 minutes a day, every day of the week, at a moderate intensity level can help lower the risk of developing HTN and delay its onset.[48] Various studies suggest that indulging in physical activities such as aerobic exercises reduces BP values by (5-7 mmHg) and dynamic and isometric resistance exercises by (4-5 mmHg).[49] A clinical trial was conducted to investigate the impact of physical exercise on patients with HTN. The randomized study revealed that physical activity resulted in an improvement in the patient's overall health and a reduction of their SBP by 8.68 mmHg.[50]

1.2.6. Obesity

The coexistence of obesity and HTN is quite common, with obesity being a major contributor to HTN. The WHO has classified obesity as a state where the body stores excessive fat, resulting in several health hazards. According to their guidelines, a body mass index (BMI) of 30 or more is indicative of obesity.[51] Patients who are obese often have an increased risk of developing HTN due to higher cardiac output and lower systemic vascular resistance. This is caused by an increase in the secretion of angiotensinogen, angiotensin-II, and an elevation in the plasma renin activity.[52] Obesity increases the blood flow to the tissues leading to increase in the volume of extracellular fluid, which in turn leads to an increase the cardiac output. Moreover, obese patients experience greater renal salt reabsorption, necessitating a higher-than-normal blood pressure to maintain sodium balance, which further contributes to the development of HTN.[53] Various lifestyle modifications and interventions can help obese patients control or prevent HTN, or delay its onset. Weight loss is one of the major lifestyle modifications, which helps in declining BMI and BP values.[54] Along with weight loss, other modifications such as participating in physical activities and dietary changes such as following the DASH diet help to reduce obesity on control HTN in obese patients.[55]

1.2.7. Elevated cholesterol, LDL, and triglyceride levels:

A primary risk factor in the development of HTN is dyslipidemia, which damages the endothelium and affects physiological vasomotor activity, resulting in elevated blood pressure and HTN onset.[56,57] Several studies have shown that an increase in the levels of total cholesterol, LDL, and triglycerides, along with a decrease in HDL levels, can lead to the onset of HTN. A study investigating the relationship between the triglyceride to HDL-cholesterol ratio and the occurrence of HTN found a link between the two variables. Lower HDL and higher triglyceride levels were found to result in a higher prevalence of HTN.[58] According to recent research examining the relationship between triglycerides and other lipid markers and the development of HTN, people with raised triglyceride levels had a 47–73% higher chance of developing HTN.[59] A study conducted over 8 years aimed to estimate the association between high LDL levels and the development of HTN. The study showed that the group with high LDL levels had a 13.8% incidence of HTN occurrence, while the group with normal LDL levels had a 7.1% incidence over the years.[60].

Relationship Between Risk Factors and HTN Prevalence

A study by Ghosh and Kumar estimated the prevalence of hypertension (HTN) and its associated risk factors among Indian adults aged 15 to 49. It was estimated that 11.3% of individuals aged 65 and older were affected, with a higher incidence in men (13.8%) compared to women (10.9%). The prevalence was greater in urban areas (12.5%) as compared to 10.6% in rural areas. Prevelance was low in states like Kerala (8.2%), Bihar (8.8%), and Delhi (8.6%) , while Sikkim (20.2%), Nagaland (17.6%), and Assam (17.6%) exhibited greater prevalemce.[61]

Z. Geevar, M.N. Krishnan, et al. conducted a comprehensive study among 1,221 young adults in Kerla aged 20-39 years , that revealed 28% adults had HTN with 20.5% being men & 7.5% women. The prevalence of HTN among high salt intake individuals was 11.1%. HTN was observed in 25% of alcohol consumers and 24.5% of tobacco users. Among those with HTN, 18% individuals had sedentary lifestyle, 15.9% were obese, 23.8% were diabetic and 16.6% had hypercholestremia.[62]

Zachariah. G., Ramakrishnan. S.. et.al estimated the prevalence of HTN among 180,355 Indian adults from 24 different Indian states. The results revealed that 30.7% of Indians had HTN and frequency increased with age. Men were more prevalent as compared to women except for the age group over 65 years where prevalence was almost same in both genders. 12.9% of individuals in study were taking anti-hypertensive medications.[63]

Singh et al. conducted a cross-sectional study in urban Varanasi with 640 individuals representing the population. The prevalence of HTN was found to be 41.7% in urban Varanasi. Out of the individuals who has HTN, 15.2% were females and 32.3% were males. HTN was prevalent in 12.9% of individuals aged 25-34 years, 34.1% of individuals aged 35-44 years, 34.7% and 32.2% of individuals aged 45-54 years and 55-64 years respectively. The prevalence of HTN was 32.1% among smokers, 34.4% among those who consumed alcohol and 16.4% in those who led a sedentary lifestyle.[64]

J. Kishore, N. Gupta, C. Kohli, and N. Kumar; conducted a study in rural Delhi and found that HTN was prevalent in 14.1% of the population. The study was conducted in 1005 subjects of either gender, and HTN was diagnosed in 14.3% of females and 13.8% of male subjects.Among those with HTN 4.7% of subjects were under the age of 35 years while 21.8% subjects were over the age of 35 years. HTN was prevalent in 17.9% of subjects who consumed tobacco, 21.3% of subjects with alcohol intake, 16.4% of overweight and 16.9% of obese subjects. Furthermore, HTN was found to be prevalent in 20.7% of subjects with elevated cholesterol, 19.5% of subjects with elevated triglyceride levels, and 14.3% of subjects with decreased HDL levels.[9]

2. DRPs in the management of HTN

Various drug-related problems arise during the management of HTN, and they interfere with the expected outcomes of drug therapy. These problems are classified into different classes, such as drug choice problems, dosing problems, adverse drug reactions, drug interactions, and drug use problems. These DRPs are required to be addressed immediately to ensure adequate therapeutic outcomes and ensure patient safety.[65]

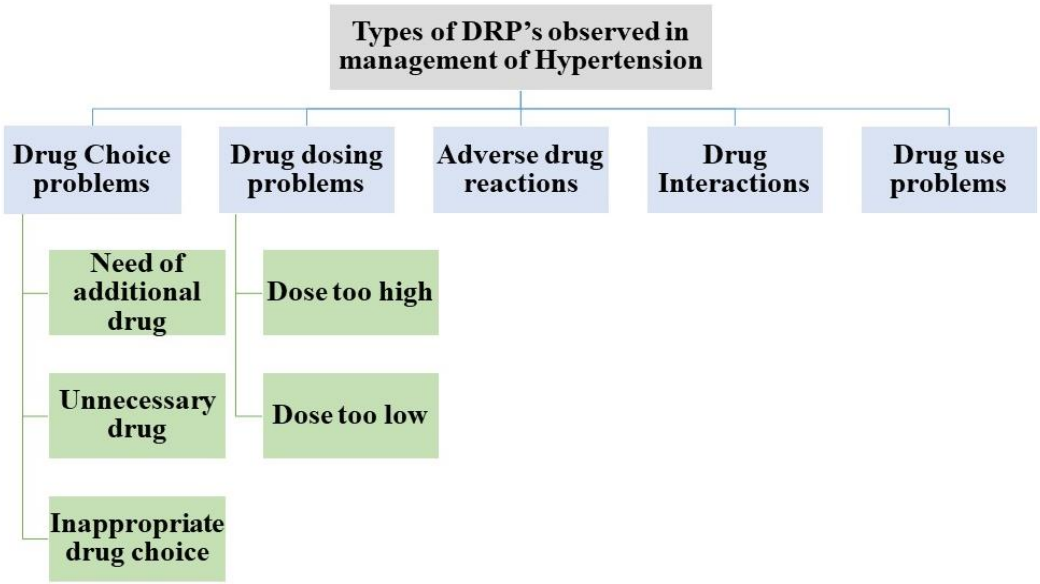


Figure 3: DRPs observed in the management of HTN: the image categorizes DRPs into five distinct groups which are further classified in Table 1.

Table 1 provides a brief description about the various DRP's observed in the management of HTN. It adequately categorizes the various classes of DRPs into sub-classes and describes each class and sub-class. Understanding and minimizing these DRPs significantly improve healthcare outcomes and ensures patient safety and well-being.

Table 1: DRPs encountered in clinical practice in the management of HTN.

S. no.	DRPs observed in the management of HTN	Description of DRP	References
1.	Drug choice problem	Additional need, unnecessary, and inappropriate medication types	[66], [67]
A.	Need of additional drug	Missing from regimen per standard treatment guidelines	
B.	Unnecessary drug	The drug is given to the patient for an indication that no longer exists	
C.	Inappropriate drug choice	A mismatch between diagnosis and medication, ignoring indications/contraindications.	
2.	Drug dosing problems	Can be of two types: dose too high or dose too low	[68]
A.	Dose too high	E.g.: ACE inhibitors in renal impairment, risking adverse effects	
B.	Dose too low	Fails to achieve desired therapeutic effect effectively	
3.	Adverse drug reactions	Unintended responses to medication, causing undesired effects, e.g.: orthostatic hypotension in the patient using anti-hypertensives	[69]
4.	Drug interactions	Medication interaction with drugs or food alters effectiveness/safety, e.g.: interaction of furosemide with NSAIDs leading to decreased diuretic effect	[70], [71]
5.	Drug use problems	Divergence between prescribed and patient-administered medication methods.	[72]

3. Association and Prevalence of DRPs in the Management of HTN

Drug-related issues such as drug choice, dosing, adverse effects, interactions, and misuse can have a significant impact on the effectiveness of HTN medication. Various studies have been conducted to estimate the prevalence and association of DRPs in HTN management. Table 2 summarizes the findings from these studies, including the types of drug-related issues identified and their prevalence rates among patients.

Table 2 Association of prevalence of DRPs in the management of HTN.

S. No.	Type of Study	No. participants involved	DRP's found inpatient	Total no. of DRP's and their Prevalence %age	References
1.	Cross-sectional study	150 hypertensive patients	Total patients with DRPs	57%	[14]
			ADR's	40%	
			Inappropriate drug administration:	94.14%	
			Drug interaction	62.14%	
			Incorrect dose	2.86%	
2.	Cross-sectional study	200 hypertensive patients	Total no. of DRP's	1261	[13]
			Drug effectiveness	29%	
			Inappropriate adherence to the drug	19%	
			Drug safety issues	12%	
			Inappropriate knowledge about disease conditions and drug use	10%	
			Unnecessary drug therapy	8%	
			Untreated disease conditions	2%	
3.	Prospective study	90 inpatients with HTN	Total no. of DRP's	261	[73]
			Drug choice problems	55.2%	
			Drug interactions	18%	
			Adverse drug reactions	11.4%	
			Drug dosing problems	10.7%	
			Drug use problems	4.2%	
4.	Retrospective study	200 patients with HTN	Total no. of DRPs	387	[74]
			Drug choice problems	22.5%	
			Drug interactions	16.3%	
			Drug dosing problems	16.0%	
			Drug use problems	12.9%	
			ADR's	6.5%	
5.	Prospective, randomized study	92 patients with pulmonary HTN	Total no. of DRP's	160	[75]
			ADR's	68.1%	
			High dose	9.4%	
			Low dose	8.1%	
			Drug use problems		

6. CONCLUSION

HTN is a common cardiovascular disease (CVD) that affects people worldwide. Its prognosis is influenced by both modifiable and non-modifiable risk factors. Effectively managing modifiable risk factors, such as reducing sodium intake, quitting smoking and alcohol, controlling obesity and high cholesterol levels, increasing potassium intake, and engaging in physical activity, is essential for controlling HTN and lowering blood pressure levels. However, managing HTN can become challenging due to drug-related problems. Physicians and pharmacists must collaborate to prevent and address drug-related problems (DRPs) in patients with comorbidities and multiple therapies in order to achieve the desired therapeutic outcomes of drug therapy.

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