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PHARMACOLOGICAL APPROACHES TO HYPERTENSION IN A TERTIARY CARE CENTRE IN NORTH INDIA: A STUDY OF PRESCRIPTION TRENDS AND RATIONALITY

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Keywords:

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ABSTRACT: Background: Hypertension is a prevalent health concern, often managed using Fixed Dose Combinations (FDCs) of antihypertensive drugs. Presently many FDCs are present in market without being assessed for safety efficacy and rationality, therefore evaluating the rationality of FDC usage is crucial for ensuring effective treatment and patient safety. **Objective:** This study aims to assess the rational use of fixed dose combinations in hypertension management at a tertiary care hospital. **Methods:** A prospective, observational study was conducted between March 2024 to July 2024. In this study a total of 93 outpatients were evaluated for prescribing pattern and rationality of Antihypertensive FDCs. Rationality was assessed using seven-point criteria. Data on patient demographics, prescribed FDCs, efficacy and dosing convenience were collected and analysed. **Results:** In this study, the prescriptions of 93 patients were analysed to observe 11 different fixed-dose combination antihypertensive agents. Of these patients, 56% were prescribed dual combination therapy. The most frequently prescribed dual combination was Telmisartan + Hydrochlorothiazide (17%), with Telmisartan + Chlorthalidone following at 14%. Analysis of the 11 different FDCs revealed that 18.2% were considered irrational, while 81.8% were deemed rational. **Conclusion:** The study highlighted the utilization pattern of fixed dose combinations in hypertension management in a tertiary care hospital. Dual combination therapies, with Telmisartan as a common component, were frequently prescribed. Although FDCs were rational in most cases but irrational FDCs were also prescribed. The findings emphasized the importance of adherence to evidence-based guidelines to ensure rational and effective hypertension management.

INTRODUCTION: Over the last thirty years, the global incidence of hypertension has surged significantly, increasing from approximately 650 million cases in 1990 to 1.28 billion in 2020 [1]. Hypertension rates in India are also on the rise. National Family Health Survey-5 (NFHS-5) demonstrated that hypertension prevalence among individuals of age 15-49 years was 22.8% (with a sample of 172,532), out of these newly diagnosed cases were 52.06% [2].

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A large number of pharmaceutical preparations contain two or more drugs in a definite ratio. Such combinations are popularly known as fixed dose combinations (FDCs). FDCs are innovative forms of drug therapy that offer distinct advantage to patients as well as physicians. Rational FDCs are efficacious but irrational combinations may be

dangerous. Fixed dose combinations are primarily used in the treatment of chronic conditions like hypertension to improve patient compliance by simplifying medication regimens. Despite their benefits, many FDCs enter the market without thorough assessment for efficacy, safety, and rationality by regulatory bodies [3].

Combination therapy, especially with single-pill combinations, is recommended by World Health Organization (WHO) for its effectiveness in managing BP and improving adherence to medication. The FDCs of drugs used in hypertension, should be sourced from three classes: Diuretics (either thiazide or thiazide-like), Angiotensin-converting enzyme inhibitors (ACEi) or Angiotensin-Receptor Blockers (ARBs), and long-acting dihydropyridine Calcium Channel Blockers (CCBs) [4].

METHODS: A prospective observational study was conducted in outpatient department Internal Medicine, Moti Lal Nehru Medical College and Hospital, Prayagraj. In this study a total of 93 prescriptions (Patients of either sex was recruited after satisfying inclusion and exclusion criteria) were evaluated for prescribing pattern and rationality of Antihypertensive FDCs used between March 2023 to July 2023.Data on prescribed FDCs, safety, efficacy, dosing convenience were collected and analysed.

Inclusion Criteria:

1. Patients of either sex and of age ≥ 18years attending the medicine department.
2. Patients diagnosed with Hypertension according to Joint National Committee (JNC)-8 criteria [5].
3. Patients on Fixed Dose Combination Antihypertensive treatment.
4. Patients willing to give consent.

Exclusion Criteria:

1. Patients of age < 18 years.
2. Pregnant and breastfeeding females.
3. Patient not giving consent.

To develop a comprehensive criterion which is useful for the evaluation of the rationality of Fixed Dose Combinations (FDCs), Policy Guidelines for Approval OFFDCs in India by MoHFW, GOI [6] was studied thoroughly, based on these guidelines the rationality was assessed using seven-point criteria as assessed by Panda *et al.* In the seven-point criteria formulated by Panda *et al.*, the highest possible score is 14, with each criterion contributing 2 points. A score of 8 or more is deemed rational [7].

The primary criteria for evaluating the rationality of fixed-dose combinations (FDCs) are the inclusion of each active pharmaceutical ingredient (API) in either the World Health Organization's Essential Medicines List (EML) or India's National List of Essential Medicines (NLEM).Furthermore, the dosage of each API must be suitable for a specified population group, with the amount and ratio of each API tailored for its intended therapeutic purpose.

Additionally, the combination should demonstrate superior efficacy and safety compared to the administration of the individual compounds separately. Each constituent drug should exhibit distinct mechanisms of action, and the FDC should either reduce the dosage requirements or the adverse effects associated with individual APIs.

The pharmacokinetic (PK) profiles of the APIs should be compatible, without negative pharmacokinetic interactions. In situations where PK parameters differ, the clinical advantages should be carefully evaluated to justify the use of the FDC [8].

Approval from Institutional Ethics Committee as well as patient consent was sought before commencement of study. Following the data collection phase, the data was categorized based on the type of therapy, such as single, dual or triple drug regimens, and the form of fixed-dose combination (FDC). Statistical analysis was then conducted using Microsoft Excel.

RESULTS: It was seen that in OPDs 56% dual drug combination therapy was prescribed followed by 43% Single drugs and 1% triple drug combination therapy **Fig. 1.**

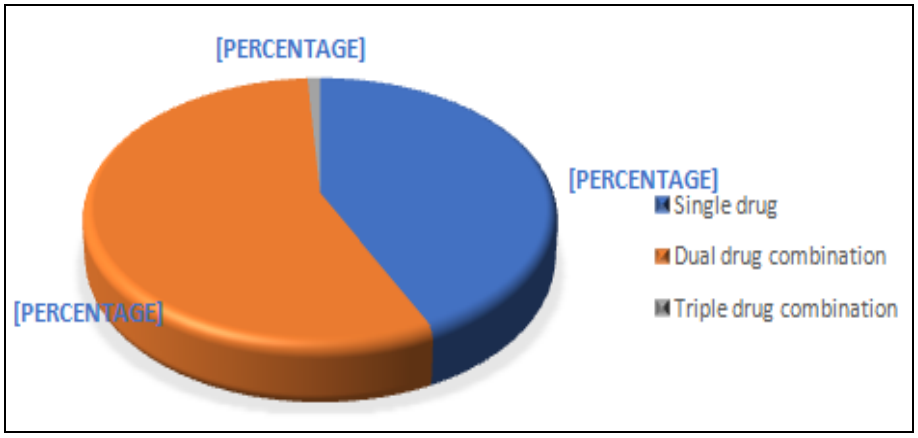

FIG. 1: PERCENTAGE OF PRESCRIBED DRUGS USED IN HYPERTENSIVE PATIENTS

Among the single drug ARBs were most frequently prescribed (19%) followed by CCBs (11%) and beta-blockers (11%). 56% of patients were prescribed dual combination therapy. The most common antihypertensive fixed dose combination therapy involved in the study was Telmisartan + Hydrochlorothiazide 17.2% followed by Chlorthalidone + Hydrochlorothiazide 13.9%, Telmisartan + Amlodipine 8.6% and Losartan + Hydrochlorothiazide 7.53% **Fig. 2.**

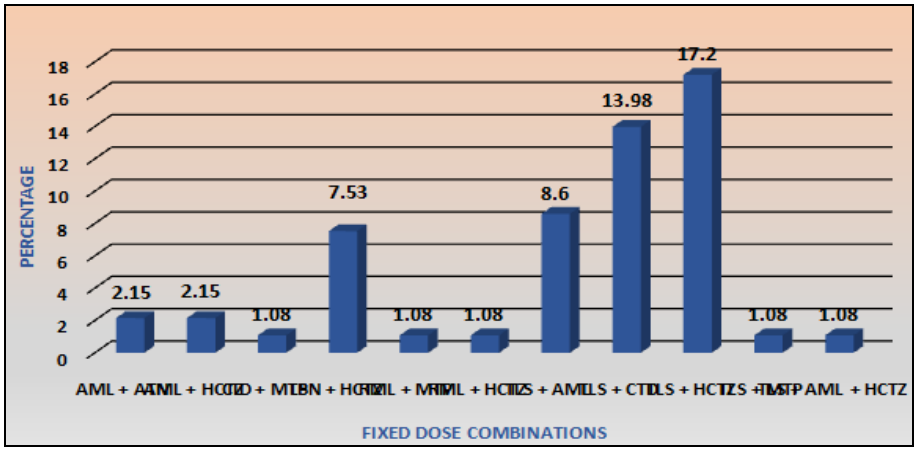

FIG. 2: DISTRIBUTION OF PRESCRIBED FDCS IN HYPERTENSIVE PATIENTS

FDCs details included brands names along with the Active pharmaceutical ingredient and strength of dosage forms **Table 1.**

TABLE 1: COMMONLY PRESCRIBED FDCS

S. no.	Brand names	Anti-hypertensive FDCs	Strengths
1.	Amlokind- AT	Amlodipine + Atenolol	40mg/5mg, 50mg/5mg
2.	Amlovas -H	Amlodipine + Hydrochlorothiazide	2.5mg/12.5mg
3.	Cilamet XL	Cilnidipine + Metoprolol	10mg/25mg
4.	Losakind- H, Losar- H	Losartan + Hydrochlorothiazide	50mg/12.5mg
5.	Ramistar- M	Ramipril + Metoprolol	25mg/2.5mg
6.	Ramistar- H	Ramipril + Hydrochlorothiazide	2.5mg/12.5mg
7.	Macsart- AM, Affotel- AM	Telmisartan + Amlodipine	40mg/5mg
8.	Macsart- CH, Telsar- CH	Telmisartan + Chlorthalidone	40mg/12.5mg, 40mg/6.25mg
9.	Telma- H, Sartel- H, Telmikind- H, Telmiluck- H, Macsart- H	Telmisartan + Hydrochlorothiazide	40mg/12.5mg, 40mg/6.25mg, 80mg/12.5mg
10.	Sartel- Beta	Telmisartan + Metoprolol	10mg/40mg
11.	Telma- AM H	Telmisartan + Amlodipine + Hydrochlorothiazide	40mg/5mg/12.5mg

FDC rationality was assessed by seven-point criteria developed by panda *et al.* The seven-point criteria have a total possible score of 14, as each criteria is worth 2 points. A score of 8 or higher is

regarded as rational. Scoring of FDCs based on criteria is as shown in **Table 2.** FDCs were rational in 81.8% of cases but 18.2% irrational FDCs were also prescribed. It was also seen that APIs of 68.9% of the FDC were present in either WHO EML or NLEM whereas APIs of 31.1% of FDCs were absent in both of them.

TABLE 2: SCORING OF FDCS USING THE SEVEN-POINT CRITERIA

S. no.	Antihypertensive FDCs	Scoring
1.	Amlodipine + Atenolol	12
2.	Amlodipine + Hydrochlorothiazide	14
3.	Cilnidipine + Metoprolol	10
4.	Losartan + Hydrochlorothiazide	14
5.	Ramipril + Metoprolol	7
6.	Ramipril + Hydrochlorothiazide	12
7.	Telmisartan + Amlodipine	13
8.	Telmisartan + Chlorthalidone	12
9.	Telmisartan + Hydrochlorothiazide	13
10.	Telmisartan + Metoprolol	7
11.	Telmisartan + Amlodipine + Hydrochlorothiazide	13

Score- 0 to 7- Irrational FDC ≥8 – Rational FDC.

DISCUSSION: In this study, the prescriptions of 93 patients were analysed to observe 10 different fixed-dose combination antihypertensive agents. The most common antihypertensive fixed dose combination therapy was Telmisartan + Hydrochlorothiazide similarly; Mohd *et al.* also concluded that Telmisartan + Hydrochlorothiazide was the most commonly prescribed FDC [9].

Combination of Telmisartan+Hydrochlorothiazide, has shown additional antihypertensive efficacy compared to monotherapies in a wide range of patients. It is well-tolerated with fewer side effects and less potassium depletion compared to hydrochlorothiazide alone, it is cost-effective as well reducing the financial burden associated with hypertension management [10]. The combination of telmisartan and hydrochloro-thiazide offers enhanced efficacy, as numerous previous studies have shown that the activation of the renin-angiotensin aldosterone system (RAAS) by hydrochlorothiazide amplifies the effectiveness of agents that block this pathway. When patients have high salt levels, their blood pressure becomes volume dependent, diminishing the antihyper-tensive effect of RAAS-blocking agents. This issue can be addressed by adding a diuretic, making the blood pressure more dependent on renin activity. Telmisartan functions as an angiotensin receptor blocker, while hydrochloro-thiazide works by inhibiting the Na+/Cl- cotransporter system [8, 11]. Potassium loss caused by diuretics can be offset by simultaneously using an ARB [12] or ACE inhibitor [13] while peripheral edema linked to calcium antagonists can be alleviated by ACE inhibitors [10, 14]. In our study analysis of FDCs revealed that 18.2% were considered irrational, while 81.8% were deemed rational. Similarly in their 2018 research, Gupta *et al.* observed that while 75% of fixed-dose combinations (FDCs) of antihypertensive drugs were deemed rational, 25% were not. Their study highlighted similar rational combinations such as Olmesartan + Amlodipine and Telmisartan + Hydrochlorothiazide, both deemed effective for their complementary mechanisms of action in controlling blood pressure [3]. In this study, we examined two combinations of RAAS inhibitors and beta blockers. The rationale behind using these combinations solely for hypertension treatment is debatable, since both drugs work by inhibiting the RAAS pathway. While ACE inhibitors or ARBs combined with beta blockers are commonly formulated as fixed-dose combinations (FDCs) for myocardial infarction and heart failure patients, employing these combinations purely for hypertension is not considered appropriate due to the minimal reduction in blood pressure that they provide [15].

Dihydropyridine CCBs along with Beta-adrenergic blockers are considered favourable combinations for treatment of hypertension. However Beta-adrenergic blockers along with non-dihydropyridine calcium antagonists should be avoided due to greater risk for bradycardia and/or atrio-ventricular block [16]. The combination therapy of ramipril and hydrochlorothiazide has been shown to be more effective and tolerable than ramipril alone. This increased efficacy is due to the complementary actions of each active pharmaceutical ingredient. While hydrochlorothiazide may lead to issues such as hypokalaemia, hyperuricemia, hyperglycaemia, and hypercholesterolemia, these side effects are mitigated by the addition of ramipril [7]. Considering FDCs of CCBs and Beta-adrenergic blockers. in a study by Manjula Devi AS *et al.* it was noted that the fixed-dose combination (FDC) of atenolol and amlodipine lacked proven efficacy and safety compared to administering the individual drugs

separately. This combination led to hypotension and bradycardia, necessitating careful monitoring of cardiac function, particularly in patients at risk of heart failure. However, it was seen that addition of amlodipine can mitigate the immediate negative hemodynamic impacts of beta-blockers. Furthermore, the fatigue often experienced with beta-blockers was lessened when used in conjunction with amlodipine [8].

Study by Sapkota *et al.* [17] stress the importance of adhering to rational prescribing guidelines to avoid irrational combinations that may lead to treatment failures or unnecessary side effects. Study highlights how irrational combinations like RAAS inhibitors with beta-blockers do not offer substantial benefits and pose risks, reaffirming the need for careful evaluation of FDCs in hypertensive patients.

CONCLUSION: Dual combination therapies, with Telmisartan as a common component, were frequently prescribed. Although FDCs were rational in 81.8% of cases but 18.2% irrational FDCs were also prescribed which is a matter of concern. The findings emphasized the importance of adherence to evidence-based guidelines to ensure rational and effective hypertension management.

Companies making FDCs should focus on synergistic effect of drugs used, less adverse drug reactions, good and rational alternatives should be promoted, irritational FDCs can be lessened, by promoting

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CONFLICT OF INTEREST: Nil

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