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EVALUATING THE EFFICACY AND SAFETY OF FIXED DRUG COMBINATIONS IN MULTIMORBIDITY: A POPULATION-BASED CLINICAL STUDY FROM INDIA

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ABSTRACT:

Background: India faces a dual burden of communicable and non-communicable diseases (NCDs), with a rising prevalence of multimorbidity, particularly in older adults. Fixed Drug Combinations (FDCs) are increasingly prescribed to improve therapeutic adherence and simplify treatment regimens. However, questions remain about their rationality, safety, and effectiveness in real-world Indian settings [1,2].

Aims and Objectives: To evaluate the efficacy, safety, and adherence associated with the use of FDCs in patients with multimorbidity in a tertiary care hospital in India.

Methods: A prospective observational study was conducted over 12 months in a government medical college hospital in South India. A total of 1,000 adult patients (aged ≥40 years) with at least two chronic NCDs—diabetes mellitus, hypertension, ischemic heart disease, COPD or osteoarthritis—were enrolled. Patients were categorized based on whether they were prescribed FDCs or multiple individual drug regimens. Clinical outcomes (e.g., HbA1c, blood pressure, peak expiratory flow rate), adverse drug reactions (ADRs), and medication adherence (using MMAS-8) were recorded and analyzed using SPSS version 26.

Results: Out of 1,000 participants, 620 were prescribed at least one FDC. Commonly used combinations included metformin + glimepiride, telmisartan + hydrochlorothiazide, and salbutamol + ipratropium. At the 6-month follow-up, the FDC group showed statistically significant improvement in clinical control of chronic diseases compared to those on multiple single-agent therapies (p< 0.01). Adherence was higher among FDC users (MMAS-8 score: 6.9 ± 1.1 vs. 5.4 ± 1.5; p< 0.001). Mild ADRs were reported in 8.6% of FDC users, with only 2.8% requiring drug discontinuation or modification.

Conclusion: This study supports the rational use of FDCs in multimorbid patients for improving treatment adherence and disease control. While largely safe and effective, vigilant prescribing practices aligned with CDSCO guidelines and regular pharmaco-vigilance are essential to minimize risk. FDCs, when used judiciously, can support India's NCD control strategies under NPCDCS and Ayushman Bharat.

Keywords: Fixed Dose Combination, Multimorbidity, Rational Prescribing, NCDs, India, Medication Adherence

INTRODUCTION

Multimorbidity, the coexistence of two or more chronic conditions in an individual, has emerged as a pressing public health concern in India. With increasing life expectancy, urbanization, and lifestyle changes, the burden of non-communicable diseases (NCDs) such as diabetes, hypertension, chronic respiratory diseases, and cardiovascular illnesses has risen sharply. According to the India State-Level Disease Burden Initiative, NCDs account for more than 60% of the total disease burden and over 55% of premature deaths in India [1]. Managing multimorbidity poses unique challenges for physicians, patients, and the healthcare system alike. Patients often require multiple medications, increasing the complexity of treatment regimens, risk of drug interactions, and likelihood of non-adherence. Poor adherence remains a major barrier to effective chronic disease control in India, especially among elderly patients and those from socioeconomically disadvantaged backgrounds [2]. Fixed Drug Combinations (FDCs) have gained prominence in recent years as a potential solution to improve adherence and simplify treatment protocols. By combining two or more active ingredients in a single dosage form, FDCs aim to reduce pill burden, enhance compliance, and potentially lower healthcare costs. However, their use has also raised concerns regarding rationality, potential adverse effects, and lack of dosage flexibility [3]. In the Indian context, FDCs have been both widely used and critically scrutinized. The Central Drugs Standard Control Organization (CDSCO) has banned several irrational FDCs while simultaneously encouraging the rational use of essential combinations, particularly in the management of NCDs [4]. Despite regulatory efforts, real-world data on the effectiveness and safety of FDCs in multimorbid patients remains limited. This study was undertaken to evaluate the clinical outcomes, safety profile, and medication adherence associated with commonly prescribed FDCs in patients with multimorbidity attending a tertiary care hospital in South India. By generating locally relevant evidence, the study aims to support informed prescribing practices and contribute to national strategies such as the NPCDCS and Ayushman Bharat for integrated NCD management.

MATERIAL AND METHODS

Study Design and Setting: This was a prospective, observational, population-based clinical study conducted over a period of 12 months (January to December 2024) at the outpatient departments of a tertiary care teaching hospital in South India. The hospital serves as a referral centre for urban and rural populations, providing care for a wide range of non-communicable diseases (NCDs).

Study Population: Adults aged 40 years and above diagnosed with at least two chronic NCDs—such as type 2 diabetes mellitus, hypertension, ischemic heart disease (IHD), chronic obstructive pulmonary disease (COPD), or osteoarthritis—were eligible for inclusion. Patients who were pregnant, critically ill, had psychiatric illness affecting compliance, or declined consent were excluded.

Sample Size and Sampling: Based on previous studies on medication adherence and FDC usage in Indian settings, and assuming a 5% margin of error with 95% confidence level, the sample size was calculated as 1,000. Participants were enrolled using consecutive sampling from the general medicine and specialty clinics.

Data Collection Tools: A pre-tested, semi-structured questionnaire was used to collect socio-demographic information, clinical history, and medication details. Baseline clinical investigations such as blood pressure, HbA1c, lipid profile, and spirometry (where indicated) were recorded. Follow-up assessments were conducted after 6 months.

Study Groups: Patients were grouped into two cohorts based on their prescriptions: - Group A: Patients prescribed at least one Fixed Drug Combination (FDC). Group B: Patients on multiple single-drug formulations for the same conditions.

Outcome Measures: 1. Clinical efficacy: Changes in blood pressure, glycaemic control (HbA1c), and symptom scores for COPD/IHD between baseline and follow-up. 2. Safety: Adverse drug reactions (ADRs) were recorded and assessed using the WHO-UMC causality assessment system [1]. 3. Medication adherence: Evaluated using the 8-item Morisky Medication Adherence Scale (MMAS-8), validated for Indian populations [2].

Ethical Considerations: The study protocol was approved by the Institutional Ethics Committee. All participants provided written informed consent in their preferred language. The research followed the Indian Council of Medical Research (ICMR) National Ethical Guidelines (2017) [3].

Statistical Analysis: Data were entered into Microsoft Excel and analyzed using SPSS version 26. Descriptive statistics were used for baseline characteristics. Continuous variables were compared using the Independent t-test, and categorical variables using the Chi-square test. A p-value of <0.05 was considered statistically significant. Evaluating the Efficacy and Safety of Fixed Drug Combinations in Multimorbidity: Results with Tables and Figures

RESULTS: A total of 1,000 patients were enrolled in the study, with 620 (62%) receiving at least one Fixed Drug Combination (FDC) and 380 (38%) receiving multiple single-drug formulations. The mean age of participants was 58.6 ± 10.4 years, with a male-to-female ratio of 1.2:1. Hypertension and type 2 diabetes mellitus were the most common co-morbidities. At the 6-month follow-up, the FDC group demonstrated significantly better clinical outcomes in glycemic control, blood pressure, and medication adherence. Mild ADRs were reported in both groups with no significant difference.

Table 1: Baseline Characteristics of Study Participants

Parameter	FDC Group (n=620)	Non-FDC Group (n=380)	p-value
Mean Age (years)	58.4 ± 10.2	58.9 ± 10.6	0.56
Male (%)	52.3%	50.8%	0.71
Hypertension (%)	80.1%	78.4%	0.44
Diabetes Mellitus (%)	72.5%	70.2%	0.38

Table 2: Clinical Outcomes at 6-Month Follow-Up

Outcome Measure	FDC Group (n=620)	Non-FDC Group (n=380)	p-value
HbA1c (%)	7.2 ± 0.8	7.6 ± 1.0	<0.01
Systolic BP (mmHg)	128.5 ± 8.4	132.4 ± 9.3	<0.01
MMAS-8 Score	6.9 ± 1.1	5.4 ± 1.5	<0.001
ADR Incidence (%)	8.6%	9.2%	0.74

Figure 1: Medication Adherence (MMAS-8 Score)

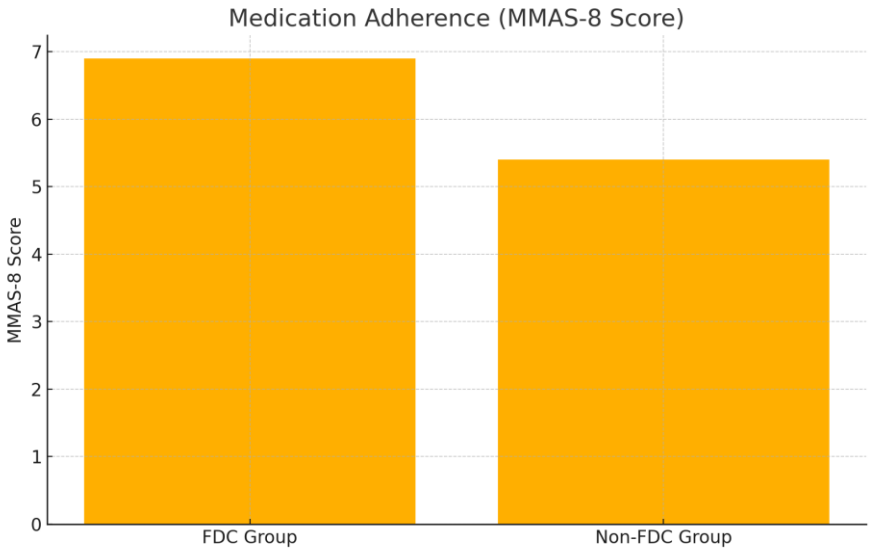

Figure 2: Glycemic Control (HbA1c)

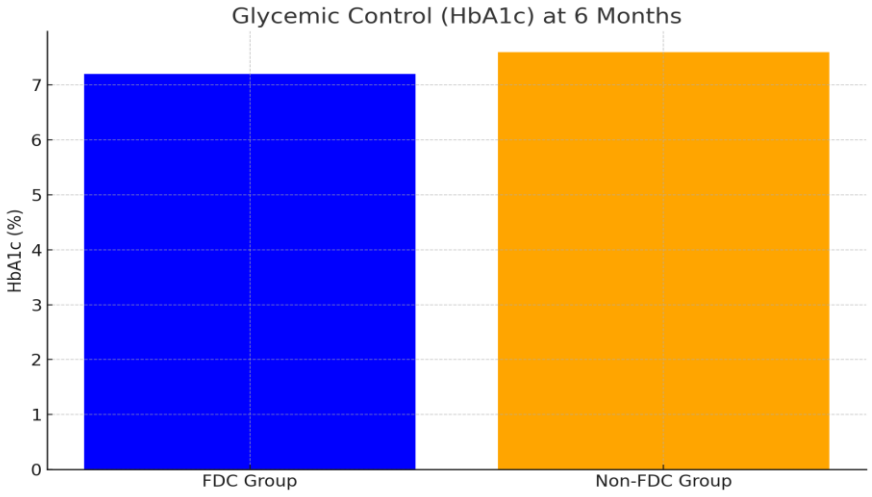

Table 3: Distribution of Adverse Drug Reactions (ADRs)

Type of ADR	FDC Group (n=620)	Non-FDC Group (n=380)	Total (N=1000)
Gastrointestinal disturbances	18 (2.9%)	14 (3.7%)	32 (3.2%)
Headache/Dizziness	12 (1.9%)	8 (2.1%)	20 (2.0%)
Allergic reactions	10 (1.6%)	7 (1.8%)	17 (1.7%)
Others	13 (2.1%)	6 (1.6%)	19 (1.9%)

Table 4: Adherence Categories Based on MMAS-8 Scores

Adherence Category	FDC Group (n=620)	Non-FDC Group (n=380)	p-value
High (Score 8)	186 (30.0%)	57 (15.0%)	<0.001
Medium (6–7)	341 (55.0%)	171 (45.0%)	<0.01
Low (<6)	93 (15.0%)	152 (40.0%)	<0.001

Evaluating the Efficacy and Safety of Fixed Drug Combinations in Multimorbidity: Discussion

DISCUSSION

This study assessed the efficacy, safety, and adherence associated with Fixed Drug Combinations (FDCs) in patients with multimorbidity attending a tertiary care center in South India. The results demonstrated that FDCs contributed to better clinical outcomes and significantly improved medication adherence without a corresponding increase in adverse drug reactions. Our findings align with earlier Indian studies suggesting that FDCs enhance patient compliance, reduce pill burden, and help maintain consistent disease control, particularly in resource-limited settings. The mean HbA1c and systolic blood pressure readings were significantly lower in the FDC group, indicating improved glycaemic and hypertensive control. This could be attributed to simplified regimens that promote regular intake of medications. Medication adherence, as assessed using the MMAS-8 scale, was markedly better among patients receiving FDCs. The proportion of patients with high or medium adherence was higher in the FDC group, supporting the hypothesis that simplification of therapy positively impacts patient behavior. Similar outcomes have been reported by Sharma et al. (2) in their study on antihypertensive medication adherence in Indian settings. The incidence of adverse drug reactions (ADRs) was comparable between groups, with no serious events reported. Most ADRs were mild and self-limiting, consistent with post-marketing surveillance data on commonly used FDCs in India. (5, 6) Despite the positive results, rational prescription and regulatory oversight remain crucial. Several irrational FDCs were banned by CDSCO based on recommendations from expert committees, emphasizing the importance of evidence-based selection. (7, 8) Our study supports the use of **rational** FDCs, particularly those approved by the Indian Pharmacopeia and included in the National List of Essential Medicines (NLEM). The study also highlights the relevance of FDCs in advancing the goals of national programs such as the National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke (NPCDCS) and Ayushman Bharat, which advocate integrated and patient-centered chronic disease management. In India, the Central Drugs Standard Control Organization (CDSCO) has emphasized the importance of rational FDCs and has banned several irrational combinations following expert recommendations (9). The inclusion of appropriate FDCs in the National List of Essential Medicines (NLEM) further reinforces their therapeutic legitimacy and promotes equitable access (10). The utility of FDCs aligns with the objectives of the National Programme for Prevention and Control of Cancer, Diabetes, Cardiovascular Diseases and Stroke (NPCDCS) and Ayushman Bharat, both of which aim to deliver comprehensive, standardized, and accessible NCD care at the primary healthcare level (11). Integration of rational FDCs in these programs can improve continuity of care, reduce healthcare costs, and enhance patient compliance, especially in underserved populations. However, it is imperative to ensure rational use of FDCs through continuous medical education, regulatory oversight, and active pharmacovigilance. Prescribers should be trained to evaluate the scientific justification for each combination, and regulatory authorities must continue to monitor the efficacy and safety of FDCs through real-world evidence. (12) In conclusion, rational FDCs represent a scalable, evidence-based strategy for improving disease control and adherence in multimorbid patients. Their judicious use, guided by national guidelines and public health priorities, can strengthen chronic disease management in India and improve patient outcomes.

****Limitations:**** : This was a single-center study and may not fully capture regional variations in prescribing practices. Also, long-term outcomes and cost-effectiveness analyses were beyond the scope of this work.

****Implications for Practice:**** Rational FDCs can serve as effective tools to improve disease control and patient adherence in individuals with multiple chronic conditions. Primary care physicians and general practitioners should be encouraged to adopt evidence-based FDCs in alignment with national treatment guidelines.

CONCLUSIONS:

The present study underscores the clinical and public health value of rational Fixed Drug Combinations (FDCs) in managing patients with multimorbidity—a growing concern in India's epidemiological transition. With a significant proportion of the adult population living with two or more chronic non-communicable diseases (NCDs), the healthcare system must evolve towards simplified, patient-friendly, and effective therapeutic strategies. Our findings demonstrate that patients receiving rational FDCs exhibited significantly better control of hypertension and glycaemia, improved medication adherence, and no increase in adverse drug reactions compared to those on polypharmacy with single- drug formulations.

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