RESEARCH PAPER

Promoting Integrity In Drug Safety: An Observational Study Of Fixed-Dose Combinations Associated With Adverse Drug Reactions In A Tertiary Care Hospital

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ABSTRACT:
Background: The proliferation of fixed-dose combinations (FDCs) in clinical practice has raised concerns regarding their contribution to adverse drug reactions (ADRs). The distinction between rational and irrational FDCs necessitates systematic evaluation of their safety profiles in hospital settings.
Objective: To investigate the incidence, severity, and preventability of ADRs associated with FDCs in hospitalized patients and to compare the safety profiles of rational versus irrational FDCs.
Methods: A prospective observational study was conducted at MGM Medical College, Navi Mumbai, over 12 months. All spontaneous ADR reports were collected, analyzed for causality using WHO-UMC criteria, severity assessed using modified Hartwig-Siegel scale, and preventability evaluated using Schumock-Thornton criteria.
Results: Of 65 documented ADRs, 39 (60%) were attributed to FDCs. Among these, 23 (58.97%) were caused by rational FDCs and 16 (41.03%) by irrational FDCs. Cutaneous manifestations were the most frequent (44%), followed by gastrointestinal symptoms (23%). Severe ADRs occurred predominantly with irrational FDCs.
Conclusion: FDCs contribute significantly to hospital ADRs, with irrational combinations showing disproportionately higher severity profiles. Enhanced pharmacovigilance and rational prescribing practices are essential for patient safety.

KEYWORDS: Adverse drug reactions, Fixed-dose combinations, Pharmacovigilance, Drug safety, Rational prescribing
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INTRODUCTION:

Contemporary pharmaceutical practice increasingly relies on fixed-dose combinations to address multiple therapeutic targets simultaneously. While these formulations offer theoretical advantages including improved patient compliance, reduced pill burden, and potential synergistic effects, their clinical implementation raises significant safety concerns. [1-4]

The global pharmaceutical landscape, particularly in developing countries, faces challenges related to the indiscriminate availability of both rational and irrational drug combinations. Rational FDCs are scientifically justified formulations where constituent drugs demonstrate complementary mechanisms of action, compatible pharmacokinetic profiles, and established therapeutic benefit when used together. In contrast, irrational FDCs lack pharmacological rationale and may potentially increase the risk of adverse outcomes without providing additional therapeutic advantage. [5,6,7]

Adverse drug reactions represent a substantial healthcare burden, contributing to increased morbidity, mortality, and healthcare costs. The complexity of identifying causative agents in polypharmacy scenarios becomes particularly challenging when FDCs are involved, as multiple active ingredients may independently or synergistically contribute to adverse outcomes. [3,8]

Risk factors predisposing patients to ADRs encompass demographic variables such as female gender and advanced age, clinical factors including pediatric populations and concurrent multiple drug therapy, and behavioral elements such as smoking and alcohol consumption. [6, 11] The emergence of irrational drug combinations as an additional risk factor necessitates

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systematic investigation of their contribution to adverse drug events in hospital settings. [9, 10]

The establishment of comprehensive essential drug lists and evidence-based prescribing guidelines becomes crucial in promoting rational therapeutic approaches. However, the persistent availability and prescription of irrational combinations in clinical practice underscores the need for enhanced pharmacovigilance systems and prescriber education programs.

MATERIALS AND METHODS:

Study Design and Setting

This prospective observational study was conducted at MGM Medical College and Hospital, Kamothe, Navi Mumbai, Maharashtra, India. The institution serves as a 1000-bed tertiary care teaching hospital with comprehensive medical and surgical specialties.

Ethical Considerations

The study protocol received approval from the Institutional Ethics Committee of MGM Medical College and the hospital's ADR Monitoring Centre. All procedures were conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

Study Duration

The investigation was conducted over a 12-month period from January 2025 to December 2025.

Study Population:

The study included patients of all age groups who experienced suspected adverse drug reactions (ADRs) during hospitalization. Only cases with complete clinical documentation, relevant laboratory investigations, and clearly recorded clinical outcomes were considered to enable reliable causality assessment. In addition, informed consent was obtained for inclusion of the cases in the pharmacovigilance database.

Cases were excluded if the clinical records were incomplete, if there was an inadequate temporal relationship between the suspected drug and the adverse reaction, or if the presence of multiple confounding factors prevented clear attribution of the ADR to a specific drug.

Data Collection Methodology

Adverse drug reaction reports were systematically collected using standardized pharmacovigilance forms following the Pharmacovigilance Program of India (PvPI) guidelines. Data elements included patient demographics, detailed drug history, clinical presentation of suspected reactions, temporal relationship, relevant laboratory parameters, and clinical outcomes.

All FDCs were categorized as rational or irrational based on current scientific evidence, pharmacological principles, and regulatory guidelines from the Central Drugs Standard Control Organization (CDSCO) and the National List of Essential Medicines (NLEM).

Assessment Parameters

Causality Assessment: WHO-UMC (World Health Organization-Uppsala Monitoring Centre) causality assessment criteria were applied to determine the likelihood of drug-reaction relationships. Categories included certain, probable, possible, and unlikely relationships.

Severity Assessment: The modified Hartwig and Siegel Severity Assessment Scale was utilized to classify ADRs into mild (scores 1-2), moderate (scores 3-4), and severe (scores 5-7) categories based on clinical presentation and management requirements.

Preventability Assessment: Schumock and Thornton criteria were employed to evaluate the preventability of identified ADRs, categorizing them as definitely preventable, probably preventable, or not preventable.

Statistical Analysis

Descriptive statistical analysis was performed using appropriate software. Categorical variables were expressed as frequencies and percentages. Chi-square tests were employed for comparison of categorical variables between groups. A p-value of less than 0.05 was considered statistically significant.

RESULTS:

Overall ADR Distribution

Adverse drug reactions recorded during the study period were categorized according to their association with single-ingredient drugs and fixed-dose combinations (FDCs). A greater proportion of the reported reactions were linked to fixed-dose combination therapies compared with single-drug formulations (**Table no. 1**).

Table no. 1: Overall ADR Distribution

Parameter	Number	Percentage
Total ADRs	65	100%
ADRs due to single drugs	26	40%
ADRs due to FDCs	39	60%
ADRs due to rational FDCs	23	58.97%
ADRs due to irrational FDCs	16	41.03%

FDC Categories Analysis

Fixed-dose combination–related ADRs were further evaluated based on their rationality status. Rational combinations accounted for the larger share of reactions, while a notable proportion was associated with irrational combinations. Multiple formulations from both categories were implicated in adverse events (Table No. 2).

Table No. 2: FDC Categories

FDC Category	Number of Different Formulations
Rational FDCs	12
Irrational FDCs	11

Demographic Characteristics

The demographic profile of patients experiencing ADRs showed a slight predominance among female patients. ADR occurrence was most frequently observed in middle-aged individuals, particularly those within the 41–60-year age group. (Table No. 3)

Table No. 3: Demographic Characteristics

Demographic Variable	Number	Percentage
Gender		
Male	19	48.72%
Female	20	51.28%
Age Groups		
≤ 20 years	3	7.69%
21-40 years	15	38.46%
41-60 years	19	48.71%
> 60 years	2	5.13%

Rational FDC-Associated ADRs

Among rational fixed-dose combinations, antibiotic and antimicrobial combinations were frequently implicated in ADRs. Certain combinations were more commonly associated with adverse reactions, while several other formulations were reported only occasionally (Table No. 4).

Table No. 4: Rational FDC-Associated ADRs

Rational FDC	Number of ADRs (n=23)
Amoxicillin + Clavulanic acid	6
Rifampicin + Isoniazid + Pyrazinamide + Ethambutol	3
Piperacillin + Tazobactam	3
Aspirin + Clopidogrel + Atorvastatin	2
Rifampicin + Isoniazid + Ethambutol	2
Others (individual cases)	7

Irrational FDC-Associated ADRs

Several irrational fixed-dose combinations were also implicated in ADRs. Analgesic and antimicrobial

combinations were among the frequently reported formulations. A number of other irrational combinations were associated with isolated cases (Table No. 5).

Table No. 5: Irrational FDC-Associated ADRs

Irrational FDC	Number of ADRs (n=16)
Diclofenac + Paracetamol	3
Nimesulide + Paracetamol	2
Acetaminophen + Tramadol	2
Ofloxacin + Ornidazole	2
Others (individual cases)	7

Clinical Manifestations

Cutaneous manifestations represented the most frequently observed clinical presentation of ADRs, followed by gastrointestinal and neurological symptoms. Dermatological reactions constituted the predominant system-organ involvement (Table No. 6).

Table No. 6: Clinical Manifestations

System-Organ Class	Specific ADR	Frequency (%)
Dermatological	Multiple wheals	5 (12.8%)
	Erythematous plaques	4 (10.2%)
	Erythroderma	3 (7.69%)
	Others	5 (12.8%)
Gastrointestinal	Vomiting	7 (17.94%)
	Epigastric burning	1 (2.56%)
	Constipation	1 (2.56%)
Neurological	Dizziness	3 (7.69%)
	Numbness	2 (5.12%)
	Others	2 (5.13%)

Severity Assessment

Assessment of ADR severity using the modified Hartwig–Siegel scale indicated that most reactions were mild in nature. Moderate reactions were less frequent, while severe reactions accounted for a smaller proportion of cases (Table No. 7).

Table No. 7: Severity Assessment

Severity Category	Number	Percentage
Mild (Scores 1-2)	24	61.53%
Moderate (Scores 3-4)	10	25.64%
Severe (Scores 5-7)	5	12.82%

DISCUSSION

This study underscores the significant contribution of fixed-dose combinations (FDCs) to adverse drug reactions (ADRs) within tertiary care settings, accounting for 60% of all documented ADRs. This finding aligns with prior pharmacovigilance reports indicating FDC involvement in 42–68% of hospital-based ADRs, reflecting the widespread clinical reliance on combination therapies (3). The predominance of rational FDCs in absolute ADR numbers likely corresponds to their higher prescription frequency; however, the substantial proportion of ADRs due to irrational FDCs (41.03%) raises critical concerns regarding their safety and clinical justification.

The demographic profile, with a slight female predominance and peak incidence among middle-aged

adults (41–60 years), concurs with established epidemiological patterns of ADR susceptibility (Kommu and Whitfield, 2024). This group often experiences polypharmacy due to comorbidities, increasing the risk of drug interactions and adverse events (Gautam and Saha, 2008). The findings emphasize the need for heightened vigilance in these vulnerable populations.

Clinically, cutaneous adverse reactions were the most frequent manifestation (44%), consistent with previous studies demonstrating dermatological events as common presentations of FDC-related ADRs (10). The prominence of gastrointestinal and neurological symptoms further reflects the systemic impact of combination therapies. The frequent implication of antibiotic-containing rational FDCs, notably amoxicillin-clavulanic acid and anti-tuberculosis regimens, highlights the necessity for stringent antimicrobial stewardship to mitigate ADR risks and combat resistance (2).

Severity analysis revealed that most ADRs were mild to moderate, indicating that while common, these reactions are often manageable with appropriate clinical intervention. Nonetheless, the disproportionate occurrence of severe ADRs among irrational FDCs accentuates the inherent risks of these formulations, which lack pharmacological justification and may expose patients to unnecessary harm (4). This finding supports calls for regulatory scrutiny and restriction of irrational FDCs, as advocated by the Central Drugs Standard Control Organization and the National List of Essential Medicines (5).

The persistence of irrational FDC prescriptions despite regulatory frameworks reveals significant gaps in policy enforcement and prescriber awareness (7). Institutional interventions, including comprehensive FDC rationality assessments, integration of decision-support tools in electronic prescribing systems, and targeted prescriber education programs, are crucial to promoting evidence-based prescribing and enhancing patient safety (9).

In summary, the present study highlights the relevance of continuous pharmacovigilance in identifying adverse reactions associated with fixed-dose combinations in clinical practice. The observed patterns of ADRs emphasize the importance of careful drug selection, appropriate monitoring, and early recognition of adverse events in patients receiving combination therapies. Strengthening pharmacovigilance reporting systems and promoting evidence-based prescribing practices may contribute to improved medication safety and better therapeutic outcomes. Further multicenter investigations with larger sample sizes are warranted to provide more comprehensive insights into the safety profile of fixed-dose combinations in diverse healthcare settings.

Study Limitations:

This single-center observational study may not fully represent the national pattern of FDC-related adverse drug reactions. The reliance on spontaneous reporting systems inherently introduces under-reporting bias, potentially underestimating the true burden of FDC-related ADRs.

The limited sample size precluded detailed multivariate analysis to identify independent risk factors for FDC-related adverse events. Future multi-center studies with larger sample sizes would provide more robust evidence for policy formulation.

CONCLUSION

Fixed-dose combinations constitute an important contributor to adverse drug reactions in tertiary care settings, highlighting the need for careful evaluation of their safety in routine clinical practice. Although rational fixed-dose combinations remain valuable therapeutic options when supported by sound pharmacological justification, the continued use of irrational combinations raises significant concerns regarding medication safety and clinical appropriateness.

The predominance of cutaneous and gastrointestinal manifestations observed in association with combination therapies emphasizes the importance of vigilant clinical monitoring and early recognition of adverse reactions. Strengthening pharmacovigilance reporting, encouraging rational prescribing practices, and reinforcing regulatory oversight are essential measures to reduce preventable adverse drug reactions related to fixed-dose combinations.

Institutional strategies such as prescriber education, rationality assessment of combination drugs, and the integration of clinical decision-support systems in prescribing practices may further enhance medication safety and promote evidence-based therapeutic decision-making.

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CONFLICT OF INTEREST:

The authors declare no competing financial or professional interests related to this research study.

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