CURRENT PRESCRIBING TRENDS AND RATIONALITY OF FIXED DOSE COMBINATIONS IN A SOUTH INDIAN MULTI SPECIALTY HOSPITAL - AN OBSERVATIONAL STUDY

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Abstract

Fixed dose drug combinations (FDCs) are defined by the World Health Organization (WHO) as a combination of two or more active ingredients in a fixed ratio of doses and in a single dosage form. Physicians prescribe a number of FDCs today in which majority of them are irrational. **Aim:** To analyze the current prescribing trends and rationality of fixed dose combinations. **Methodology:** Prospective Observational Study carried out over a period of 6 months. The study involved 325 out-patient's prescription in general medicine department. All the necessary and relevant information were collected from out-patient prescription and patient medical records using the data collection form. The EML list of WHO (World Health Organisation) 2021 and NLEM (National List of Essential Medicines) 2015 were used for study. **Result:** The majority of general medicine department patients were in age group of 46-60 years. A total of 468 FDCs were prescribed in the study, 357 (76.28%) were oral dosage form and most of them 116 (24.79%) of total FDCs were analgesics. In rationality criteria, 184 (39.32%) of FDCs in EML from WHO and 153 (32.69%) of FDCs were from NLEM. The most of FDCs were irrational 196 (41.88%). **Conclusion:** Awareness and education about irrational FDCs, FDCs containing banned or controversial ingredients will help develop rational prescribing practices among prescribers.

Keywords: NLEM, FDC, WHO, EML, Irrational

Introduction

Fixed dose drug combinations (FDCs) are defined by the World Health Organization (WHO) as a combination of two or more active ingredients in a fixed ratio of doses and in a single dosage form. Drugs from different pharmacological groups with complementary mechanism of action should be combined in FDCs. When they are combined in a single formulation, the safety, efficacy and bioavailability profiles of the established drugs change, and hence, FDCs are treated as new drugs.[1]

As per the Drugs and Cosmetic Act 1940, any new drug and the authorization to market drug is to be given by the drug control general of India (DCGI). Before the approval of any drug, the Central drugs standard control organization (CDSCO) undergoes a process with respect to their quality, safety and efficacy. It is an accepted fact that FDC's is treated since a new drug for the reason that by combining two or more drugs. The safety, efficacy and bioavailability of the individual active pharmaceutical ingredients may change. The DCGI monitors the drug formulations including the combinations of drugs from the angle of safety, effectiveness and rationality.

Globally, there is a rising movement to license FDC's products for the market place. Appendix VI of Schedule Y specifies the necessities for authorization for marketing of variety of types of FDC's. FDA guidelines apply to manufacture/import and marketing approval of FDC's as a complete pharmaceutical product considered as new drug as per Rule 122 (E) of Drugs and Cosmetics Act 1940 and their Rules 1945.

Unfortunately, many FDC's are being introduced in India are usually irrational. The most pressing concern with irrational FDC's is that they expose patient's to unnecessary risk of adverse reactions, for instance, paediatric formulations of Nimesulide and Paracetamol. Nimesulide alone is more antipyretic than Paracetamol, more anti- inflammatory than aspirin, and equivalent in analgesia to any of the NSAIDS alone, so efficacy gains are unlikely with added Paracetamol. However, the patient's may be subject to increased hepatotoxic effects due to the combination[2].

There is no synergism when two drugs acting on the same enzyme are combined. Thus, combining two NSAIDs does not and cannot improve the efficacy of treatment. It only adds to the cost of therapy and more importantly to the adverse effects and the 'muscle relaxants' in some of these combinations are of questionable efficacy.[3]

The common approach for the approval of the FDC's is the bioequivalence between the FDC and the mono drugs previously used. The demonstration of bioequivalence between the FDCs and the mono drugs can be very difficult and sometimes, especially insoluble molecules in mono-drugs can complicate the biopharmaceutical and pharmacokinetic behaviors. The BE condition and the acceptance criteria for FDC components are listed in FDA, EMEA and in local regulations.[4]

Aim and Objective

The aim of this study is to analyze the current prescribing trends and assess the rationality of fixed-dose combinations (FDCs). The objectives include classifying and analyzing the distribution of FDCs based on FDA classification, determining the number of FDCs prescribed per prescription, and identifying the most frequently prescribed FDCs. Additionally, the study aims to evaluate the inclusion of these FDCs in the National List of Essential Medicines (NLEM) 2015 and the WHO Essential Medicines List (EML) 2021. Furthermore, the rationality of FDCs will be assessed using a standardized scoring scale.

Materials and Methods

A prospective, observational study was conducted in the general medicine department of a Teritiary care teaching hospital in Tamil Nadu from November 2021 to February 2022, analyzing 325 outpatient prescriptions. Data on patient demographics, medical history, and oral FDC prescriptions were collected from case sheets and medical records, excluding parenteral fluids, veterinary, and cosmetic formulations. The study assessed prescribing patterns using the WHO EML 2021 and NLEM 2015 and evaluated FDC rationality with a 7-point WHO Rationality Scoring Scale. Ethical approval was obtained, and informed consent was secured.

Results

The age-wise distribution of FDC usage was analyzed among 325 patients included in the study. Among them, 28 patients (8.62%) were aged below 18 years, 32 (9.58%) belonged to the 19-30 years age group, 80 (24.62%) were in the 31-45 years category, 98 (30.15%) were in the 46-60 years group, and 87 (26.77%) were above 60 years. The majority of patients in the general medicine department belonged to the 46-60 years age group. The mean age of the study population was 43.03±18.40 years. (Table 1)

The gender-wise distribution of FDC prescriptions among 325 patients showed that 176 (54.15%) were male, while 149 (45.85%) were female. The findings indicate that male patients were more frequently prescribed FDCs in the general medicine department.(Table 2)

A total of 468 FDCs were identified in 325 patient prescriptions. Among them, 214 prescriptions (65.85%) contained one FDC, which accounted for 45.73% of the total FDCs. Additionally, 82 prescriptions (25.23%) contained two FDCs (35.04%), 26 prescriptions (8%) had three FDCs (16.67%), and 3 prescriptions (0.92%) included four FDCs (2.56%). These results suggest that most prescriptions contained only one FDC. (Figure 1)

The study further analyzed the number of active pharmaceutical ingredients (APIs) per FDC prescription. Out of 468 FDCs, 325 (69.44%) contained two APIs, 104 (22.22%) had three APIs, and 39 (8.33%) contained four APIs. The findings indicate that the majority of FDCs were composed of two APIs. (Figure 2)

In terms of dosage form distribution, out of 468 prescriptions, 357 (76.28%) contained oral FDCs, 86 (18.38%) were topical formulations, and 25 (5.34%) were parenteral dosage forms. This suggests that oral dosage forms were the most commonly prescribed. (Figure 3)

The study also classified FDCs based on FDA categories. Among the 468 FDCs, 116 (24.79%) were analgesics, 104 (22.22%) were vitamin supplements, 74 (15.81%) were antibiotics, 67 (14.32%) were cough preparations, 35 (7.48%) were antacids, 21 (4.49%) were antihypertensives, 19 (4.06%) were antidiabetics, 14 (2.99%) were antiparkinsonism drugs, and 8 (1.71%) were antitubercular drugs. Analgesics and vitamin supplements were the most frequently prescribed categories. (Figure 4)

Regarding prescription patterns, 422 (90.17%) of the FDCs were prescribed using brand names, while only 46 (9.83%) were prescribed with generic names. In the analgesic category, 8 FDCs (1.71%) were prescribed using generic names, whereas 108 (23.08%) were in brand names. Among antacids, 9 (1.92%) were prescribed generically, while 26 (5.56%) were brand name prescriptions. Similarly, in the antibiotic category, 8 (1.71%) were generics, whereas 76 (16.24%) were branded prescriptions. Notably, all cough preparations (67; 14.32%) and vitamin supplements (104; 22.22%) were prescribed exclusively by brand names. (Figure 5)

The most commonly prescribed FDCs included Ibuprofen 400mg + Paracetamol 325mg (41; 8.76%), Pantoprazole 40mg + Domperidone 10mg (37; 7.91%), Amoxicillin 500mg + Clavulanic Acid 125mg (35; 7.48%), a multivitamin combination (29; 6.20%), Cefpodoxime 200mg + Clavulanic Acid 125mg (28; 5.98%), Aceclofenac 100mg + Paracetamol 500mg (23; 4.91%), and Cefixime 200mg + Clavulanic Acid 125mg (21; 4.49%). (Table 3)

The rationality assessment of FDCs was based on WHO and NLEM criteria. Among 468 FDCs, 184 (39.32%) were listed in the WHO EML, and 153 (32.69%) were part of the NLEM. Additionally, 245 (52.35%) of FDCs were in appropriate intended doses, 145 (30.98%) had appropriate intended use, 84 (17.45%) had different mechanisms of action, 67 (14.32%) showed pharmacokinetic and pharmacodynamic interactions, 119 (25.43%) facilitated dose reduction of APIs, and 135 (28.85%) were associated with adverse drug reactions. (Table 4)

The overall rationality assessment revealed that 196 (41.88%) of the FDCs were irrational, 167 (35.68%) were semi-rational, and only 105 (22.44%) were classified as rational. These findings highlight the need for a more evidence-based approach to FDC prescribing to ensure safety and efficacy. (Figure 6)

Table 1. Age wise distribution of data

S.NO	AGE CATEGORY	No of Patients (n=325)	%
1	> 18 years	28 (8.62%)	8.62
2	18-30 years	32 (9.85%)	9.85

3	31-45 years	80 (24.62%)	24.62
4	46-60 years	98 (30.15%)	30.15
5	60 years Above	87 (26.77%)	26.77
Mean±SD		**43.03±18.40**	

Table 2. Gender wise distribution of data

S.NO	GENDER	NO OF PATIENT'S	%
1	Male	176	54.15
2	Female	149	45.85
	Total	325	100

Table 3. Commonly Prescribed FDCs

S.NO	COMMONLY PRESCRIBED FDC	FREQUENCY	%
1	Tab.Cefpodoxime 200mg + Clavulanic Acid 125mg	28	5.98
2	Tab.Amoxicillin 500mg + Clavulanic Acid 125mg	35	7.48
3	Tab.Cefixme 2000mg + Clavulanic Acid 125mg	21	4.49
4	Tab.Calicum Citrate 1000mg+Magnesium 100mg+Zinc 4mg+Vitamin D3IU	27	5.77
5	Tab.Vitb1 5mg +Vit B2 5mg + Vit B3 45mg + Vit B6 1.5mg + Vit B9 1mg + Vit B12 5mcg + Vit A 5000IU + Vit C 75 Mg + Vitamin E 15 IU	29	6.20
6	Ibuprofen 400mg + Paracetamol 325mg	41	8.76
7	Tab.Aceclofenac 100mg+Paracetamol 500mg	23	4.91
8	Tab.Pantoprazole 40mg + Domperidone 10mg	37	7.91
	TOTAL	**241**	51.50

Table 4. Rationality Criteria

S.NO	RATIONALITY CRITERIA	FREQUENCY	%
1	API from EML of WHO	184	39.32
2	FDCs in EML of NLEM	153	32.69
3	Dose of API appropriate for intended use	245	52.35
4	Proportion of API appropriate for intended use	145	30.98
5	API should have different MOA	84	17.95
6	PK and PD interaction	67	14.32
7	FDC facilitate dose reduction of API	119	25.43
8	FDC Facilitate Adverse Drug Reaction	135	28.85

Figure 1. Occurrence of FDCs per prescription

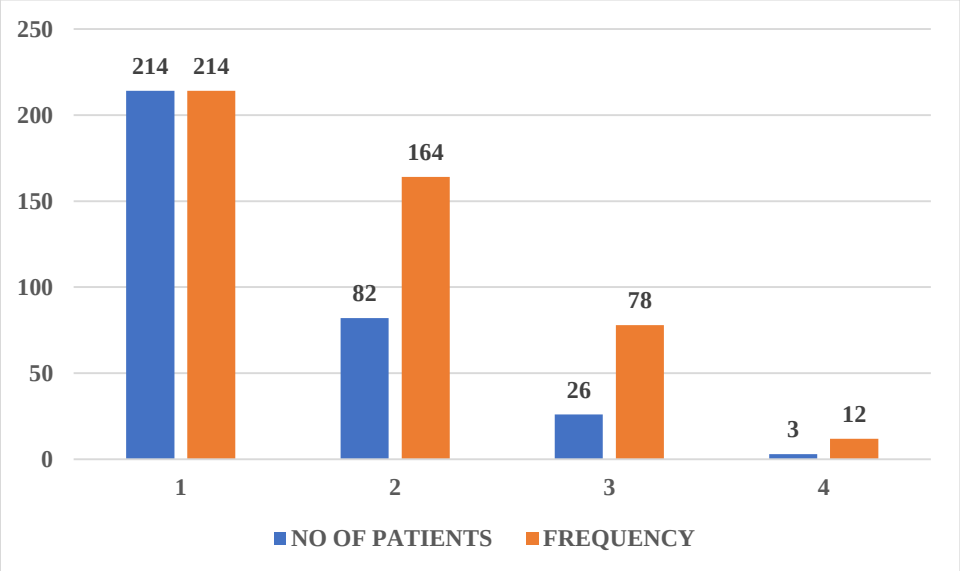


Figure 2. No of API per prescription FDC

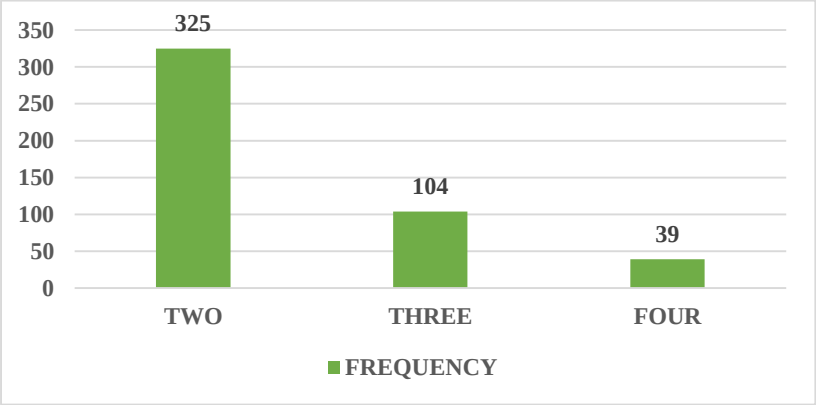


Figure 3. Dosage form of FDCs

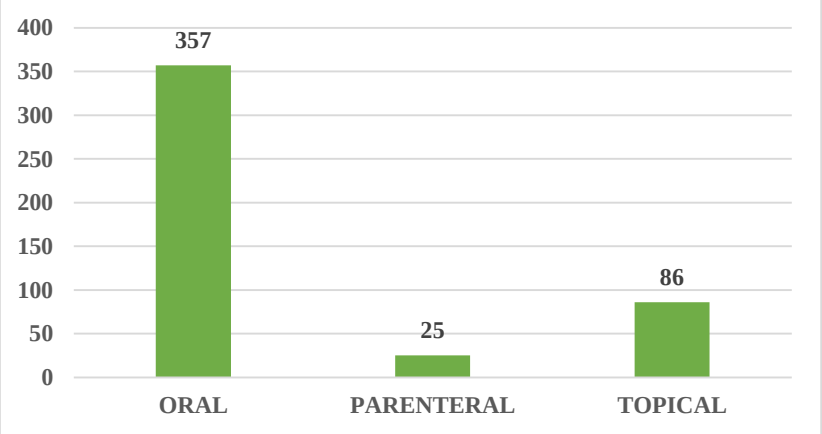


Figure 4. Classification of FDC

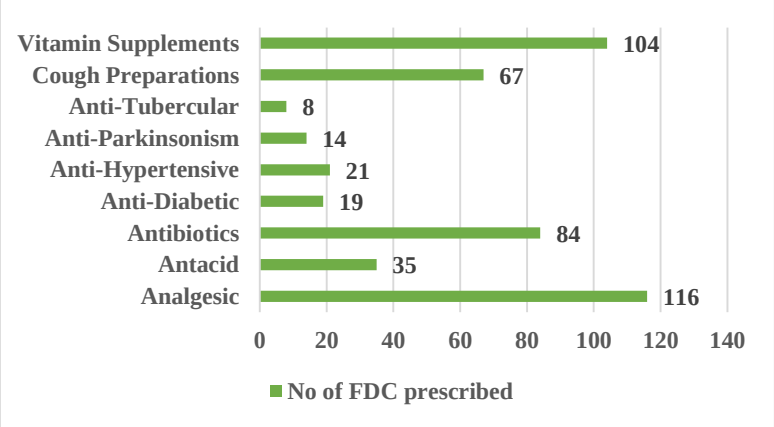


Figure 5. Prescription with Generic name Vs Brand Name

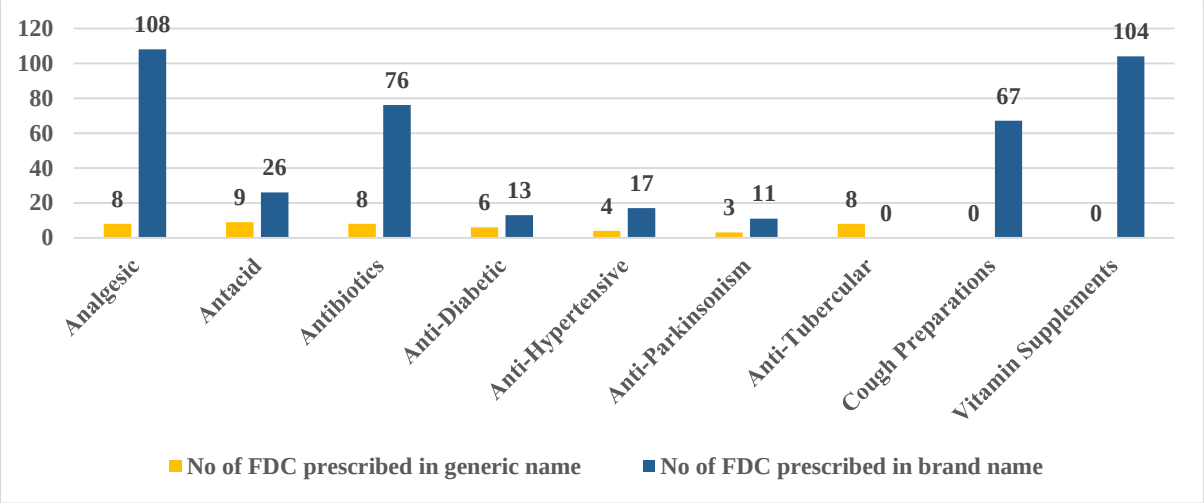
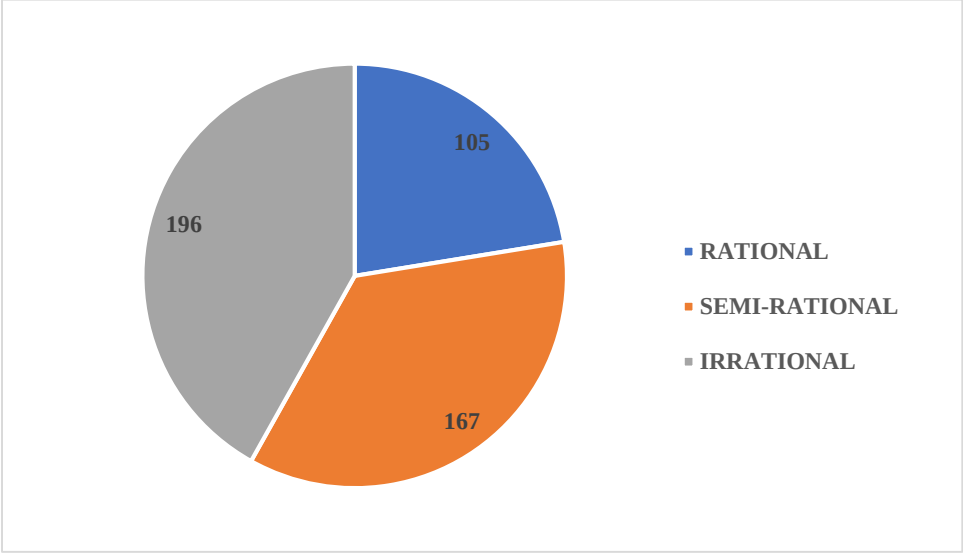


Figure 6. Rationality of FDC Prescribed



Discussion

The present study assessed Fixed-Dose Combinations (FDCs) with a special focus on their rationality. Most studies on FDCs have primarily examined prescribing patterns in different setups and diseases. In our study, FDCs were found to be used more frequently in males (54.15%) and in the age group of 46-60 years. Similarly, a study conducted in Ahmedabad, India, reported a higher number of FDC prescriptions in the 31-49 years age group (23.7%) (Balat J D et al., 2014). This trend could be attributed to the greater availability of adult-dose FDCs or the higher number of adult patients admitted to the medicine department.

Among the total 468 FDCs analyzed for rationality, oral dosage forms were the most common (76.28%), followed by topical (18.38%) and parenteral (5.34%) formulations. Similar findings were observed in the study by Balat et al., where oral route prescriptions accounted

for 92.7%, followed by topical (5.9%) and parenteral (1.4%) routes ($p < 0.001$). Additionally, Shah et al. (2015) reported that all cardiovascular FDCs were administered orally.

In our study, 34.15% of patients received more than one FDC (up to four), and 25.23% of prescribed FDCs contained more than two Active Pharmaceutical Ingredients (APIs) (up to four). A study conducted in India reported an increase in adverse reactions in more than half of the FDCs, highlighting the necessity of appropriate selection and usage of these combinations. Furthermore, a study among dental clinicians and residents revealed a lack of knowledge and awareness regarding FDCs (Poudel A et al., 2017). The influence of pharmaceutical companies in promoting unnecessary FDCs to prescribers necessitates that healthcare professionals be well-equipped with appropriate knowledge and skills for rational prescribing. Hospital pharmacists play a crucial role in providing accurate information regarding medicines.

Brand name prescribing was dominant in our study, with 90.17% of FDCs being prescribed under brand names and only 9.83% under generic names. Brand name prescribing appears to be more convenient than generic prescribing, as it eliminates the need to specify individual API doses. However, a lack of understanding of API composition and dosage may lead to harmful consequences. Furthermore, brand prescribing complicates procurement and dispensing in hospital pharmacies. Encouraging generic prescribing in developing countries is essential, as it can reduce the financial burden on patients.

Among the 468 FDCs analyzed, antibiotics accounted for 15.81%, with the highest number of brands found in the amoxicillin 500 mg + clavulanic acid 125 mg combination. Both the Nepal and WHO Essential Medicines Lists (EMLs) consider this combination essential, and other studies also regard it as rational (Pradhal S et al., 2017). However, the cefixime 200 mg + clavulanic acid 125 mg combination, despite its frequent use, is absent from both EMLs. This combination is deemed irrational since clavulanic acid primarily prevents beta-lactamase-mediated degradation of penicillin antibiotics. Regulatory authorities must establish strict criteria to evaluate the rationality of FDCs before granting marketing authorization.

In our study, the most frequently prescribed FDCs were analgesics (24.79%), followed by vitamin supplements (22.22%), cough preparations (14.32%), antacids (7.48%), antihypertensives (4.49%), antidiabetics (4.06%), antiparkinsonism drugs (2.99%), and antitubercular drugs (1.71%). Vitamin B and calcium combinations were the most common supplements, aligning with findings from previous studies (Gautam C S et al., 2008). Despite similarities in composition, variations in dosage among different brands contribute to brand loyalty and patient dependency on specific products. This may be a marketing strategy employed by manufacturers. Unregulated use of nutritional FDCs without proper assessment can lead to increased financial burden, toxicity risks, and potential drug interactions. Regulatory authorities must thoroughly evaluate FDC combinations and dosages before granting approval.

Only 32.69% and 39.32% of FDCs prescribed in our study were included in the EMLs of Nepal and WHO, respectively. In contrast, a South Indian study reported that only 12% of

FDCs were from the WHO EML and 6.4% from the Indian EML. Some FDCs contained similar compositions to EML-listed combinations but had mismatched doses. Additionally, the most commonly used five FDCs in our study were absent from both EMLs. The fact that 63.41% and 70.75% of APIs were not included in the Nepal and WHO EMLs, respectively, raises concerns about their safety, efficacy, and cost-effectiveness. WHO emphasizes the use of essential medicines due to their proven benefits, but the lack of comprehensive studies and regular EML updates may contribute to the continued use of non-listed FDCs. This study highlights the urgent need to reassess the rationality and necessity of market-available FDCs and update EMLs accordingly.

Our analysis revealed that 52.35% of FDCs were prescribed at an appropriate intended dose, 30.98% had appropriate intended use, and 17.45% had different mechanisms of action. WHO defines rational FDCs as those offering proven advantages over single-drug therapy in terms of therapeutic effect, safety, adherence, or resistance prevention. However, 6.81% of FDCs in our study were deemed irrational due to the absence of complementary mechanisms of action. For example, combinations such as paracetamol 500 mg + ibuprofen 400 mg and ampicillin 250 mg + cloxacillin 250 mg lacked synergistic effects and posed an increased risk of additive side effects. Notably, analgesic FDCs (24.79%) were the most commonly used, with ibuprofen 400 mg + paracetamol 500 mg being the highest-prescribed combination. Previous studies in India reported that NSAID combinations constituted two-thirds of FDC sales between 2011 and 2012. The combination of two NSAIDs is highly undesirable due to the associated gastrointestinal risks (McGettigan P et al., 2015).

Overall, our study found that 41.88% of FDCs were irrational, 35.68% were semi-rational, and only 22.44% were classified as rational. The rationality of marketed FDCs remains a major concern. Hospital Drug and Therapeutic Committees must remain vigilant and conduct rigorous studies to promote the appropriate use of FDCs. The findings of this study underscore the need for stringent regulatory oversight and evidence-based guidelines to ensure the rational prescribing of FDCs.

Conclusion

FDCs offer benefits like reduced pill burden and improved adherence but pose significant concerns regarding their rationality. This study highlights the widespread use of irrational and semi-rational FDCs, emphasizing the need for stringent regulatory scrutiny and evidence-based prescribing. The dominance of brand-name prescribing, inappropriate combinations, and variations in formulations further complicate rational drug use. Strengthening guidelines, increasing awareness, and promoting generic prescribing can improve safety, efficacy, and cost-effectiveness. Continuous evaluation by hospital committees and active involvement of pharmacists in educating prescribers are essential to ensuring rational FDC use.

Conflict of Interest

The authors declare no conflict of interest

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