EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 10
Issue: 4
145-153
Year: 2023

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

Sharukh Hossain*, Ayub Hossain, Harul-Al- Rashid and Dr. Shiv Kumar Shete

Sree Dattha Institute of Pharmacy.

***Corresponding Author: Dr. Sharukh Hossain**
Sree Dattha Institute of Pharmacy.

Article Received on 22/01/2023 **Article Revised on 12/02/2023** **Article Accepted on 05/03/2023**

ABSTRACT
The main aim of the study was to analyze the current prescribing trends and rationality of fixed dosecombinations. The therapy with FDCs reduce the polypharmacy or pill burden, which in turn can improve patient compliance. However, the rationality and justification of their uses always raises doubt and it can lead to controversial usage of drugs. Most commonly, the clinicians obtain information from the medical representatives apart from obtaining the information through peer group, resources like MIMS, CIMS, and continuing medical education programs. Insufficient or often biased information can lead to inappropriateness in the use of drugs. Strengthening of the regulatory guidelines, provision of continued updated unbiased information about the drug products and their safety should help in minimizing the inappropriate and irrational use of drugs. Awareness and education about irrational FDCs, FDCs containing banned or controversial ingredients will help develop rational prescribing practices among prescribers. Rational combination of drugs to formulate FDCs and the appropriate use of FDCs can definitely improve adherence to the therapy, safety, and reduce the cost of therapy. However, efforts to increase awareness regarding the correct use of FDCs should be a constant objectivefor the pharmacists.

KEYWORDS: Current Prescribing Trends, Rationality of fixed dose, South Indian Multi Specialty Hospital, Observational Study.

INTRODUCTION
Fixed portion blends, sanity, WHO rules, fundamental medications list, public rundown of fundamental prescriptions Fixed portion drug mixes (FDCs) are characterized by the World Wellbeing Association (WHO) as a mix of at least two dynamic fixings in a decent proportion of dosages and in a solitary measurement structure.[1] Drugs from various pharmacological gatherings with corresponding component of activity ought to be consolidated in FDCs. At the point when they are consolidated in a solitary plan, the wellbeing, viability and bioavailability profiles of the laid out drugs change, and thus, FDCs are treated as new medications.[2] Doctors endorse various FDCs today in which larger part of them are silly. FDCs are broadly acknowledged when it offers reasonable benefits over the items with single dynamic drug fixings (Programming interface).[3] Benefits of FDCs incorporate improved adequacy, decreased unfavorable medication response (ADR), give more extensive range of antibacterial action, diminished entanglements, simplicity of organization and decreased polypharmacy. The utilization of mix drugs with fixed portion helps display its belongings with less pills or portion, in this manner working on the patient consistence. It might likewise diminish the expense and deal the unfortunate patients a lower generally speaking medical care cost. The medications in blend might give a synergistic or an added substance impact. The utilization of antimicrobial FDCs like amoxicillin+clavulanic corrosive and ritonavir+lopinavir for the treatment of irresistible sicknesses might slow or defer the fulfillment of antimicrobial obstruction. There might be a decline in symptoms of individual medications when these medications are given in blend. In any case, there are sure disservices that are related with the utilization of FDCs. These incorporate potential bioavailability issues, trouble in evaluating ADR, rise of obstruction, expansion in cost of treatment and unfortunate patient consistence as they differ to change to FDCs. The dosing timetable of individual constituent of FDCs might vary and this might bring about unyielding dosing routine. There might be communication among constituents of FDCs and this might bring about antagonistic impacts, especially while drugs having a place with a similar pharmacological class are utilized.[4-6] The expanded number of remedies with FDCs involves worry as it might foster silly recommending designs in medical clinics. It forces

superfluous monetary weight, increment the event of ADR including sensitivity, hospitalization and at last decreasing the personal satisfaction. In any case, the benefits and disservices can commonly cover.[7]

The main aim of the study was to analyze the current prescribing trends and rationality of fixed dose combinations

METHODOLOGY

This chapter is comprised of the study design, site, sample of the study population data collection, data analysis etc.

Study design and site

A Prospective, Observational Study design was conducted in general medicinedepartment of the Global Hospital, Hyderabad. The study design consists of questionnaires.

Demographic data and relevant medical history were obtained from all patient's case sheet and medical records.

Study period: The current Prospective, Observational Study was carried out at Global Hospital,Calicut over a period from August 2022 to December 2022.

Study Population: The study involved 325 out-patient's prescription in general medicine department ofNational Hospital.

STUDY CRITERIA

Inclusion criteria

All the prescriptions the all-age group and both gender containing oral FDCs were separated and required data were copied in data collection form at the time of out-patient hospital visit.

Exclusion Criteria

Categories of FDCs like parenteral fluids used for hemodialysis & peritoneal dialysis, veterinary and cosmetics from Dermatology.

Source of data: All the necessary and relevant information were collected from out-patient prescription and patient medical records using the data collection form.

Study procedure: All the patient's /patient's attender gave informed written consent prior to their inclusion in this study. The study involved 325 patient's prescription in general medicine department. Data were collected in between duration and hospital name.

Ethical Approval The ethical clearance was approved from institutional ethical committee and hospital authority has sanctioned.

Statistical analysis: The collected data was analyzed by using Microsoft Excel 2010, and results were expressed in number and percentage by using table and bar-diagram.

RESULTS AND DISCUSSION

General description The present study was carried out in out-patient general medicine of Global Hospital, Hyderabad. We were recruited 325 patient's prescription according to the inclusion criteria.

SOCIO DEMOGRAPHIC CHARACTERISTIC DISTRIBUTION

Age wise data distribution data for FDCs

The age wise distribution was done in a total of 325 patients were taken in this study. In > 18 years, age group were 28 (8.62%), In 19-30 years, age group were 32 (9.58%), In 31- 45 years age group were 80 (24.62%), In 46-60 years age group were 98 (30.15%) and above 60 years age group were 87 (26.77%). The majority of general medicine department patients were in age group of 46-60 years old patients. The mean age was 43.03±18.40 years.

Table 1: Age wise data distribution data for FDCs.

S.NO	AGE CATEGORY	TOTAL	%
1	> 18 years	28	8.62
2	18-30 years	32	9.85
3	31-45 years	80	24.62
4	46-60 years	98	30.15
5	60 years Above	87	26.77
	Total	325	100
Mean±SD		**43.03±18.40**	

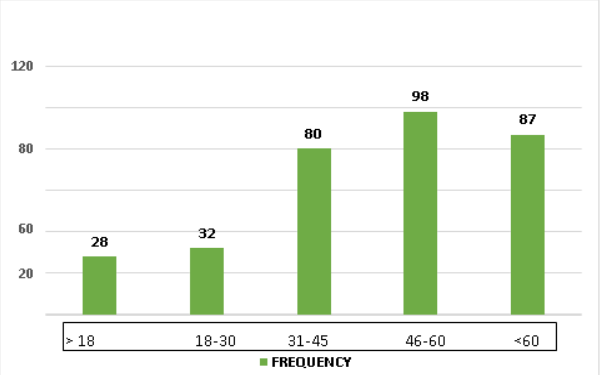

FIG. 1: AGE GROUP OF FDCs.

Gender wise data distribution data for FDCs

The study reveals about gender wise distribution of 325 patient's. In that the male patient's were 176 (54.15%) and female patient's were 149 (45.85%). In general medicine, male patient's were more in number.

Table 2: Gender wise data distribution data for FDCs.

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

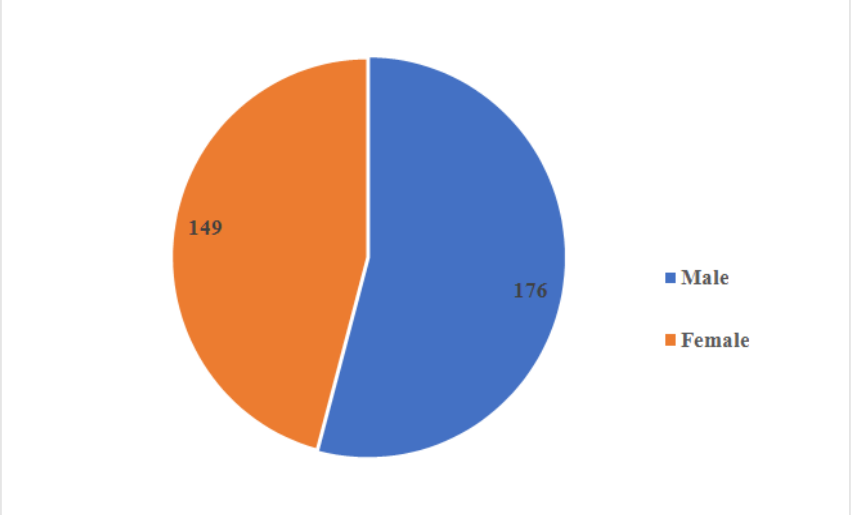

Fig. 2: Gender Wise Data Distribution Data For FDCs.

Occurrence of no of FDCs per prescription

A total of 325 patient's prescription, 468 FDCs were found. In those 214 (65.85%) patient's prescriptions contains 214 (45.73%) of one FDC. Followed by, 82 (25.23%) of patient prescription contains 164 (35.04%) of two FDCs, 26 (8%) of patient's prescription contains78 (16.67%) of three FDCs, 3 (0.92%) of patient's prescription contains 12 (2.56%) of four FDCs. These results showed that most of the patient's prescription had 1 FDC.

Table 3: Occurrence of No of FDCs Per Prescription.

S.NO	NO OF FDCs	NO OF PATIENT'S	%	FREQUENCY	%
1	1	214	65.85	214	45.73
2	2	82	25.23	164	35.04
3	3	26	8.00	78	16.67
4	4	3	0.92	12	2.56
	TOTAL	325	100	468	100

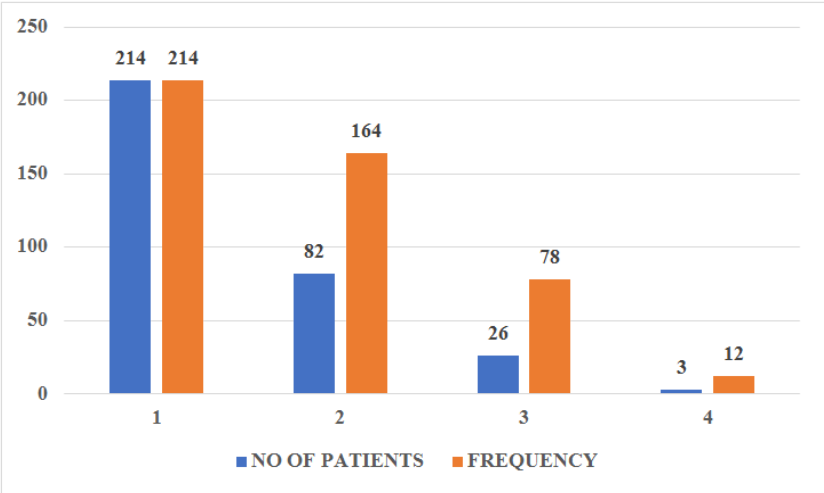

Fig. 3: Occuerance of No of Fdcs Per Prescription.

No of APIs per prescription FDC

Table 4 states no of Active Pharmaceutical ingredients per prescription. Out of 468 FDCs, 325 (69.44%) of FDCs had two APIs, followed by 104 (22.22%) of FDCs had 3 APIsand 39 (8.33%) of FDCs had 4 APIs. These results showed, most of the FDCs had 2 APIs.

Table 4: No of Apis Per Prescription.

S.No	No of Apis Per FDC	Frequency	%
1	Two	325	69.44
2	Three	104	22.22
3	Four	39	8.33
	Total	**468**	**100**

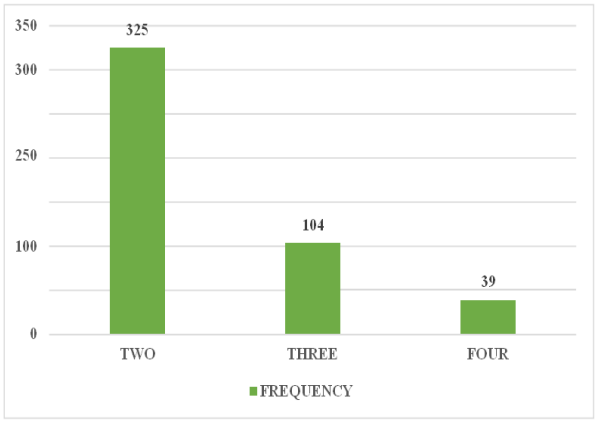

FIG. 4: NO Of APIs Per Prescription.

Dosage form of FDCs

Out of 468 patient's prescription, most of the patient's prescription 357 (76.28%) had oral dosage form of FDCs, followed by 86 (18.38%) of patient's prescription had topical dosage form of FDCs and 25 (5.34%) of patient's prescription had parenteral dosage form of FDCs.

Table 5: Dosage Form of FDCs.

S.No	Dosage Form of FDCs	Frequency	%
1	Oral	357	76.28
2	Parenteral	25	5.34
3	Topical	86	18.38
	TOTAL	**468**	**100**

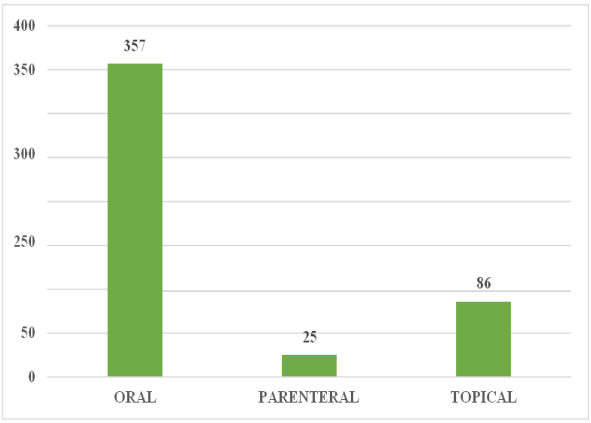

Fig. 5: Dosage Form Of FDCs.

Classification of FDC

This study reveals that FDA classification of FDCs in patient's prescription. Out of 468FDCs, most of the FDCs 116 (24.79%) were in analgesics, followed by 104 (22.22%) of FDCs in vitamin supplements, 74 (15.81%) of FDCs were in antibiotics, 67 (14.32%) of FDCs were in cough preparations, 35 (7.48%) of FDCs were in antacids, 21 (4.49%) of FDCs were in anti-hypertensives, 19 (4.06%) of FDCs were in anti-diabetics, 14 (2.99%) of FDCs were in anti- parkinsonism and 8 (1.71%) of FDCs were in anti-tubercular drugs.

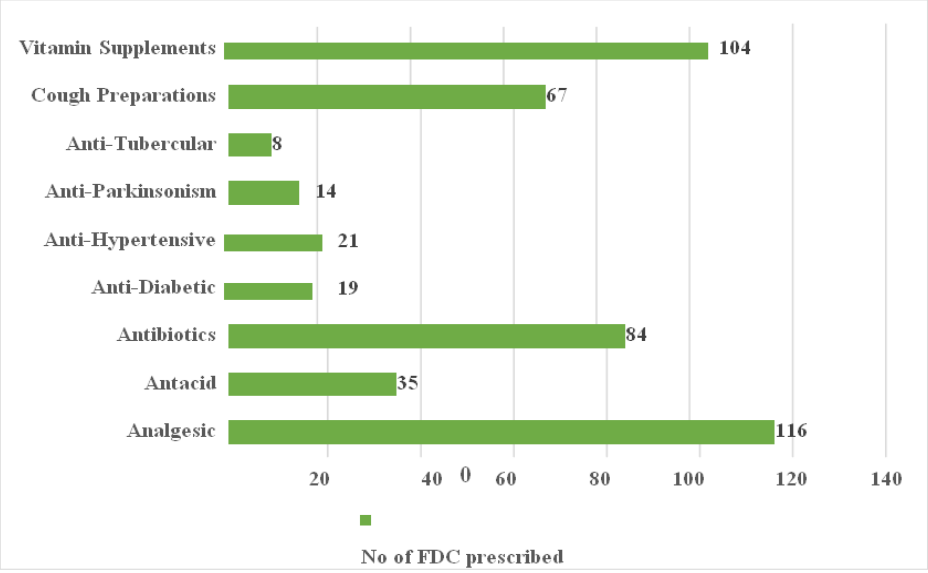

Fig. 6: No of Fdc Prescribed.

Table 6: No Of Fdc Prescribed.

S.no	FDC category	No of FDC	%	No of FDC	%	No of FDC	%

		prescribed		prescribedin generic name		prescribedin brand name	
1	Analgesic	116	24.79	8	1.71	108	23.08
2	Antacid	35	7.48	9	1.92	26	5.56
3	Antibiotics	84	17.95	8	1.71	76	16.24
4	Anti-Diabetic	19	4.06	6	1.28	13	2.78
5	Anti-Hypertensive	21	4.49	4	0.85	17	3.63
6	Anti-Parkinsonism	14	2.99	3	0.64	11	2.35
7	Anti-Tubercular	8	1.71	8	1.71	0	0.00
8	Cough Preparations	67	14.32	0	0.00	67	14.32
9	Vitamin Supplements	104	22.22	0	0.00	104	22.22
	Total	468	100	46	9.83	422	90.17

Prescription with Generic name Vs Brand Name

Out of 468 FDCs, most of the FDCs were prescribed in 422 (90.17%) brand name and 46 (9.83%) of FDCs were prescribed in generic name. The detailed generic and brand name of FDCs in prescription were in below. In analgesic category, 8 (1.71%) of FDCs prescribed in generic name and 108 (23.08%) of FDCs prescribed in brand name, in antacids 9 (1.92%) of FDCs prescribed in generic nameand 26 (5.56%) of FDCs prescribed in brand name, in antibiotics 8 (1.71%) of FDCs prescribed in generic name and 76 (16.24%) of FDCs prescribed in brand name, in anti-diabetics 6 (1.28%) of FDCs prescribed in generic name and 13 (2.78%) of FDCs prescribed in brand name, in anti-hypertensives 4 (0.85%) of FDCs prescribed in generic name and 17 (3.63%) of FDCs prescribed in brand name, in anti-parkinsonism category, 3 (0.64%) of FDCs prescribed in generic name and 11 (2.35%) of FDCs prescribed in brand name, in anti-tubercular drugs 8 (1.71%) of FDCs prescribed in generic name and no FDCs prescribed in brand name, in cough preparations 67 (14.32) and vitamin supplements 104 (22.22%) all FDCs were prescribed in brand name only.

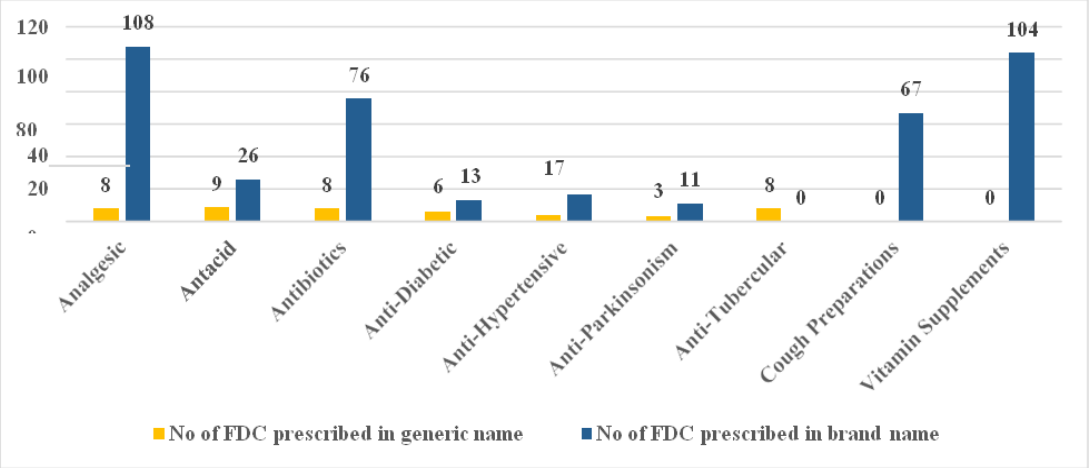

Fig. 7: FDCs Prescribed By Generic Name Vs Brands Name.

Commonly Prescribed FDCs

Table 8 reveals most commonly prescribed FDCs. In that, most of the FDCs 41 (8.76%)were Tab.Ibuprofen 400mg + Paracetamol 325mg, followed by 37 (7.91%) FDCs were Tab.Pantoprazole 40mg + Domperidone 10mg, 35 (7.48%) of FDCs were Tab.Amoxicillin 500mg + Clavulanic Acid 125mg, 29 (6.20%) of FDCs were 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, 28 (5.98%) of FDCs were Tab.Cefpodoxime 200mg + Clavulanic Acid 125mg, 23 (4.91%) of FDCs were Tab. Aceclofenac 100mg+Paracetamol 500mg, 21 (4.49%) of FDCs were Tab.Cefixme 2000mg + Clavulanic Acid 125mg.

Table 8: Commonly Prescribed FDCs.

S.NO	COMMONLY PRESCRIBED FDC	FREQUENCY	%
1	Tab.Cefpodoxime 200mg + Clavulanic Acid125mg	28	5.98
2	Tab.Amoxicillin 500mg + Clavulanic Acid 125mg	35	7.48
3	Tab.Cefixme 200mg + Clavulanic Acid 125mg	21	4.49
4	Tab.Calicum Citrate 1000mg+Magnesium100mg+Zinc 4mg+Vitamin D3IU	27	5.77
5	Tab.Vitb1 5mg +Vit B2 5mg + Vit B3 45mg + VitB6	29	6.20

	1.5mg + Vit B9 1mg + Vit B12 5mcg + Vit A 5000IU + Vit C 75 Mg + Vitamin E 15 IU		
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

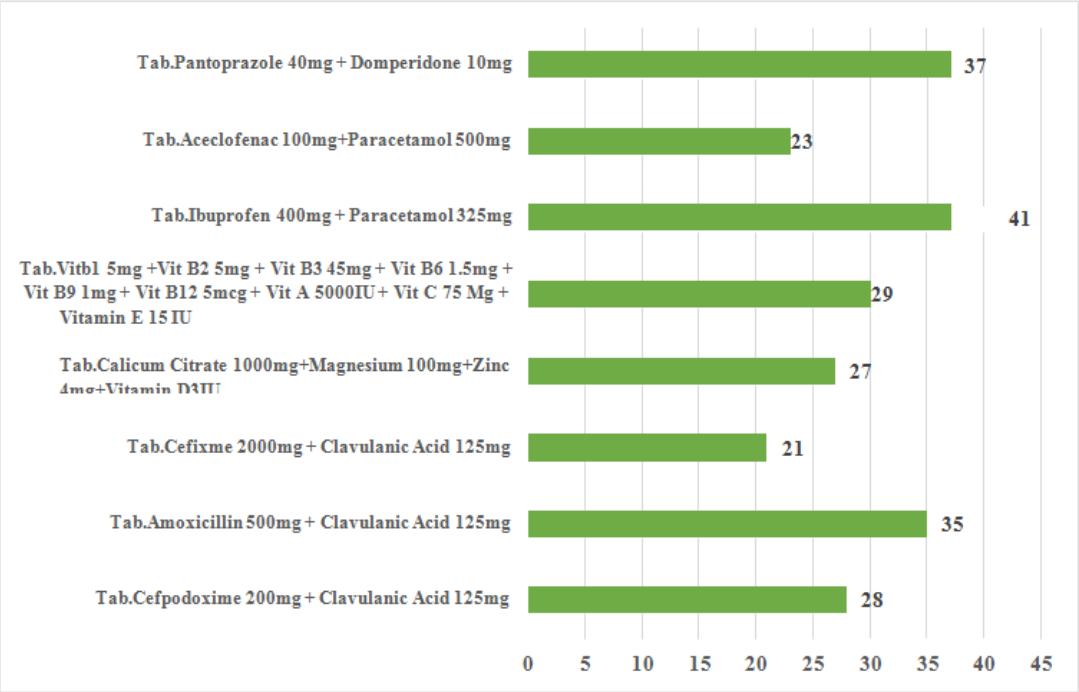

FIG. 8: Commonly Prescribed FDCs.

Rationality Criteria

Table 9 reveals the rationality criteria of 468 FDCs. In rationality criteria, 184 (39.32%) of FDCs in EML from WHO and 153 (32.69%) of FDCs were from NLEM. 245 (52.35%) of FDCs were in appropriate intended dose, 145 (30.98%) of FDCs were in appropriate indented use, 84 (17.45%) of FDCs have different mechanism of action, 67 (14.32%) of FDCs have pharmacokinetic and pharmacodynamic interactions, 119 (25.43%) of FDCs facilitates the dose reduction.

Table 9: 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 forintended use	245	52.35
4	Proportion of API appropriate forintended 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 ofAPI	119	25.43
8	FDC Facilitate Adverse DrugReaction	135	28.85

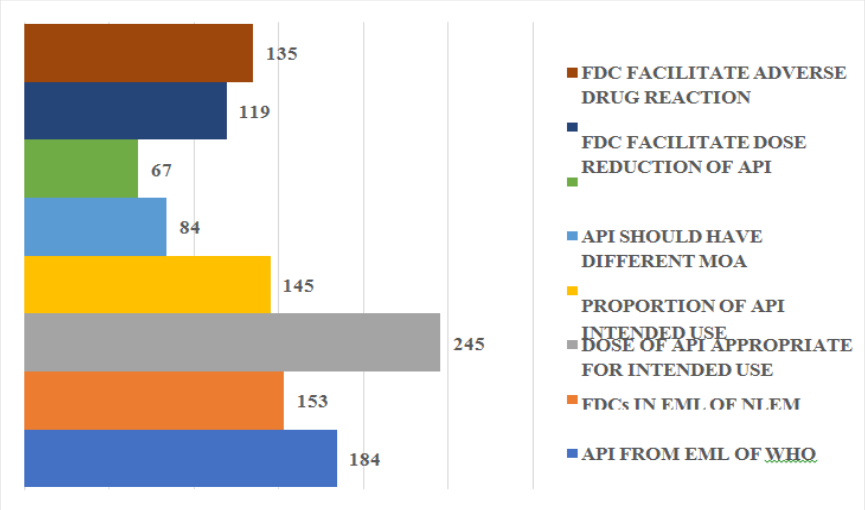

FIG. 9: Rationality Criteria.

Rationality

Table 10 showed rationality of FDCS. The most of FDCs were irrational 196 (41.88%). Out of 468 FDCs 105 (22.44%) of FDCs were rational and167 (35.68%) of FDCs were semi- rational.

Table 10: Rationality.

S.NO	RATIONALITY CRITERIA	FREQUENCY	%
1	Rational	105	22.44
2	Semi-Rational	167	35.68
3	Irrational	196	41.88
	Total	468	100

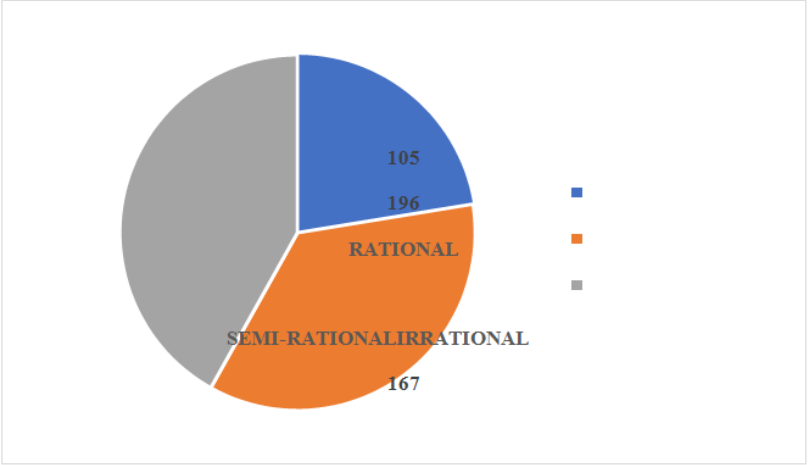

FIG. 10: Rationality.

DISCUSSION

Present study was done on assessment of FDCs with special inference to their rationality. Most of the studies on fixed dose combinations were related to prescribing pattern of combinations in different set up and diseases. In our study FDCs were comparatively found to use in higher in males 54.15%. In age group of 46-60 years old. y. Similarly, a study of Ahmedabad, India showed high number of FDCs prescribed to 31 to 49-year patients (23.7%). (Balat J D et al., 2014)The reason could be the higher availability of adult dose FDCs or the higher number of an adult aged patient admitted to the medicine department.

Out of total 468 FDCs taken for rationality, 357 (76.28%) maximum combinations were in oral dosage form followed by 86 (18.38%) in topical and rest 25 (5.34%) in parenteral dosageform. Similar result was seen in Balat et al., combinations were most commonly prescribed byoral route (92.7%) followed by topical (5.9%) and parenteral (1.4%) routes ($p < 0.001$). According to Shah et al., all cardiovascular fixed dose combinations have oral dosage form (Shah S et al., 2015).

The 34.15% of patients received more than one FDC up to four, and 25.23% of prescribed FDCs contain more

than two APIs up to four in our study. A study carried out in India reported increased in adverse reaction in more than half of FDCs, while the FDCs in thatstudy and of our is not compared. Therefore, the appropriate need-based selection and use of FDC is required. However, a study among dental clinicians and residents reported that they had poor knowledge and awareness of FDC. (Poudel A et al., 2017). The pharmaceutical company encourages physicians to prescribe their FDC even though they are not required by patients. Therefore, the prescriber should be equipped with appropriate knowledge and skill torationally prescribe FDCs, and the hospital pharmacist is a desired professional to provide appropriate information regarding medicines in hospital.

Most of the FDCs were prescribed in 422 (90.17%) brand name and 46 (9.83%) of FDCs were prescribed in generic name. FDC prescribing in brand name seems to be easier than in generic. Generic writing requires mentioning doses of composition but the brand name writing directly indicates composition as the specific brand name has specific doses of composition. However, the absence of true knowledge about the composition and dose of APIof FDCs leads to harmful consequences. The brand prescribing makes it difficult to arrange and dispense a particular brand by the hospital pharmacy. The generic prescribing and dispensing is desirable in developing countries as it reduces the expense of patients.

In our study 74 (15.81%) of FDCs were in antibiotics, the highest numbers of different brands were found in antibiotic drugs and specifically in the case of amoxicillin 500 mg and clavulanic acid 125 mg tab. The EML of Nepal and WHO both considered this FDC as essential. This combination is considered rational by other studies also. (Pradhal S et al., 2017).Generally, higher use of medicine has higher brand and market competition. On the other hand,the most used antibiotic cefixime 200 mg and clavulanic acid 125 mg tab had two brands; this combination is not listed in both EML of Nepal and WHO. Additionally, this FDC is considered irrational because clavulanic acid is supposed to prevent the destruction of beta-lactam ring of penicillin antibiotics only. The regulatory body is responsible to make criteria and check the rationality of FDCs scrutinously before manufacturing and marketing authorisation.

In our study most of the FDCs 116 (24.79%) were in analgesics, followed by 104 (22.22%) ofFDCs in vitamin supplements, 67 (14.32%) of FDCs were in cough preparations, 35 (7.48%) of FDCs were in antacids, 21 (4.49%) of FDCs were in anti-hypertensives, 19 (4.06%) of FDCswere in anti-diabetics, 14 (2.99%) of FDCs were in anti-parkinsonism and 8 (1.71%) of FDCswere in anti-tubercular drugs. among them, vitamin B combination and calcium combination were the majors. Vitamin supplements were commonly used in other studies as well. (Gautam C S et al., 2008). In case of vitamin supplements, the combination drug was very much similar to each other, but their combination dosage was different. There were ten brands and equally ten generic items in vitamin supplements. The unique combination compels patients to search for a particular brand. The slight changes in API and dose are probably the marketing strategy of manufacturers to promote their brand. Therefore, patients must be assessed thoroughly abouttheir nutritional deficiency and the requirement of a specific dose of vitamins. The regulatory body must study combinations and doses of FDC before giving approval for marketing. Higher use of nutritional FDCs without proper study can increases financial expenses, unwanted toxicities, and interactions.

The very few 32.69% and 39.32% FDCs were prescribed from EML of NLEM and WHO, respectively, in our study. While it was 12% from EML of WHO and 6.4% from EML of India in the study of South India. There were few FDCs which have a similar composition to EML but their doses were not matched. And, most commonly used five FDCs were also notpresent in either EMLs. Similarly, the majority of APIs that are 63.41% and 70.75% were notpresent in EML of Nepal and WHO, respectively. WHO encourages essential medicines use as they are safe, efficacious, cost-effective and able to meet the priority health needs of patients? From the above result, it can be said that either the commonly used FDCs were not safe, efficacious, and cost-effective for priority condition or they were not studied properly and updated EML on a regular basis. The current study emphasised the need to find the rationality and importance of FDCs practiced in the market and update the EML accordingly.

In our study 52.35% of FDCs were in appropriate intended dose, 30.98% of FDCs were in appropriate indented use, 17.45% of FDCs have different mechanism of action. According to WHO, FDCs are rational when the combination has a proven advantage over single compounds administered separately in therapeutic effect, safety, and adherence or in delaying the development of drug resistance. The combination should act by different mechanism and act as a booster for another. However, 6.81% of FDCs (n=3) that are paracetamol 500 mg and ibuprofen 400 mg tablet, paracetamol 125 mg and ibuprofen 100 mg per 5 ml, and ampicillin 250 mg and cloxacillin 250 mg capsule have a different mechanism of action and no complementary action. These combinations are considered irrational because the combinationdoes not have synergistic or additive action, rather the side effects are additive (Shah S et al.,2015, Ravichandran A et al., 2017). Additionally, analgesics (24.79%) were the mostly used FDC among all other categories; and Ibuprofen 400 mg and paracetamol 500 mg was the highly used FDC among them. A study conducted in India showed that NSAIDs combination had covered two-thirds of FDCs sold in 2011 to 2012. The combination of two NSAIDs is considered highly undesirable, as it has been found to be associated with gastrointestinal risk. (McGettigan P et al., 2015). In our study the most of FDCs were irrational 196 (41.88%).

Out of 468 FDCs 105 (22.44%) of FDCs were rational and167 (35.68%) of FDCs were semi-rational. The study of marketed FDCs rationality is becoming a major concern. The drug and therapeutic committee of the hospital has to be alert and conduct a rigorous study to promote appropriate use of FDC.

CONCLUSION

The therapy with FDCs reduce the polypharmacy or pill burden, which in turn can improve patient compliance. However, the rationality and justification of their uses always raises doubt and it can lead to controversial usage of drugs. Most commonly, the clinicians obtain information from the medical representatives apart from obtaining the information through peer group, resources like MIMS, CIMS, and continuing medical education programs. Insufficient or often biased information can lead to inappropriateness in the use of drugs. Strengthening of the regulatory guidelines, provision of continued updated unbiased information about the drug products and their safety should help in minimizing the inappropriate and irrational use of drugs. Awareness and education about irrational FDCs, FDCs containing banned or controversial ingredients will help develop rational prescribing practices among prescribers. Rational combination of drugs to formulate FDCs and the appropriate use of FDCs can definitely improve adherence to the therapy, safety, and reduce the cost of therapy. However, efforts to increase awareness regarding the correct use of FDCs should be a constant objectivefor the pharmacists.

REFERENCES

1. Guidelines for registration of fixed dose combination medicinal products. WHO Technical report series number 929. Geneva: World Health Organization; 2005.142 report number 39.
2. Rayasam SP, Dudhgaonkar SS, Dakhale GN, Hire RC, Deshmukh PS, Gaikwad NN. The irrational fixed dose combinations in the Indian drug market: an evaluation of prescribing pattern using WHO guidelines. Int J Basic Clin Pharmacol 2013;2(4): 452-57.
3. Prajapati K, Shah S Desai M. Critical analysis of cardiovascular and central nervous system fixed dose combinations available in Indian Market. JCDR, 2016; 10(12): 36-39.
4. Dahiya A. Fixed dose drug combinations in India-Is there enough scientific evidence. J Macrotrends Health Med., 2014; 2(1): 85-94.
5. Najmi A, Aiman U. A critical appraisal of rational and irrational fixed drug combinations. Asian J Pharm Sci Technol, 2015; 5(4): 335-37.
6. Vijayakumar TM, Jayaram J, Cheekireddy VM, Himaja D, Teja YD, Narayanasamy D. Safety, efficacy and bioavailability of fixed dose combinations in Type 2 Diabetes Mellitus: A systematic updated review. Curr Ther Res Clin Exp, 2017; 84: 4-9.
7. Balasubramanian J, Radhika N, Badarinath AV. The crave of fixed dose combination in Indian market. Asian J Pharm Clin Res., 2014; 7(4): 106-10.