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ASSESSMENT OF RATIONALITY OF FIXED DOSED COMBINATIONS (FDCs) PRESCRIBED IN MEDICINE OUTPATIENT DEPARTMENT OF A TERTIARY HEALTHCARE INSTITUTE

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ABSTRACT

Background: Fixed Dose Combinations (FDCs) are defined by WHO as combination of two or more active ingredients in a fixed ratio of doses. As the risk-benefit assessment is essential before choosing a combination therapy, this study was done about the presence of CDSCO/ WHO listed FDCs in the OPD prescriptions and their rationality assessment. **Methods:** It was done by the Department of Pharmacology from September 2017 to February 2018. All prescriptions from Medicine OPD of a tertiary healthcare hospital were screened for FDCs. Each FDC was checked for its presence in recent CDSCO and WHO essential medicines list. Parameters recorded were-

1. Name of combination drugs with doses.
2. Drug class.
3. Year of approval by CDSCO.
4. Rational/ Semi rational/ Irrational based on Rationality Scoring Scale.

Rationality assessment was done according to standard reference books. Drug interactions were checked by the "Drug Interaction Checker" provided by www.webmd.com.

Results: Number of prescriptions analysed were 700, in which 241 (34.4%) FDCs were present. Due to repetitions, actually 31 categories of FDCs were found. Out of these, 25.8% were rational, 70.9% semi rational and 3.3% irrational. 67.7% were approved while 32.3% not approved by DCGI. 80.9% of them were approved after the year 2000 and rest before that. Among the nonapproved FDCs, 20% were rational and 80% semi rational. **Conclusions:** Though the prevalence of FDCs in the prescriptions is high, only about 26% of them fulfil the rationality criteria. About 68% FDCs were DCGI approved while 32% were not. Hence, drug regulatory bodies should take urgent action to stop the free flow of irrational FDCs and to encourage rational FDCs.

KEYWORDS: Fixed dose combinations, Rationality scoring scale, Rational, Semi rational, Irrational.

INTRODUCTION

Fixed Dose Combinations (FDCs) are defined by the World Health Organization as combination of two or more active ingredients in a fixed ratio of doses.[1] The use of FDCs is a widespread clinical practice for various disease conditions. Since there is an increasing trend to develop and market these drugs, more than one-third of all the new drug products introduced worldwide during the last decade were FDCs.[2] Recent WHO Essential Medicines List contains about 15 oral and injectable FDCs excluding vaccines, antiseptics & disinfectants.[3] On the other hand, the CDSCO list approved by DCGI contains about 1275 FDCs (Since 1961 to November 2017).[4]

FDCs are beneficial when they have been formulated and developed on the basis of comprehensive pharmacokinetic & pharmacodynamic principles to increase their efficacy. They can improve clinical outcomes and patient compliance by decreasing complexity of the drug dosing schedule. In addition, the cost of an FDC may be less as the packaging cost minimizes. The reduction in adverse effects is also a beneficial point. So, all FDCs should ideally follow rational pharmacotherapy (Right drug in right manner- dose, route, frequency, duration etc., to right patient at right cost).[5] However, it is staggering to know that there has been an alarming rise in irrational FDCs in recent past.[5] An important concern is that not only there is an increase in cost, but these FDCs also expose patients to an unnecessary risk of adverse drug reactions.

Since the risk- benefit assessment is always essential before choosing a combination therapy, we did this study about the presence of CDSCO/ WHO listed FDCs in the OPD prescriptions and their rationality assessment according to the Rationality Scoring Scale.[6,7]

MATERIALS AND METHODS

This is a prospective study on FDCs prescribed in the Medicine outpatient department of a tertiary care hospital. It was carried out by the Department of Pharmacology over a period of 6 months from September 2017 to February 2018.

Inclusion criteria: All prescriptions from Medicine OPD containing FDCs.

Exclusion criteria: FDCs like parenteral fluids, vaccines and nutraceuticals.

All prescriptions from the Medicine OPD of a tertiary healthcare hospital were captured and screened for FDCs. Each FDC was checked for its presence in recent updated CDSCO and WHO essential medicines list and following parameters were recorded.

1.Name of the combination drugs with doses.

2.Drug class.

3.Year of approval by CDSCO.

4.Rational or irrational based on Rationality Scoring Scale.

Rationality Scoring Scale.[6,7]

Sr. No.	Rationality Criteria	Yes	No
1	Active Pharmacological Ingredient (API) from NLEM[8]&WHO EML[3]	All API (+1) At least one API (0.5)	0
2	Dose of API appropriate for intended use	+1	0
3	Proportion of API appropriate for intended use	+1	0
4	API should have different mechanism of action	+1	0
5	Pharmacokinetic and Pharmacodynamic interaction	Favorable (+1) Not favorable (-1)	0
6	FDC facilitates dose reduction of API	+1	0
7	FDC facilitates ADR reduction	+1	0

Maximum score= 9, Minimum score= 0

FDCs are graded as Irrational (0-<3), Semi-rational (3-<6), Rational (6-9).

Rationality assessment was done according to standard reference books. Along with other references, all drug interactions were also checked by the "Drug Interaction Checker" provided by www.webmd.com.

RESULTS

The total number of prescriptions analyzed in the study were 700, in which 241 (34.4%) FDCs were present. As there were repetitions, actually 31 different categories of drug combinations were found, as shown in Table 1.

Table 1: FDC Parameters.

Sr. No.	Name of FDC	Class	Dose	Frequency	Year of Approval	Score (Rational or Irrational)
1.	Diclofenac + Paracetamol	Analgesics	Diclo 50mg + PCM 500mg	72	January 2008	2 (Irrational)[9,10]
2.	Diclofenac + Paracetamol	Analgesics	Diclo 50mg + PCM 325mg	1	Not approved	6 (Rational)[11]
3.	Diclofenac + Paracetamol + Serratiopeptidase	Analgesics	Diclo 50mg + PCM 325mg + Ser 15mg	2	Not approved	5.5 (Semi rational)[10]
4.	Amoxycillin + Clavulanic acid	Antimicrobial drug	Amox 500mg + Clav 125mg	56	January 1995	6 (Rational)[12]
5.	Amoxycillin + Clavulanic acid	Antimicrobial drug	Amox 500mg + Clav 125mg	7	April 1990	6 (Rational)[12]
6.	Amoxycillin + Clavulanic acid	Antimicrobial drug	Amox 200mg + Clav 28.5mg per 5ml syrup	2	Not approved	6 (Rational)[12]
7.	Sulfamethoxazole + Trimethoprim	Antimicrobial drug	Sulfa 800mg + Tri 160mg	1	July 1970	6 (Rational)[13]
8.	Aspirin + Rosuvastatin + Clopidogrel	Antiplatelet & hypolipidemic	Asp 75mg + Rosu 10mg + Clopi 75mg	19	Not approved	3.5 (Semi rational)[14]
9.	Aspirin + Rosuvastatin + Clopidogrel	Antiplatelet & hypolipidemic	Asp 150mg + Rosu 20mg + Clopi 150mg	2	Not approved	3.5 (Semi rational)[14]
10.	Atorvastatin + Clopidogrel	Antiplatelet & hypolipidemic	Ator 10mg + Clopi 75mg	1	Not approved	4 (Semi rational)[15]
11.	Atorvastatin + Aspirin	Antiplatelet & hypolipidemic	Ator 10mg + Asp 75mg	1	January 2008	4 (Semi rational)[16,17]
12.	Atorvastatin + Aspirin	Antiplatelet & hypolipidemic	Ator 20mg + Asp 150mg	1	January 2008	4 (Semi rational)[16,17]
13.	Aspirin + Clopidogrel	Antiplatelet	Asp 75mg + Clopi 75mg	3	November 2002	5 (Semi rational)[14,16]
14.	Aspirin + Clopidogrel	Antiplatelet	Asp 150mg + Clopi 75mg	27	November 2002	5 (Semi rational)[16]
15.	Ramipril + Metoprolol	Antihypertensive	Rami 5mg + Meto 50mg	1	February 2007	5 (Semi rational)[18]

16.	Ramipril + Metoprolol	Antihypertensive	Rami 2.5mg + Meto 25mg	10	February 2007	5 (Semi rational)[18]
17.	Telmisartan + Amlodipine + Hydrochlorthiazide	Antihypertensive	Telmi 40mg + Amlo 5mg + HCTZ 12.5mg	3	October 2010	5 (Semi rational)[18,19]
18.	Telmisartan + Chlorthalidone	Antihypertensive	Telmi 40mg + Chlor 12.5mg	2	Not approved	4.5 (Semi rational)[18]
19.	Telmisartan + Hydrochlorthiazide	Antihypertensive	Telmi 40mg + HCTZ 12.5mg	2	August 2003	5 (Semi rational)[18]
20.	Telmisartan + Amlodipine	Antihypertensive	Telmi 40mg + Amlo 5mg	1	March 2009	6 (Rational)[18]
21.	Furosemide + Spironolactone	Antihypertensive	Furo 20mg + Spirono 50mg	7	September 1984	7 (Rational)[20,29]
22.	Glimepiride + Metformin	Oral Antidiabetic	Glime 1mg + Met 500mg	9	November 2002	5 (Semi rational)[10]
23.	Glimepiride + Metformin	Oral Antidiabetic	Glime 2mg + Met 500mg	2	November 2002	5 (Semi rational)[10]
24.	Caffeine + Chlorpheniramine + Paracetamol + Phenylepherine	Analgesic + Antihistaminic	Caff 30mg + Chlor 2mg + PCM 500mg + Phenyl 10mg	1	Not approved	4 (Semi rational)[21]
25.	Paracetamol + Dicyclomine	Analgesic antispasmodic	PCM 500mg + Dicyclo 20mg	2	Not approved	4 (Semi rational)[22]
26.	Voglibose + Metformin	Oral Antidiabetic	Vogli 0.3mg + Met 500mg	1	June 2010	4.5 (Semi rational)[23]
27.	Omeprazole + Domperidone	Antiulcer prokinetic	Omepra 20mg + Dom 30mg	1	May 2005	5 (Semi rational)[24]
28.	Tramadol + Acetaminophen	Analgesics	Trama 37.5 + Aceta 325mg	1	June 2011	6 (Rational)[25]
29.	Teneligliptin + Metformin	Oral Antidiabetic	Teneli 20mg + Met 500mg	1	January 2016	4.5 (Semi rational)[10,23]
30.	Gliclazide + Metformin	Oral Antidiabetic	Glicla 80mg + Met 500mg	1	April 2005	4.5 (Semi rational)[10,23]
31.	Diclofenac + Metaxalone	Analgesic & muscle relaxant	Diclo 50mg + Meta 400mg	1	Not approved	3.5 (Semi rational)[26]

Out of those FDCs analyzed, 25.8% (8) were rational, 70.9% (22) were semi rational and 3.3% (1) irrational (Figure-1).

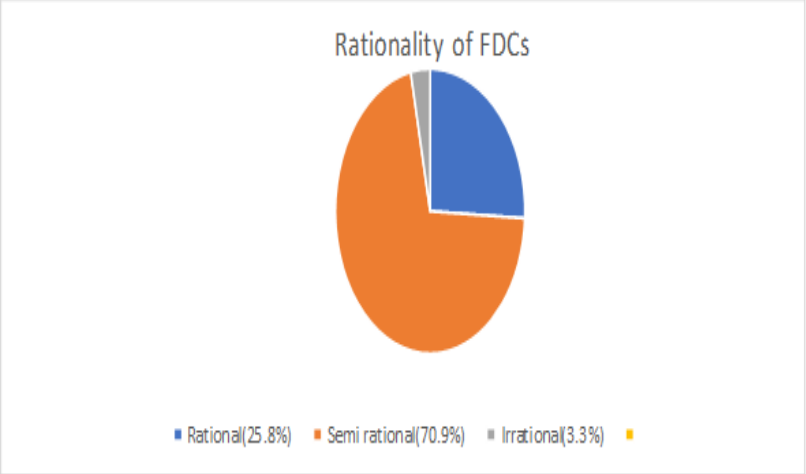

Figure. 1.

According to frequency, the most commonly prescribed FDC was Tab Diclofenac 50 mg + PCM 500mg (29.8%) followed by Tab Amoxycillin 500mg + Clavulanic acid 125mg (23.2%) and Tab Aspirin 150mg + Clopidogrel 75mg (11.2%) (Figure-2).

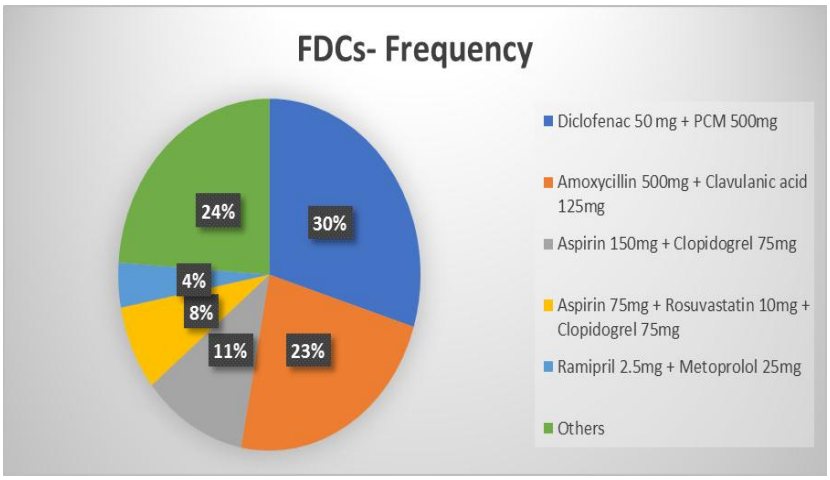

Figure. 2.

According to different categories of FDCs, antihypertensive drugs were most common (22.6%), followed respectively by oral antidiabetic drugs and antiplatelet-hypolipidemic combination (16.1% each), analgesics and antibiotics (12.9% each), antiplatelets (6.6%), analgesic- anti histaminic (3.2%), analgesic- antispasmodic (3.2%), analgesic- muscle relaxant (3.2%) and antiulcer- prokinetic (3.2%) (Figure-3).

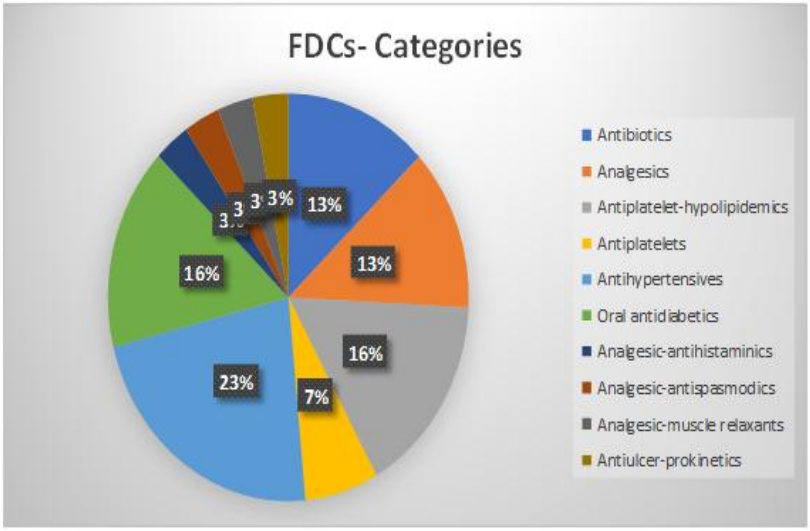

Figure. 3.

21 FDCs out of 31 (67.7%) were approved while 10 (32.3%) were not approved by DCGI. 17 out of 21 FDCs (80.9%) were approved after the year 2000 and rest were approved before that. Among the nonapproved FDCs, 2 (20%) were rational, while 8 (80%) were found semi rational.

DISCUSSION

The results of this study show that a large number of FDCs are available in Indian market which are frequently prescribed by the Medicine OPD of this tertiary healthcare institute in Mumbai. Unfortunately, their rationality assessment showed that majority had a score <6 (about 74%) indicating less prevalence of rational FDC prescription. This is in consistence with the study done by Rayasam et al in 2013[27] and Shah et al in 2015.[28]

Surprisingly, the most frequently prescribed FDC Tab Diclofenac 50 mg + PCM 500mg (29.8%) was found irrational according to the Rationality Scoring Scale as the dose of Paracetamol should ideally be 325mg to avoid hepatotoxicity, as documented by FDA.[9,11] As a consequence, the combination Tab Diclofenac 50 mg + PCM 325mg is rational.

The commonly prescribed antimicrobial combination Amoxycillin + Clavulanic acid and Sulfamethoxazole + Trimethoprim were found rational. Similarly, the antihypertensive combination Telmisartan + Amlodipine and Furosemide + Spironolactone & analgesics Tramadol + Acetaminophen were also rational and approved by DCGI.

Regarding antiplatelet and hypolipidemic combinations, no favorable pharmacodynamic and pharmacokinetic interactions were found among the drugs. Apart from obtaining better patient compliance, as they are being prescribed for prevention of ischemic cardiovascular disease, there is no other benefit. Some studies say that an unfavourable interaction is seen with the combination of Atorvastatin + Clopidogrel, which is significant decrease in antiplatelet activity by competing through cytochrome pathway metabolism. But, according to Tatro D, this interaction is seen when Fluvastatin or Simvastatin is co administered with Clopidogrel, not with Atorvastatin, Pravastatin and Rosuvastatin.[15]

Clopidogrel in combination with Aspirin significantly reduces collagen induced platelet aggregation compared with both monotherapies, suggesting a synergistic platelet inhibitory effect. In addition, the combined treatment results in a mild inhibition of aggregation induced by stimulation of platelet thrombin receptor and is more effective in inhibiting platelet activation by thrombin. Aspirin acts by inhibiting cycloxigenase and thromboxane synthase irreversibly while Clopidogrel alters surface receptors on platelets and inhibits ADP as well as fibrinogen induced platelet aggregation. But a major drawback of this combination is increased risk of bleeding which should be monitored especially in case of stroke patients.[14,29]

Hypokalemia produced by furosemide is controlled by spironolactone. The dose of Spironolactone is reduced in the combination when compared to monotherapy. This FDC has also demonstrated high antihypertensive efficacy when compared with high doses of Furosemide and Spironolactone monotherapy. Similarly, the combination of Telmisartan and Hydrochlorothiazide has advantage of improved efficacy since numerous previous studies have demonstrated that activation of renin angiotensin-aldosterone system by Hydrochlorothiazide enhances the effects of agents acting through blockade of this pathway.[7,20,29]

CONCLUSION

The present study has demonstrated that the prevalence of FDC in the prescriptions is high (about 34%). But, only about 26% of the marketed FDCs fulfil the rationality criteria. Unfortunately, about 71% are semi rational and 3% irrational. Average low scoring of FDCs in this study was due to the lack of evidence for efficacy and safety in many of them. Irrational FDCs unnecessarily add cost, adverse effects, and resistance also (in case of antimicrobial agents).

Among those analysed, about 68% were DCGI approved while 32% were not. Hence, drug regulatory bodies should take urgent action to stop the free flow of irrational FDCs and to encourage rational FDCs. Also, further studies are warranted in order to substantiate the rationality of those combinations which did not comply with all the criteria in the current study.

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