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Fixed Dose Drug Combinations In India- Is There Enough Scientific Evidence

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Abstract

Fixed Dose Drug Combinations (FDCs) are commonly prescribed drugs worldwide. They increase compliance to treatment particularly in non communicable diseases. They may decrease resistance in certain infectious diseases like HIV, Tuberculosis. Indian market is flooded with FDCs, the scientific rationale of whose are largely unknown. This study was designed to find out the exact number of FDCs in India. This study also aimed to analyze the prescribing trends and evaluate the rationality of FDCs being prescribed in a tertiary care hospital. The study found that there are approximately 3500 FDCs in India. The prescription audit revealed that majority of the prescribed FDCs lacked scientific evidence and many of them are irrational. However, the FDCs offer a cost advantage to the patient.

Keywords: *Fixed Dose Drug Combinations (FDCs), Rationality, Scientific evidence, Drug formulations*

1. 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 (WHO TRS 929, 2005). FDCs are commonly prescribed drug formulations as they offer many advantages such as ease of administration or intake by a patient in conditions where multiple drugs have to be taken. There is also an increase in compliance with the use of FDCs and the individual constituents of the FDC may show synergistic effects (Kumar 2008). The use of FDCs for the treatment of infectious diseases (Tuberculosis, Malaria and HIV) may slow or delay the attainment of antimicrobial resistance (Warren, 2001). There may be a decrease in side effects of individual drugs when these drugs are used in combination (Messereli et al, 2000). However, there are certain disadvantages that are associated with the use of FDCs. These include potential bioavailability problems when some drugs are used in combination with other drugs (Ellard et al,1986). The dosing schedule of individual constituents of a FDC may differ and this may result in inflexible dosing regimens. There may be interactions among constituents of a FDC and this may result in

adverse effects (Kumar, 2008). Also there may be an increase in the incidence of adverse effects with the use of FDCs, particularly when drugs belonging to the same pharmacological class are used.

As mentioned above there are both advantages and disadvantages with the use of FDCs. Hence to be useful a FDC should fulfill the guidelines that have been laid down by the WHO for the use of FDCs. General Principles of these guidelines mention that the combinations of drugs in the FDC should be safe and efficacious. All the constituents should have additive effect, the combination should increase adherence to treatment. The FDC should decrease the cost of treatment. Individual components of a FDC should act by a different mechanism, their pharmacokinetic profile should be similar and they should not result in any drug interactions.

There are thousands of drug formulations in India and many of them are FDCs. The economic share of FDCs in the pharmaceutical market, in India is estimated at 500-600 million US Dollars annually (Kumar, 2008). In the period between 1999 to 2011 The Drug Controller General India (Indian Drug Regulatory Authority) approved 1506 drugs out of them 568 were FDCs (Kataria et al, 2012). This number is large when compared to the Essential Medicines List of WHO and India. The WHO Essential Medicine List 2011 includes a total of 359 medicines out of which only 23(6.5%) are FDCs. The National Essential Medicines List of India 2011 includes a total of 390 medicines out of which only 3.9% are FDCs. FDCs are commonly prescribed drugs all over the world and they constituted 75% of prescribed drugs in one prescription audit (Kasturi etal, 1996). In other study out of the total prescriptions, 22% of prescriptions contained at least one FDC(Devi et al, 2012). Most commonly prescribed FDCs were multivitamin combinations, and second most common were antipyretic-anti inflammatory combinations. While the most commonly prescribed antimicrobial combinations were antiprotozoal antibacterial combinations (Raut et al, 2012). The scientific rationale of some of the FDCs that are available in Indian market have been questioned by various studies (Devi et al, 2012). Drug Controller General of India (DCGI) has provided a list of FDCs that have been banned . Despite this notification some of these banned continue to be marketed in India (Chugh and Lhamo, 2012).

The regulation of FDCs in India is another contentious issue. The FDCs are approved by the DCGI for marketing in India. However State Licensing Authorities (SLA) in different states of India also has the power to allow marketing permission in that particular state. There has been no uniformity in the different states as regards to grant of permission to manufacture such combinations. This has led to a situation where a State Licensing Authority grants a product not permitted by another State Licensing Authority. This has contributed to the large number of FDCs in India (Kataria et al, 2012). The use of FDCs offer a number of advantages, but the FDCs have to be of known efficacy and rationality. Since the medical and economic consequences of these drug formulations have to be borne by the patients, it is important that we have data as regards their composition and scientific basis. A consideration of the cost comparison of the FDCs versus individual drugs is also important for the patient.

There is lack of information on the exact number and composition of the FDCs in India. The appropriateness and rationality of the many of the available FDCs is not known. The

pharmacoeconomics of the FDCs and the cost comparison between the cost of individual drugs and the FDC is not available in India. There is no official record of the exact number of drug formulations and FDCs in India. This study was carried out to collect data and provide an estimate about the number of drug formulations and FDCs in India.

This study also aimed to analyze the prescribing trends with regards to FDCs. In addition the FDCs prescribed in these prescriptions were subjected to a rationality analysis and cost analysis.

2. Material & Methods

This study was conducted in a tertiary care hospital in New Delhi, India after approval by the Institutional Ethics Committee/Institutional Review Board. This study was carried out to analyse the Fixed Dose drug Combinations (FDCs) in India and to evaluate the rationality of these FDCs. A prescription analysis of 5000 prescriptions was carried out. Following this the FDCs were subjected to a quantitative, qualitative and cost analysis.

2.1 Quantitative Analysis

There is no official record of number of drug formulations and FDCs in India. A quantitative analysis of FDCs was performed from Drugs Today. Drugs Today is a commercial source of drug information and is widely referred to by physicians in India (Misra, 2012). The Pharmacological Index of Drug Today has been divided into 14 sections. These sections are Cardiovascular System, Musculoskeletal system, Antimicrobial agents, Central Nervous System, Alimentary System, Genitourinary system, Respiratory System, Dermatology drugs, Ophthalmology drugs, Oropharyngeal system, Hormones, Nutrition, Drugs affecting Metabolism and Surgicals and Vaccines. The number of individual drugs, the number of FDCs and the number of drug formulations were assessed.

2.2 Prescription Audit

A prescription audit was conducted. Five thousand prescriptions (5000) were collected between January 2013 and January 2014. The following was recorded in each prescription proforma: 1) The number of drugs prescribed, 2) The number of FDCs prescribed, 3) The constituents of FDCs, 4) The presence of the FDCs in the WHO Essential Medicine List 2011 and National Essential Medicine List, India 2011, 5) The prescribing of The FDC using a generic name, 6) The pharmacological system to which the FDCs belonged.

For the qualitative analysis of the prescribed FDCs, a rationality analysis was done using a rationality score based on the WHO criteria of a rational FDC and used by Roy et al and Devi et al. The rationality score was based on 7 point criteria. The criteria were as follows:

1) Number of constituents in the FDC (score) – 2 (4), 3(3), 4(2), 5(1), >5(0)

2) Do individual constituents belong to the same pharmacological class –Yes (0), No (1)

3) Do individual constituents have same mechanism of action- Yes (0), No (1)

4) Presence of any banned constituent as per the Drugs Controller General India Order - Yes (0), No (1)

5) Inclusion of the FDC in the National Essential Medicine List 2011, India- Yes (1), No (0)

6) Inclusion of the FDC in the WHO Essential Medicine List- Yes (1), No (0)

7) Cost of FDC (combination of drugs) is less than the cost of individual constituents in the same strength- Yes (1), No (0)

Maximum score= 10, Minimum score= 0

FDCs were graded as per the above mentioned scores. A rational FDC had a higher score, whereas a lower score indicated less rationality.

In addition the availability of scientific evidence for the FDCs was assessed using accessible electronic and print sources of drug information. The availability of scientific evidence was assessed from print media like Medical journals, standard Pharmacology and Medicine text books, Pharmacopoeias, Formulary etc. In the electronic media all the prominent online databases like Cochrane database, Pub Med, Medline and Copernicus were accessed. The A systematic review of all the published articles using Cochrane Library, Pub Med, Medline, Clinical Trials.gov, Google scholar, bliographies was conducted.. All studies related to FDCs which included Randomised controlled trials (RCTs), metaanalysis of RCTs, placebo-controlled, single-blind, double-blind, open label, prospective trials were screened and analyzed.

Cost analysis was done for the FDCs; where the cost of each FDC per unit dose was assessed and a cost comparison was done between the cost of the FDC and the cost of individual constituents.

3. Results

3.1 Quantitative analysis

The quantitative analysis showed that a total of 1,051 drugs are available in India according to Drugs Today. The total number of FDCs in India is 3,596. The total number of drug formulations in India is 37,482. Antimicrobial agents as a class contained the highest number of individual drugs, 151(14.4% of all the drugs). Central nervous system had the second highest number of individual drugs, 129(12.3%). Nutrition as a class had the highest number of FDCs, 1441(40.1% of all FDCs). The second highest number of FDCs was present in musculoskeletal system, 421 (11.7%). Out of the total 3,596 FDCs a significant proportion of the FDCs (39.8%) had 5 or more than 5 constituents. Two constituents were present in 34.2% of the FDCs. Three constituents were present in 19.1% of the FDCs and four constituents were present in 6.9% of the FDCs. In the pharmacological system of Nutrition, 80% FDCs had 5 or more than 5 constituents.
A summary of results of quantitative analysis has been represented in Table-1

Table-1: Quantitative analysis

Pharmacological System	**Total Drugs**	**Total Drug Formulations**	**Total FDCs**
Antimicrobial agents	151	10805	372
Central Nervous System	129	338	3535
Cardiovascular System	125	1740	128
Alimentary System	81	3724	250
Metabolism	107	655	17
Hormones	71	1487	60
Dermatology Drugs	65	1214	99
Musculoskeletal System	64	4777	421
Respiratory System	58	252	2529
Surgicals and Vaccines	54	367	39
Nutrition	41	5034	1441
Genitourinary System	39	364	42
OphthalmologyDrugs	22	600	50
Oropharyngeal System	44	651	87
Total	1051	37482	3596

3.2 Prescription Audit

3.2.1 General analysis

A prescription analysis of 5000 prescriptions was done. The general prescribing indicators have been represented in Table-2

Table-2: Prescribing Indicators

Prescribing Indicator	
Mean age (± Standard Deviation)	41.33±8.09 years
Males	56.2%
Females	43.8%
Average number of drugs per prescription	3.93±1.73
Drugs Prescribed According To Generic Name (%)	31.1 %
Drugs Prescribed according to WHO EML 2011 (%)	67.1%
Drugs prescribed according to NEML, India 2011 (%)	73.4%
Drugs Prescribed As Injections (%)	0.74%
Drugs prescribed as FDCs (%)	7.45%

WHO EML: WHO Essential Medicine List; NEML, India: National Essential Medicine List, India

3.2.2 FDC analysis

As mentioned above that 7.45% prescriptions had FDCs. Approximately thirty three percent (33.5%) of FDCs had 2 constituents, 5.3% of FDCs had three constituents. Four constituents were present in 15.2% of FDCs and 5 or more than 5 constituents were present in 45.9% of the FDCs. Only 1.2% of the FDCs were prescribed according to their generic names. Approximately 20% of the FDCs (19.7%) were present in the WHO EML 2011 and 18.9% FDCs were present in the NEML, India 2011. Majority of the FDCs belonged to the vitamins and minerals (53.3% of prescribed FDCs). The second most commonly prescribed FDCs were FDCs of Antimicrobial agents (22.9% of FDCs). The third highest prescribed FDCs were from the system of gastrointestinal drugs (10.3% of FDCs). The most commonly prescribed FDC was a vitamin formulation with a brand name Becosule. This alone constituted 45.5% of all the prescribed FDCs. The second most common FDC was a antibiotic formulation of Amoxicillin 500 mg and Clavulanic acid 125 mg, it constituted 18.6% of the total prescribed FDCs. The third most common FDC was from the gastrointestinal drugs, formulation with brand name of Digene. It is a antacid preparation, available in a “Gel’’ formulation and has 4 constituents. It constituted 9.4% of the prescribed FDCs.

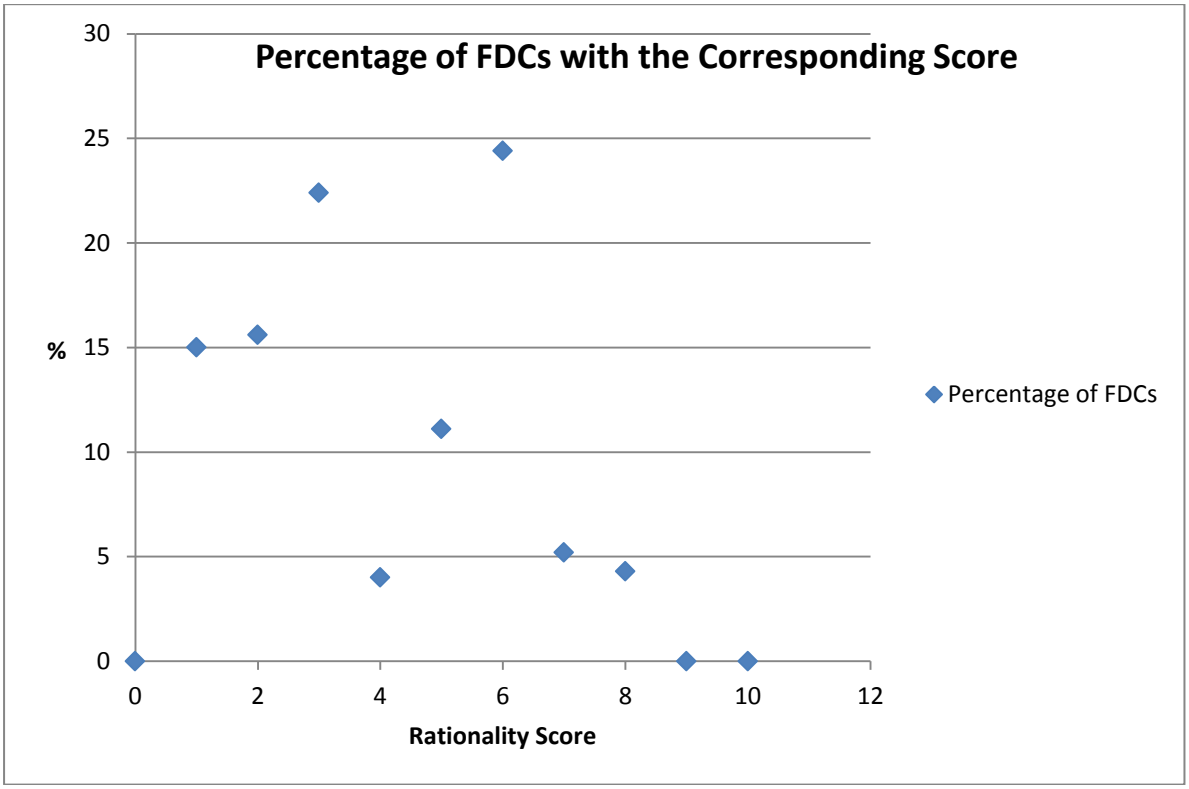
3.2.3 Scientific evidence for the prescribed FDCs

Scientific evidence was available only for 9.1% of the prescribed FDCs.

3.2.4 Rationality analysis of prescribed FDCs

The rationality analysis revealed that majority of the FDCs had rationality scores in low to intermediate range. A score of 6 was assigned to 26.4% of FDCs, 22.4% FDCs had a score of 3, 15.6% FDCs had a score of 2 and 15% FDCs had a score of 1. No FDC was assigned a score of 0. The rationality of FDCs has been represented in Figure-1

Figure-1: Rationality scoring of FDCs



3.2.5 Cost analysis of prescribed FDCs

The cost analysis revealed that 82% of the prescribed FDC was cheaper as compared to the sum cost of their individual constituents.

4. Discussion

4.1 Quantitative analysis

The quantitative analysis revealed that there the total number of individual drugs was 1,051, which were present in 3,596 FDCs. It shows that on a average the number of FDCs in each system as three times the number of individual drugs. The system of Nutrition had only 3.9% of drugs whereas it had 40% of all the FDCs. There were a total of 37,482 total drug formulations. Only an estimate is available on the number of drug formulations based on different studies (Kataria et al, 2012). Previous estimates have quoted the number of drug formulations in India as being in thousands. We found no other study which had analyzed the drug formulations in Indian market in quantitative terms. So there was no other study with which we could compare the results of our quantitative analysis. However, what is obvious is that the total number of

drug formulations and FDCs available is very large in India. The total number of drugs in the WHO and National Essential Medicine List is much lesser in comparison.
In the general analysis of the FDCs; in the cardiovascular system the number of individual drugs and the number of FDCs were comparable, while in most other systems the number of FDCs was roughly two to ten times the number of individual drugs. There was a FDC containing enalapril and ramipril. In central nervous system; in the subclass of drugs used in peripheral neuropathy, there were only 5 individual drugs while the number of FDCs was 253. In the alimentary system, in the subclass of digestive enzyme preparations there were 83 FDCs (33%) out of a total 253 FDCs in this system. The FDCs of digestive enzyme preparations are banned by the DCGI. In the respiratory system; pseudoephedrine was one of the most common constituent of the FDCs in this system.

4.2 Prescription analysis
The prescription audit done to assess extent of use of FDCs in prescriptions in a Government, tertiary care, teaching hospital showed that FDCs were 7.45% of all the prescribed drugs. This is much lesser than has been observed in other studies done in both public and private health sector. Only 1.2% FDCs were prescribed according to their generic name; 19.7% percent FDCs were included in the WHO EML 2011 and 18.9% percent belonged to the National EML 2011. These findings are similar to the findings in other studies (Rathnakhar, 2011, Pillay et al, 2013).
A prescription audit in Coimbatore, India which assessed the rationality of cardiovascular drugs in 606 prescriptions; it was seen that 21% of drugs prescribed were FDCs (Devi et al, 2012). Only 11.1% FDCs were prescribed according to the Indian EML 2011 and WHO EML 2011. This is a finding similar to our study. In a prescription audit of 994 prescriptions, 43.5% drugs were FDCs. Similar to the finding in our study, 95% FDCs in this study were prescribed according to the brand names. In this prescription audit also, the most commonly prescribed FDC was by the brand name of Becosule (Rayasam et al, 2013). A study in Pune, India also reported that 55% of prescriptions contained FDCs and only 13% FDCs were in accordance with the WHO EML 2011(Pillay et al, 2013). Vitamins and minerals were the most common FDCs prescribed in this audit. Fifty three percent (53%) of the FDCs belonged to vitamins and minerals and 23% of FDCs were from the antimicrobial agents followed by gastrointestinal system (10.3%), and analgesics. This pattern of use of drugs is very similar to that observed in other drug utilisation studies (Rayasam et al, 2013, Pillay et al, 2013, Devi et al, 2012).

The availability of scientific evidence is very low. This is a matter of concern for the Indian Drug Regulatory authorities as such a large number of FDCs are available in the Indian market without scientific evidence. These findings are in agreement to previous studies which have assessed the availability of scientific evidence (Devi et al, 2012, Roy et al, 2012).
The rationality scores of the prescribed FDCs were also in the low to intermediate range. This aspect also raises questions about the scientific rationale of the FDCs available in India.
However, a positive aspect of the FDCs is their cost. That majority of the FDCs offer cost advantage to the patients is a consolation.

5. Conclusions

There are thousands of drug formulations including FDCs that are available in India. The scientific evidence for majority of FDCs in the prescription analysis is lacking. The rationality of the prescribed FDCs ranged was generally on the lower side. The FDCs offer economic advantage as the cost of FDCs is lower than the cost of the individual constituents of these FDCs. There is an urgent need to remove irrational FDCs by strict regulatory interventions. This is important for patient safety and care.

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