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A Study on Evaluation of Rationality of Fixed Dose Combinations

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ABSTRACT

In India Fixed Dose Combinations(FDCs) have drawn the attention of health service providers and the service recipients. Therefore, the development of fixed dose combinations (FDCs) is becoming increasingly important from a public health perspective. The objective was to study the prescribing pattern and to assess the rationality of fixed dose combinations using seven point criteria. During the study period a total of 100 patients were enrolled based on inclusion and exclusion criteria. The study population includes an overall 56% male with an average age of 46.15 ± 19.33 years. A total of 538 drugs were prescribed to the patient with a mean of 5.38±5.77.The major therapeutic category of drugs prescribed were antibiotics (30.03%), antihypertensives (12.63%) and others (13.01%).The study population had 130 FDCs in which again antibiotics topped the list, followed by Anti-diabetics. Among these 92 contributed to antibiotic FDCs belonging to 15 different groups. The average interaction per prescription was 1.96±3.72.The FDCs involved in drug interaction were aspirin+clopidogrel, amoxicillin+ clavulanic acid. The average length of stay for study population was found to be 5.73±2.19 days. The rationality was assessed using 7 point criteria with a maximum scoring of 14. The most commonly prescribed combination were Piperacillin + Tazobactam (25.38%) and Amoxicillin+ Clavulanic acid(16.92%).Among the combinations, 26.6% scored 13 while 66.66% scored 9-12 and 6.66%scored 7. The results indicated that majority of FDCs especially antibiotics were rational.

Keywords: Fixed Dose Combinations (FDCs), Rational Drug Use (RDU), Essential Drug List (EDL), National List Of Essential Medicines (NLEM), World Health Organization (WHO)

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INTRODUCTION

Rational drug use (RDU) is conventionally defined as "patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time and at the lowest cost to them and their community"[1] . The promotion of rational drug use involves a wide range of activities such as the adoption of the essential drug concept, training of health professionals in RDU and development of evidence-based clinical guidelines. Unbiased and independent drug information, continuing education of health professionals, consumer education and regulatory strategies are also vital to promote RDU. The importance of RDU relates to its impact on the health of individuals, communities, health care cost and the environment. Irrational drug use leads to ineffective and unsafe drug treatment, worsening or prolonging of illness, adverse drug reaction and increases the cost to the patient, government or insurance system. Widespread antibiotic resistance is partly due to the irrational use of antibiotics. Some of the common irrational drug use problems are polypharmacy, over use of injections, self medication, misuse of antibiotics, use of irrational fixed dose combinations, etc.

Steps in rational prescribing:

Rationality is based on specific steps. These are:

- Specific diagnosis made
- Whether drug therapy is indicated along with non-pharmacological interventions like diet, exercise, counseling and other life style modifications.
- Risk-benefit ratio
- Therapeutic objective and efficacy of drug.
- If not cured by a drug, determine the cause of the disease.
    - **E.g.** antibiotic therapy depends on microorganism involved and its sensitivity.
- Determine the drug of choice based on drug related factors and patient related factors which include presence of concomitant disease, hepatic and renal dysfunction, pregnancy and lactation, age, genetic factors and drug interactions.

It has been found that over 80,000 formulations are marketed in India which includes several FDCs and other single drug formulations, while the 17th list of essential medicine has mentioned only about 25 FDCs[2].

To develop a comprehensive criteria which will be useful and unbiased for the evaluation of FDCs, the guidelines of WHO "Draft guidelines for registration of fixed dose combination medicinal product" accessed on 13th March 2005 and the "Note for guidance on fixed-dose

combination medicinal products" by the Committee for Proprietary Medicinal Products (CPMP), Europe and several research papers were carefully studied[3]. These are well-known guidelines, which serve as benchmark towards a rational FDCs. Publication of Essential Medical List by government of India in 2003 was another major step towards implementation of rational use of medicines[4.]

According to WHO, the core list of Essential Medicines presents a list of minimum medicine needs for a basic health care system, listing the most efficacious, safe and cost-effective medicines for priority conditions. The priority conditions are selected on the basis of current and estimated future public health relevance, and potential for safe and cost-effective treatment. Although there are thousands of fixed dose combinations that are available in world market but WHO has approved only 25 FDCs and included the same in the 17th edition of WHO essential drug list 2011[5]and the same is given in Table 1 and Table 2 list out some of the common synergistic FDCs of antimicrobials.

Table 1. Fixed dose combinations mentioned in 17th edition of WHO essential drug list

S.No	Drugs	Form	Strength
1	Amoxicillin + Clavulanic acid	Tablet	500 mg+125 mg
2	Lidocaine+Epinephrine	Injection	1 or 2%+1:200,000
3	Imipenem + Cilastatin	Injection	250 mg+250 mg
4	Sulfamethoxazole	Tablet	100 mg+20 mg
	+Trimethoprim	Oral	400 mg+80 mg
		Liquid	200mg+40mg/15ml
5	Sulfamethoxazole	Injection	80 mg+16 mg/ml
	+Trimethoprim		(in 5 ml ampoule)
6	Isoniazid + Ethambutol	Tablet	150 mg+400 mg
7	Rifampicin + Isoniazid	Tablet	150 mg+75 mg
			300 mg+150 mg
8	Rifampicin+Isoniazid +Ethambutol	Tablet	150mg+75mg+275mg
9	Isoniazid+Pyrazinamide+ Rifampicin	Tablet	75 mg + 400 mg + 150 mg.
			150 mg + 500 mg + 150 mg
10	Efavirenz+Emtricitabine+ Tenofovir	Tablet	600mg+200mg+300mg
11	Emtricitabine + Tenofovir	Tablet	200mg+300mg
12	Stavudine+Lamivudine+ Nevirapine	Tablet	30mg+150mg+200mg
13	Zidovudine+Lamivudine	Tablet	300mg+150mg
14	Zidovudine+Lamivudine+ Nevirapine	Tablet	300mg+150mg+200mg
15	Artemether + Lumefantrine	Tablet	20mg + 120mg
16	Levodopa + Carbidopa	Tablet	100 mg + 10 mg, 250 mg+25 mg
17	Ferrous salt + Folic acid	Tablet	60 mg+400 µg
18	Sulfadoxine + Pyrimethamine	Tablet	500 mg+25 mg
19	Artesunate + Amodiaquine	Tablet:	25 mg + 67.5 mg; 50 mg + 135 mg;
			100 mg + 270 mg.
20	Levodopa + Carbidopa	Tablet	100 mg + 10 mg; 250 mg + 25 mg.
21	Ferrous salt + Folic acid	Tablet	60 mg iron + 400 micrograms folic

			acid
22	Oral Rehydration	Powder	Salts Sodium chloride 3.5 g/L + Trisodium citrate dihydrate 2.9 g/L + Potassium chloride 1.5 g/L + Glucose 20.0 g/L
23	Ethinylestradiol +levonorgestrel.	Tablet:	30 micrograms + 150 micrograms.
24	Ethinylestradiol+ norethisterone**.**	Tablet	35 micrograms + 1 mg
25	Estradiolcypionate+medroxyprogesterone acetate	Injection	5 mg + 25 mg.

Table. 2. Examples of some of synergistic FDC antimicrobials:-

Drugs	**Mechanism of action**
Sulphamethoxazole+Trimethoprim	Trimethoprim is inhibitory for a wide range of bacteria, a combination with a sulphonamide marked synergy is being reported
Amoxicillin +Clavulanic acid	Clavulanic acid enhances the antibacterial spectrum of amoxicillin most beta –lactamse producing isolates suspectible to the drug.In clinical trials,amoxicillin /clavulanic acid is clinically and bacterilogically superior to amoxicillin alone and atleast as effective as numerous other comparative agents
Imipenem + Cilastatin	Coadministration of imipenem with a renal dehydropeptidase inhibitor, Cilastatin prevents its renal metabolism in clinical use. Thus increase the efficacy and extend spectrum covers septicaemia, neutropenic fever , and intra-abdominal , lower respiratory tract ,genitourinary ,gynaecological, skin and soft tissues and bone and joint infections.
Piperacillin+Tazobactum	Combining tazobactum a beta-lactamase inhibitor with the piperacillin successfully restores the activity of piperacillin against beta-lactamase producing bacteria.

Guidelines for selection of FDCs in infectious diseases

WHO highlights combination therapy only when monotherapy fails or is not tolerated. The combination is rational when drugs have different mechanism of action and patterns of effects. The discovery of compounds with antimicrobial activity is perhaps the best defense for fighting infectious diseases. Antibiotics are one of the most commonly used group of drugs .The selection of FDCs should be based on certain aspects such as :

- The drugs in the combination should act by different mechanisms.
- The pharmacokinetics must not be widely different.
- The combination should not have supra-additive toxicity of the ingredients.

The conceptual basis for combination treatment of infectious disease is somewhat different from conditions such as hypertension, in which the drug target is human tissue. In infectious disease, the drug target is an evolutionarily unrelated microbe, and drug side effects are of less concern

than the loss of efficacy caused by the emergence of drug-resistant strains[6].

Combinations to be avoided[7]

The banned lists of FDCs are analgesics with paracetamol and anti anxiety-drugs with alprazolam or paracetamol with analgin combinations. The rejected lists of FDCs include antibiotic combinations like ofloxacin and cefixime or anti-fungal/allergy drug combinations like fluconazole and cetrizine (tablet). For banned and rejected drugs the process involved is, taking them out of the market and withdrawal manufacturing licenses.

Various background information and increasing number of FDCs in prescription prompted us to conduct a detailed prospective study about the prescribing pattern and evaluation of rationality of fixed dose combinations which will be helpful the health care professionals to decrease the irrational use of FDCs.

MATERIALS AND METHODS

Study site : General Medicine department, pulmonology, gynecology and pediatrics department of a 640 bedded multi specialty private corporate hospital.

Study design: Prospective-observational study.

Study period: Period of 6 months (March 2012- August2012).

Inclusion criteria:

All willing in patients who were getting admitted to the study site during the study period with at least one FDCs prescribed in their prescription.

Exclusion criteria:

The patients who were unwilling to participate in the study and terminally ill and prescription not containing at least one FDCs were not included in the study.

Data collection:

All the cases with FDCs admitted in the study department were recorded. Patient data was collected in the specially designed data entry format which includes patient's demographic details, past medical histories including medications, clinical lab data and present therapy. Before data collection patients were informed about the study objectives and the written consent from patients or their care givers was obtained.

Data analysis:

The obtained cases were thoroughly analyzed to evaluate the rationality of fixed dose combinations and the utilization patterns of drugs prescribed including the dose, route of administration, duration of therapy, ADR and drug interactions. The data analyzed also included

the results on patient's demographics (Age, Sex etc). Cost of the FDCs was compared with total cost of individual components. The dose of the individual Active Pharmaceutical Ingredients(APIs) were verified from standard textbooks[8] and reference in pharmacology and therapeutics .The cost data of the individual components as well as the FDCs was obtained from CIMS (Current Index Of Medical Specialties') and other software's of reliable drug reference.

Study protocol:

A comprehensive seven-point criterion developed by panda et al[9] was used for the evaluation of rationality f the FDCs. These criteria include all the dimensions of defining a rational FDC and appropriate weighting (score) has been attached to each criterion. The total score thus obtained by a FDC will reflect its standing on the scale. The first point in the seven-point criteria for evaluating the rationality of FDCs is that each active pharmaceutical ingredient(API) of the combination should preferably be in the ' essential medicines list'(EML)[5] of WHO or in the National List of Essential Medicines (NLEM)[4] of India. Secondly, the dose of each API should meet the requirements for a defined population group. The dose and proportion of each API present in FDC should be appropriate for the intended use. Thirdly, the combination should have the advantage of established evidence of efficacy and safety. Further, the overall cost of the combination should preferably be less than the cost of the individual components. The FDC should facilitate either the reduction of the dose of individual drugs or their adverse effects. The PK parameters of each API should not be affected. There should be no unfavourable pharmacokinetic interaction between the APIs. In case of the pharmacokinetic parameters being different, the clinical benefit should be taken into consideration. Lastly, the individual drugs should have different mechanism of action. The maximum scoring of the seven point criteria was 14 with each criterion carrying a score of 2.

RESULTS AND DISCUSSION

The total number of patients included in the study was 100. The study population includes 56% of males and 44 % of females and the age of the study population ranged from 12-87 years with a mean age of 46.15 ± 19.33 years. The details are given in Table 3

Table 3, Age Distribution Of Study Population

	Age (Years)	Percentage(n=100)
1	12-18	10
2	19-35	25
3	36-50	26
4	51-64	24
5	65-74	8
6	75-90	7

The social history, education status, employment status, dietary habits were found to be at higher risk factors for developing diseases. The past medical history and diagnostic details revealed that around 50% of the study population was suffering from T2DM and 40% or more with systemic hypertension and the past medication history revealed that the major category of drugs prescribed were belonged to anti-diabetic drugs 46.47%, followed by 29% antihypertensive drugs and listed in Table 4.

Table: 4. Past medication history

S.no	Past medication history	Percentage patients
1	Antidiabetic drugs	33
2	Antihypertensive	25
3	Lipid lowering drugs	7
4	Chronic kidney disease	4
5	Others	2

Laboratory tests carried out on the study population performed site had shown that 68% had undergone blood sugar test ,which was found to be related with the 50% population with a diagnosis T2DM and 23% had sensitivity test done and the major organisms identified were *E.coli* , *Staphylococcus pneumonia and Enterobacter* and the drug Amikacin was found to be more sensitive to *E.coli* and *Klebsiella.* The study populations were prescribed with 538 drugs which includes 30.03% antibiotics and 12.63% antihypertensives followed by other category drugs and are shown in Figure1.

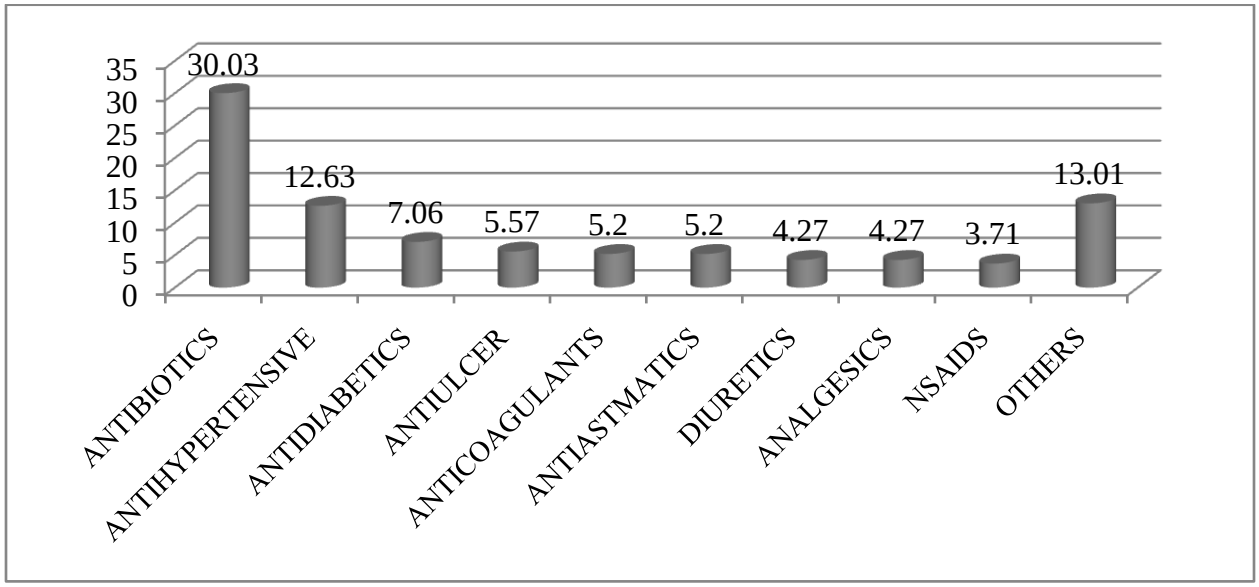

Figure 1 Drugs Prescribed (n=538)

Depending on the categories of FDCs prescribed, total number of FDCs was 130 with an average of 1.3 ± 2.60. The major category of FDCs was antibiotics followed by cardiovascular drugs. The prescription analysis for drug interactions revealed that 70% of patients had at least 1

interaction, and 30% had no drug interaction at all. The average interaction per prescription was found to be 1.96±2.04. The most commonly found drug interactions were Norfloxacin + Insulin, Ofloxacin +Prednisolone and Levofloxacin +Theophylline. The average length of stay for the study population was found to be 5.73± 2.19 days. The results of the assessment of rationality showed that for approximately 80% of the FDC's, the individual components were present in any one or both the EMLs. For 20% of the FDCs atleast 1 component was absent in both the EMLs. Clinical evidence on safety and efficacy was established for 100 % of the FDCs prescribed and the same was documented. Out of 15 antibiotic FDCs prescribed, 7 FDCs (46.66%) were found to be more cost effective than their individual components. The scoring criteria used in the study could award a maximum of 14 points to an FDC which indicate a better rationality and as the score reduces the rationality too reduces. It was found that 4 FDCs scored 13 points , which reflect a total match with the criteria for evaluating FDCs, 1 FDC scored 7, 4 FDCs scored between 8 & 10 , 6 FDCs scored between 11 & 12 .The results of scoring by each criterion in the present study are shown in Table 5 and presence of active pharmaceutical ingredients in EML of WHO or NLEM of INDIA or both are given in Figure 2. In a similar study Neetesh K Jain *et al*[10] in 2009 developed a 7 point criteria for evaluating the rationality of FDCs. These criteria includes all the dimensions of defining a rational FDCs and appropriate weighing score had also been attached to each criterion. The total score thus obtained by a FDC will reflect its standing on the scale; it is to be noted that the score should not be viewed individually. Manjula Devi *et al* (2011)[11] also carried out a similar study for evaluation of rationality of fixed dose combinations containing cardiovascular drugs and reported that the selected FDC drugs were rational by using the 7 point criteria scale.

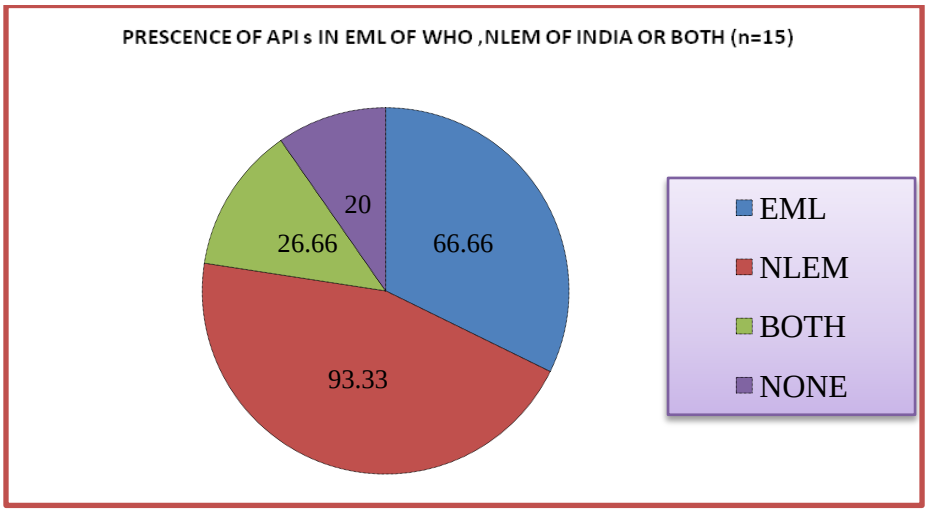

Figure 2. Presence of APIs in WHO or NLEM of India OR both (n =15)

Table 5. Scoring by criteria

Sl. No.	FDC		1* EML		NLEM		2*	3*	4*	5*	6*	7*	Total Score
1	Amoxicillin Clavulanic acid	+	√	√	√	x	Yes	Yes	No	Yes	No	Yes	11
2	Pipercillin Tazobactam	+	×	×	×	×	Yes	Yes	Yes	No	No	Yes	10
3	Cefperazone+ Sulbactam		×	×	×	×	Yes	Yes	Yes	Yes	No	Yes	12
4	Cefipime Tazobactam	+	×	×	×	×	Yes	Yes	No	Yes	No	Yes	10
5	Ceftriaxone Sulbactam	+	√	×	√	×	Yes	Yes	Yes	No	No	Yes	11
6	Ceftriaxone Tazobactam	+	√	×	√	×	Yes	Yes	Yes	No	No	Yes	11
7	Ofloxacin Ornidazole	+	×	×	√	×	Yes	Yes	No	No	No	Yes	9
8	Ofloxacin Tinidazole	+	×	×	√	√	Yes	Yes	No	No	No	Yes	9
9	Amoxicillin+ Tazobactum		√	×	√	×	Yes	Yes	No	Yes	No	Yes	11
10	Cefotaxime+ Tazobactam		√	×	√	×	Yes	Yes	Yes	Yes	No	Yes	13
11	Cefotaxime+ Ornidazole		√	×	√	×	Yes	Yes	No	Yes	No	Yes	13
12	Cefixime+ Ornidazole		√	×	×	×	Yes	Yes	Yes	Yes	No	Yes	13
13	Imipenem+ Cilastatin		√	×	√	×	Yes	Yes	No	No	Yes	Yes	7
14	Trimethoprim+ Sulphamethoxazole		√	×	√	×	Yes	Yes	Yes	Yes	No	Yes	13
15	Norfloxacin+ Tinidazole		×	×	×	√	Yes	Yes	No	Yes	No	Yes	11

Evidence on safety and efficacy is utmost importance when the two drugs are combined together as a single formulation. The results of the study clearly demonstrated that in most of the FDCs, the clinical evidence on safety and efficacy was established.

CONCLUSION

On the basis of the comprehensive criteria, the study has made a systematic point-by-point evaluation of fixed dose combinations especially on antibiotics. Evidence of safety and efficacy is utmost importance when the two drugs are combined together as a single formulation. The attempt made to use a system of scoring in relation to each FDC, satisfying the criteria. The results of this study clearly demonstrate that majority of FDCs were found to comply with the criteria developed for the assessment of rationality and the combinations were present either in

EML of WHO or NLEM of India or both. The dose and proportion of each API present in the FDCs were appropriate for the intended use.

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