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ASSESSMENT OF RATIONAL USE OF FIXED DOSE COMBINATION IN COMMUNITY PHARMACIES OF RESOURCE LIMITED SETTINGS OF ANDHRA PRADESH

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ABSTRACT: Fixed dose combination (FDC's) is the term, which generically used to mean a particular combination of active ingredient irrespective of the formulation or brand. Now a day's irrational FDCs are more rapidly being marketed, which results in serious ADRs and reduction of patient quality of life. The study aims at assessing the rational usage of fixed dose combinations in community pharmacies by collection and evaluation of FDCs by using seven-point assessment scale, and development of FDC education tool for practicing rational use. The six months prospective interventional study, carried at community pharmacies where different FDCs were collected. All data regarding demographics details were collected in a suitably planned data collection form, base line survey, first visit and second visit was conducted using ten point questionnaires. Based on responses awareness was provided for appropriate use through FDCs educational tool. The data obtained were entered in Microsoft excel and graph pad instat software, the score of base line was compared with second follow up using Wilcoxon matched pair test. Out of 404 FDCs collected 144 meets the criteria of rationality. Significant improvement ($p < 0.0001$) in the knowledge, attitude, and practice in the study group showed that pharmacist education at community pharmacies. Similarly a significant improvement ($p < 0.05$) was observed, also assessed the rationality among community pharmacies. In conclusion development of fixed-dose combinations is becoming increasingly important from public health perspective. It is prerequisite in order to educate every working pharmacist about the rationality of FDCs and safeguard patient health outcomes.

INTRODUCTION: The rational drugs use stands for provision of appropriate medicines in required doses at an adequate period of time, and at the lowest cost to patients as per their individual clinical needs. [1, 2] In order to promote or initiate rational use of medicines or rational drug therapy, The World Health Organization (WHO) implemented the concept of an essential drugs list for the first time in 1977 and its regular updates of the model essential drug list for every two years. [3]

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Similarly after two decades in India, the Delhi society for promotion of rational use of drugs (DSPRUD) formed to promote the rational use of drugs. In April 2013 World Health Organization had released 18th model essential drug list which contains 353 formulations and 26 fixed dose combinations (FDC's) and National List of Essential Medicines (NLEM) of India has 348 essential drugs, including 16 fixed dose combinations [1, 2, 4].

In general Fixed Dose (drug) Combination is defined as "a combination of two or more active pharmaceutical ingredients or compounds formulated as a single medicine irrespective of its dosage form designed. [5] According to food and drug administration, USA defines a fixed dose

combination product as a product composed of any combination of a drug and device or a biological product and a device or a drug and a biological product or a drug, device and a biological product use for treatment. [2, 6, 7]

In FDCs, drugs from different pharmacological groups having complementary mechanism of action should be combined, there are some particular factors which contribute to the rationality of FDCs, such as pharmacokinetics of drugs, mechanism of drugs and toxicological study of drugs among specific combinations. The main concept of rational drug therapy focuses on safety, efficacy and good quality of drug to be used in treatment. Based on the number of constituent drugs present in a product, FDC's are of few types, one dose combination drugs, two dose combination drugs, three dose combinations drugs and four dose combination drugs.

FDCs are an innovative products, their main merit is being increase in patient's compliance, reduction in pill burden, as well as decreased complications and the economic impact. The safety of the marketed FDCs changes when they are combined in a single formulation.

These are certain fixed dose combinations of drugs (FDC's) in which are very essential prepared by 18th WHO model list of essential drugs. [8] The national List of Essential Medicines (NLEM) of India has 348 essential drugs, including 16 fixed dose combinations (National List of essential medicines, 2011). [3, 9, 10] As two side of coin, FDC's also have both merits and demerits, hence prescription of fixed dose combination should be based on evidence based medicines and clinical ground by evaluating risk / benefit ratio of particular FDC. [5]

Now a day there is rapid growing concern about irrational usage of FDCs in developing countries like India, which causes increase in the occurrence of adverse drug reactions, allergic reactions and hospitalization, which results in reduced quality of life and increased economic impact. The widely moving drugs in India are highly profitable FDCs which include analgesics, tonics, antibiotics, cough and cold preparations. Combining two or more drugs in a single dose results in change in safety, bioavailability profile; thus FDCs are treated as innovative drugs. [11]

The rational concept of FDCs has not yet penetrated in the minds of many pharmacists (or health care professionals); hence awareness about rational usage of FDCs is most important to reduce the occurrence of possible adverse events and to reduce the economic burden.

MATERIALS AND METHODS:

Study Design:
Prospective interventional study

Study Duration:
Six months (May – October 2015)

Study Site:
Community pharmacies located at Anantapuramu district, Andhra Pradesh., India.

Study population: 27 Community Pharmacies

Inclusion Criteria:

- All the community pharmacist who are working in and round Anantapur.
- Pharmacist who are willing to participate in the study.

Exclusion Criteria:

- Other health care professionals (physicians, nurses, lab technicians) are excluded from this study.
- Pharmacists who are not willing to participate in our study.
- Pharmacists who are working in the hospital and outside the Anantapur district are excluded from our study. .

Study Procedure:
This present entire study was divided in to two main phases.

Phase I: Evaluation of rationality of FDCs availability in community pharmacy settings

- A total of 27 community pharmacies have been selected located at Anantapuramu district, Andhra Pradesh., India.

- After that total of 404 fixed dose combinations have been collected and subjected to evaluation of rationality of FDCs using standard data collection form.

- Based on the above criteria rationality and irrationality of FDCs present in the community pharmacies were evaluated and recorded, with help of Fixed Dose Combination Rationality Scale, panda et al 2006.

Phase II: Evaluation of impact of education programme on knowledge levels regarding usage of FDCs.

- A total of 200 community pharmacists were recruited in study, working at both governmental integrated and nongovernmental integrated community pharmacy settings areas on Anantapur dist.

- After that, their demographic details have been collected on their willingness. Recruited subjects from different community pharmacy settings were conducted survey about baseline knowledge about rationality of FDCs.

- And after a time period of two months awareness survey about rational use of fixed dose combinations and its usage in their pharmacies by using educational tool, consisting of ten questionnaires with three options for responds of relative questions.

- Over all, This FDCs awareness survey was conducted in three visits at three different time periods. Questionnaire was prepared by the requirement basis.

- For the above questionnaires scoring is given from 1point to ten points, each point for each question. Based on the score obtained awareness has been provided for rational consideration of FDCs during their practice in their community setting areas.

Statistical Analysis:

- All the base line characteristics are represented by descriptive statistics.

- Impact of pharmacist intervention on rationality of FDCs was assessed by Wilcox on Matched Paired-t test by using graph-pad In Stat (3.10 versions).

- *p* – Value < 0.05 was considered as statistically significant results.

RESULTS: In our study, a total of 27 community pharmacies were covered and 404 fixed dose combinations were collected and assessed.

All the collected FDCs are subjected to evaluation by using seven point assessment scale which include seven different criteria's. Total results are recorded and reported in **Table 1** (Seven point assessment scale criteria for FDC's)

TABLE 1: SEVEN POINT ASSESSMENT SCALE CRITERIA FOR FDC'S

S.no	Questionnaires	No. of FDCs (met this criteria) n=404	Percentage (%)
1	Drugs in FDC should have different mechanism of action?	376	93.6
2	FDC should not widely differ in their pharmacokinetics?	311	76.2
3	There should not have any interaction between ingredients and does not have supra additive toxicity?	286	70.4
4	FDCs should have favorable risk-benefit ratio?	260	64.3
5	Safety, ingredients should be stable in combination or should not react chemically?	351	86.8
6	Active pharmaceutical ingredient should be enlisted in WHO (or) NLEM	376	93.9
7	Dose of FDCs should fulfill their requirements?	283	70.1

From the above data it is clear that only 70.4% of FDCs are known to have interactions between constituent in a single FDC product. 93.9% drug are in WHO list. The rational and irrational proportions of FDC's are obtained, recorded and reported in **Table 2** (Rationality/Irrationality Proportions).

TABLE 2: RATIONALITY/IRRATIONALITY PROPORTIONS

Total Number of FDCs	Rational FDCs		Irrational FDCs	
	Number	Percentage	Number	Percentage
404	144	35.%	260	64.3%

The current study comprises of two hundred pharmacists working at community pharmacy settings, the demographic particulars id reported in **Table 3** (Demographic details of Pharmacists).

TABLE 3: DEMOGRAPHIC DETAILS OF PHARMACISTS

S.no	Characteristics		Study population (n = 200)	Percentage (%)
1	Gender	Male	125	62.5
		Female	75	37.5
2	Age (Years)	18-22	65	32.5
		23-26	80	40
		27 and above	55	27.5
3	Education level	Graduates	165	82.5
		Diploma	35	17.5

Survey was conducted about knowledge levels in all pharmacists' in community settings by using a ten point questionnaire assessing scale. This survey was conducted for the same pharmacist's in two visits, before and after implementation of FDCs awareness tool as intervention, after two months of survey to assess the level of FDCs knowledge in pharmacists the results of which are reported in **Table 4** (Pharmacist's knowledge About Fixed Dose Combination-Base Line responses), **Table 5** (Pharmacist's knowledge About Fixed Dose Combination-First visit responses) and **Table 6** (Pharmacist's knowledge About Fixed Dose Combination-Second visit responses)

TABLE 4: PHARMACIST'S KNOWLEDGE ABOUT FIXED DOSE COMBINATION-BASE LINE RESPONSES

S. no	Knowledge criteria questions	Yes	No	Don't know
1	Have you observed Fixed dose combinations (FDCs) in prescription?	115(57.5%)	50(25%)	35(17.5%)
2	Knowledge about Standard protocol for FDCs prescribing?	35(17.5%)	110(55%)	55(27.5%)
3	Knowledge about the single expiry date of FDCs?	95(47.5%)	60(30%)	45(22.5%)
4	Do you know about FDCs possibility of side effects than individual drugs?	40(20%)	50(25%)	110(55%)
5	Patient compliance can be improved by using simpler dosage schedule of FDCs?	85(42.5%)	55(27.5%)	60(30%)
6	Do you have Knowledge about any FDCs that has been banned?	35(17.5%)	55(27.5%)	110(55%)
7	DO you explain patient about FDC doses?	43(21.5%)	86(43%)	71(35.5%)
8	Do you provide any directions regarding the use of FDC?	35(17.5%)	110(55%)	55(27.5%)
9	Are you aware whether the FDC is rational or not?	68(34%)	76(38%)	56(28%)
10	Have you come across any FDC in which drug interacts?	20(10%)	80(40%)	120(60%)

TABLE 5: PHARMACIST'S KNOWLEDGE ABOUT FIXED DOSE COMBINATION-FIRST VISIT RESPONSES

S. no	Knowledge Criteria questions	Yes	No	Don't know
1	Have you observed Fixed dose combinations (FDCs) in prescription?	40(20%)	140(70%)	20(10%)
2	Knowledge about Standard protocol for FDCs prescribing?	118(59%)	60(30%)	22(11%)
3	Knowledge about the single expiry date of FDCs?	126(63%)	54(27%)	20(10%)
4	Do you know about FDCs possibility of side effects than individual drugs?	107(53.5%)	50(25%)	43(21.5%)
5	Patient compliance can be improved by using simpler dosage schedule of FDCs?	137(68.5%)	41(20.5%)	22(11%)
6	Do you have Knowledge about any FDCs that has been banned?	98(49.01%)	57(28.5%)	45(22.5%)
7	DO you explain patient about FDC doses?	121(60.5%)	79(39.5%)	0(0.0%)

8	Do you provide any directions regarding the use of FDC?	85(42.5%)	60(30%)	55(27.5%)
9	Are you aware whether the FDC is rational or not?	147(73.5%)	37(18.5%)	16(8.0%)
10	Have you come across any FDC in which drug interacts?	75(37.5%)	82(41%)	43(21.5%)

TABLE 6: PHARMACIST'S KNOWLEDGE ABOUT FIXED DOSE COMBINATION-SECOND VISIT RESPONSES

S. no	Knowledge Criteria questions	Yes	No	Don't know
1	Have you observed Fixed dose combinations (FDCs) in prescription?	120(60%)	45(22.5%)	35(17.5%)
2	Knowledge about Standard protocol for FDCs prescribing?	127(63.5%)	40(20%)	33(16.5%)
3	Knowledge about the single expiry date of FDCs?	115(57.5%)	55(27.5%)	30(15%)
4	Do you know about FDCs possibility of side effects than individual drugs?	140(70%)	35(17.5%)	25(12.5%)
5	Patient compliance can be improved by using simpler dosage schedule of FDCs?	130(65%)	45(22.5%)	25(12.5%)
6	Do you have Knowledge about any FDCs that has been banned?	110(55%)	55(27.5%)	35(17.5%)
7	DO you explain patient about FDC doses?	121(60.5%)	40(20%)	39(19.5%)
8	Do you provide any directions regarding the use of FDC?	156(78%)	30(15%)	14(7%)
9	Are you aware whether the FDC is rational or not?	147(73.5%)	37(18.5%)	16(8.0%)
10	Have you come across any FDC in which drug interacts?	75(37.5%)	82(41%)	43(21.5%)

Comparative analysis between these responses had been done, using paired two tailed analytical method and were found statistically significant, their results are reported in **Table 7** (Responses of comparative analysis)

TABLE 7: RESPONSES OF COMPARATIVE ANALYSIS

Comparison of responses between baseline and first visit		Comparison of responses between first and second visit		Comparison of responses between baseline and second visit	
57.10±10.01	105.40±10.12	94.50±13.54	124.10±7.12	124.10±7.12	67.0±11.37

DISCUSSION: The current study evaluated the rationality of fixed dose combinations (FDC's) in community pharmacies of a healthcare resource limited setting of Andhra Pradesh., India, which showed a more vibrant irrational FDC's consumption than rational FDC's. A total of 45% of FDCs are rational, which fulfilled all the World Health Organization (WHO) criteria for FDCs. The most common examples were sulphamethoxazole plus trimethoprim, amoxicillin plus clavulanic acid and oral rehydration solutions. Out of 404 FDC's collected 144 had been justified for being a rational. In this study, there were only 35% FDC's which are rational, among them 15% were outside the list of FDC's in the WHO Essential Medicine List and National List of Essential Medicines (NLEM).

Consuming more than one drug leads unwanted drug interactions (ADRs), which leads to life threatening, dangerous, increasing financial burden as well as decreases quality of life. Usage of FDC's is important or justified in serious conditions like AIDS, tuberculosis and clinically relevant serious situations. But usage has been very common from cold to serious respiratory tract infections, which resulted in very popular, rapid marketing of irrational FDC's. The manufacturer's rip the benefit of vast sales of FDC's which leads to unethically or irrational usage. The Indian government had banned several FDC's, till date 24 FDC's are banned in India with in a period of five years. Hence, randomized control trails are required for critical evaluation of FDC's before marketing.

Our study also obtained the responses towards knowledge on FDC's use among pharmacists in community settings by comparison of their responses between baseline, first and second visit, which showed a better positive reciprocation on FDC's use through an intervention of education programme during the study.

CONCLUSION: In conclusion, development of fixed-dose combinations is becoming increasingly important from public health perspective. It is prerequisite in order to educate every working

pharmacist about the rationality of FDCs and safeguard patient health outcomes.

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