



## EVALUATION OF KNOWLEDGE AND AWARENESS OF THE PRESCRIBERS ABOUT FIXED DOSE COMBINATION: A CROSS SECTIONAL STUDY

**Dr Sanjay A. Dabhade\***

Assistant Professor Pharmacology, Dr D.Y. Patil medical college, Pimpri Pune \*Corresponding Author

**Dr Sangeeta Dabhade**

Professor Pharmacology GMC, Miraj Dist. Sangli

### ABSTRACT

Out of FDC available in the market very few are present in 'WHO essential drug list and 'national list of essential medicine.' FDC should be formulated and developed on the basis of comprehensive pharmacological principles. It is essential that prescriber should have knowledge about guidelines and pharmacological principles used to manufacture and market the FDC. Hence this study was conducted to evaluate the knowledge and awareness of the prescribers about the guidelines and pharmacological principles used to consider the FDC as rational. It was a cross-sectional, observational, study conducted in 100 prescribers. Only 20% prescribers knew that the FDC is considered as rational if the individual drugs in it acts by different mechanisms. 54% prescribers couldn't decide that the FDC is a new drug in spite of availability of the individual drugs in the market. Knowledge and awareness about the rational drug use is a prerequisite for universal health care and this necessarily constitutes evaluation of FDC of its rationality by the prescribers. It is observed that knowledge about FDC is lacking in prescribers. The new combinations are 'new drugs' and hence each FDC has to undergo clinical trials and safety studies to qualify for entering the market. Strict scrutiny of FDC in general and new FDC in particular becomes necessary. Undermining of this aspect affects access to the drugs in the developing country like ours. As patient's health lies in the hands of healthcare professionals, awareness of the prescribers about rational prescribing of FDC is essential and it should be included in the undergraduate teaching. This study recommends that there is urgent call to enhance prescriber's knowledge to critically appraise FDC. Further more effective legislation and its implementation is needed to circumvent availability of irrational FDC.

**KEYWORDS :** Fixed dose combination, rational drug use, Knowledge and awareness

### INTRODUCTION:

In India, more than 80,000 commercial formulations are available either as single drug formulations or fixed-dose combinations (FDC)<sup>1</sup>. High number of FDC with different combinations are being marketed in India, most of the time this causes confusion instead of helping the doctor. Hence the knowledge about the rationality and the guidelines about manufacturing and marketing of FDC is necessary.<sup>2</sup> Critical appraisal of FDC is becoming important for public health perspective<sup>3</sup>.

FDC are defined by the World Health Organization (WHO) as combination of two or more active ingredients in a fixed ratio of doses<sup>4</sup>. FDC should be developed on the basis of comprehensive pharmacological principles<sup>5</sup>. The use of FDC may offer several benefits like simple treatment regimens, increase adherence, improve patient outcomes and sometimes reduced cost. Furthermore, it can broaden spectrum of activity, but some disadvantages like different pharmacokinetics of the constituent drugs, increases the chances of unfavourable drug interactions & adverse drug effects<sup>6</sup>.

FDC are considered as new drugs and must comply the Schedule Y for marketing approval in India<sup>7</sup> Rationality status of many FDC marketed in India is not clear<sup>4</sup> The proliferation of FDC in Indian market has raised questions on their safety, rationality and justification<sup>7</sup> On this backdrop it is essential that prescriber should have knowledge about guidelines and pharmacological principles used to manufacture and market the FDC. Hence this study was planned to evaluate the knowledge and awareness of the prescribers about the guidelines and pharmacological principles used to consider the FDC as rational.

### MATERIALS & METHODS:

#### Study design:

A cross-sectional study was conducted in general practitioners in Pune, Maharashtra.

A structured questionnaire was designed to know the awareness and guidelines about FDC. Questionnaire was validated after pilot study. This validated questionnaire was given to study population. Survey was conducted during November, 2018 to January, 2019.

#### Inclusion criteria:

Modern medicine, Ayurveda and homeopathy practitioners practicing Modern medicine were included.

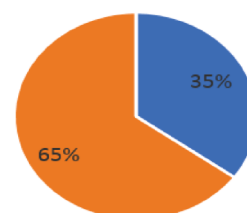
#### Exclusion criteria:

Siddha, Unani etc. prescribers were excluded.

**Sample Size:** 100 prescribers were included Percentage of responses were calculated and the data is represented in suitable graphical and tabular forms.

### RESULTS:

Qualification of prescribers



■ Modern medicine ■ AYUSH

**Fig. 1: Streamwise qualification of the prescribers**

Fig. 1 shows that 35% prescribers were from modern medicine and 65% were from AYUSH stream.

**Table:1 Knowledge and awareness of prescribers (in percentage) about FDC and guidelines about it:**

	Questions /statements	Agreed (%)	Disagreed (%)	Don't Know (%)
1	FDC is merely a combination of two or more drugs.	67	19	14
2	Do you think that FDC always improves compliance?	78	19	3
3	FDC is justified if it prevents drug resistance.	24	20	56
4	Effect of individual drugs in FDC is the same as that of drugs given individually.	74	23	3
5	Do you think that dose adjustment becomes difficult while using FDC?	42	50	8
6	Cost-effectiveness is important justification for a rational FDC.	68	23	9
7	In FDC, the drugs in the combination should act by different mechanisms.	20	61	19
8	FDCs are new drug despite of availability of individual drugs in that FDC	22	24	54
9	In a FDC, it is difficult to find out which drug is responsible for adverse effects.	56	23	21
10	The FDC should potentiate the therapeutic efficacy than the individual drug used alone.	34	51	15
11	The FDC is justified when it demonstrates decrease in the incidence of adverse effect of drugs.	76	12	12
12	The FDC is not justified when it demonstrates pharmacokinetic mismatch and having peak efficacy at different time.	34	10	56
13	FDC is justified when it reduces the dose of individual drugs.	41	51	8
14	The FDC is justified if it demonstrates pharmacodynamic advantage.	34	2	64

Table 1 shows the prescribers knowledge about FDC. 67% prescribers agreed that FDC is merely a combination of two or more than two drugs.

74% prescribers agreed that the effect of individual drugs in FDCs is the same as that of drugs given individually.

61% prescribers were not aware that the FDC is considered as rational if the individual drugs in it acts by different mechanisms.

54% prescribers couldn't decide that the FDC is a new drug in spite of availability of the individual drugs.

51% prescribers dis-agreed that the FDC should potentiate

therapeutic efficacy than the individual drugs. 56 % couldn't decide that the FDC is not justified if it demonstrates pharmacokinetic mismatch.

#### DISCUSSION:

The knowledge possessed by the prescribers is indicative of their understanding of the subject and it gets reflected into the actual practice. Knowledge and awareness of the doctors about the rational drug use is prerequisite for universal health care and this necessarily constitutes evaluation of FDC for its rationality. Obviously, knowledge about FDC is of paramount importance.

In clinical practice, prescribing FDC is increasing<sup>8,9</sup>. There are certain advantages with the use of FDC but inadequate knowledge leads to inappropriate and indiscriminate use of it and may leads to irrational prescription,<sup>10</sup> increased risk of adverse drug reactions and emergence of antibiotics resistance.<sup>11</sup>

In this study, the prescribers assume that FDC is merely a combination of two or more drugs. This underlines that most of the doctors are unable to analyse the rationality of FDC which is a matter of concern.

Even though 78% prescribers are aware that use FDC improves patient's compliance but half of the prescribers were not aware that dose adjustment becomes difficult while using it. In this study, 20% of prescribers were aware that the constituent drugs of the FDC should act by different mechanisms. Admane et al<sup>12</sup> found it in 23% prescribers. The FDC should potentiate therapeutic efficacy, this fact was known to 34% prescribers<sup>13</sup>.

Study participants were unaware of the fact that when two or more drugs, already approved individually, are combined for the first time in an FDC, then under the law the product is deemed to be a New Drug as per the Drugs and Cosmetics Act (Rule 122 (E))<sup>14</sup> and it has to undergo the procedure applicable to New Drugs such as clinical trials to determine safety and efficacy.

Once such FDCs receive approval from CDSCO, manufacturers can approach State Drugs Authorities to obtain manufacturing licenses. Unfortunately, some State Drug Authorities have issued manufacturing licenses for a very large number of FDCs without prior clearance from CDSCO<sup>15,16</sup>.

Hence the Indian pharmaceutical market consists of large number of unapproved FDC, whose safety and efficacy were never tested and is putting patients' lives at risk.<sup>17</sup> Ishrar SMG et al<sup>18</sup> found that only 24% prescribers were aware that FDC are new drugs despite of availability of constituent individual drug in the market.

The FDC is rational if the pharmacokinetics of the constituent drugs match with each other. The cost effectiveness is one of the important parameters to consider the FDC rational. This study observed that very few doctors were aware of these facts. Hence selection of rational FDC among available FDC becomes tough job.

There are evidences that very few FDC are rational and meet pharmacological principles. There are 27 FDC (414 medicines) in the 19<sup>th</sup> WHO List of Essential Medicines (EML) and 24 FDC (376 medicines) in National List of Essential Medicines (NLEM) 2015 of India. Despite of authorities having knowledge of the basic principle of formulating FDC, Indian medicine market has become the world leader of FDC. Studies have shown that the pharmaceutical companies are not following guidelines and pharmacological principles and

many FDC are not having proper justification for their rationality<sup>19</sup>.

In this study prescribers were not having adequate knowledge to decide rationality of the FDC such inadequate knowledge may be due to lack of sensitization during undergraduate and post-graduation training, sparse number of CME stressing upon FDC and unavailability of authentic sources of information about FDC. As patient's health lies in the hands of healthcare professionals, awareness of the prescribers about advantages, disadvantages and rational prescribing of FDC is essential and it should be included in the undergraduate teaching.<sup>20</sup>

Gupta R et. Al<sup>21</sup> reported the need to improve knowledge on the rationality for using fixed dose combinations, EML, and banned fixed dose combinations in India to promote the rational use of FDC.

### CONCLUSIONS:

Indian medicine market is flooded with FDC, most of them are not from NLEM and WHO essential drug list and CDSCO approved. It shows that such large number of FDC is nothing to do with healthcare needs of the population. This problem could be ended if the prescribers are aware of this menace and have ability to evaluate the rationality of FDC. This study has observed that most of the prescribers have shown dearth of such knowledge and hence this study recommends that there is urgent call to enhance prescriber's knowledge to critically appraise FDC. Further more effective legislation and its implementation is needed to circumvent availability of irrational FDC.

**Conflict of interest:** None.

### Acknowledgement:

Authors would like to thanks to the doctors who participated in the study.

**Source of funding:** No

### REFERENCES:

- Jayeshbhai Dineshchandra Balat. (2014), "A Study of Use of Fixed Dose Combinations in Ahmedabad." *India Indian J Pharmacol*, 46(5): 503-509.
- World Health Organization.(1992), The Use of Essential Drugs. WHO Technical Report Series 825. Geneva.
- WHO technical report series; 929. "WHO Expert Committee on Specifications for Pharmaceutical Preparations: Thirty-Ninth Report."
- Article O, Dalal. (2016), "Assessment of Rationality of Fixed Dose Combinations." *Approved in CDSCO List*, 10 :2014-7.
- Pradhan S, Panda A, Sahu S, Behera JP (2017), "An evaluation of prevalence and prescribing patterns of rational and irrational fixed dose combinations (FDCs): a hospital-based study." *Int J Med Sci Public Health*, 6:58-62
- Auwal F, Dahiru MN, Abdu-Aguye SN. (2019), "Availability and rationality of fixed dose combinations available in Kaduna." *Nigeria. Pharm Pract (Granada)*, 17(2):1470. doi:10.18549/PharmPract.2019.2.1470
- Prajapati K, Shah S, Desai M. (2016), "Critical Analysis of Cardiovascular and Central Nervous System Fixed Dose Combinations Available in Indian Market." *J Clin Diagn Res*, 10(12):FC36-FC39.
- [https://www.researchgate.net/publication/242541408\\_Emergence\\_of\\_Irrationality\\_in\\_Fixed\\_Dose\\_Combinations](https://www.researchgate.net/publication/242541408_Emergence_of_Irrationality_in_Fixed_Dose_Combinations)
- Kumar SP (2008), "Fixed dose combinations (FDCs)." *Rational Drugs*, 31 & 32:1-3.
- Sen A. (2002), "Indian market's fixation with fixed dose combinations." *Rational Drug Bull*, 12:1-2.
- [https://www.researchgate.net/publication/261000511\\_Combination\\_drugs\\_Are\\_they\\_rational](https://www.researchgate.net/publication/261000511_Combination_drugs_Are_they_rational)
- Admane P, Hiware S, Mahatme M. (2017), "Assessment of knowledge, attitude and practices among the residents and interns about rational fixed drug combinations in tertiary health care centre in Central India." *Int J Basic Clin Pharmacol [Internet]*, 6(9):2172-6. <https://www.ijbcp.com/index.php/ijbcp/article/view/1817>
- Amitav S. (2002), "Indian markets fixation with FDCs (editorial)" *rational drug bulletin*, 12:13.
- Government of India Ministry of Health and Family Welfare.(2005) The Drugs and Cosmetics Act and Rules (Available from: <http://www.cdsc0.nic.in/writereaddata/Drugs&CosmeticAct.pdf>)
- Parliament of India 2012. (Available from: <http://164.100.47.5/newcommittee/reports/englishcommittees/committee%20on%20health%20and%20family%20welfare/59.pdf>)
- <https://doi.org/10.1371/journal.pmed.1001826>
- Ligade VS, Thakar TM, Dengale SJ. (2019), "Fixed dose combinations of anti-tubercular, antimalarial and antiretroviral medicines on the Indian market:

critical analysis of ubiquity, sales and regulatory status." *Trop Med Int Health*, 24(2):238-246.

- Ishrar SMG, Rathinavelu M and Reddy YP (2016), "Assessment of Rational Use of Fixed Dose Combination in Community Pharmacies of Resource Limited Settings of Andhra Pradesh." *Int J Pharm Sci Res*, 7(5): 2181-86
- Gupta YK, Ramachandran SS. (2016). "Fixed dose drug combinations: Issues and challenges in India." *Indian J Pharmacol*, 48(4):347-349.
- Gautam CS, Aditya S. (2006), "Irrational drug combinations: Need to sensitize undergraduates." *Indian J Pharmacol*, 38:169-70.
- Gupta R, Malhotra P, Malhotra A. (2018), "Assessment of knowledge, attitude, and practices about prescribing fixed dose combinations among doctors - An observational study." *Natl J Physiol Pharm Pharmacol*, 8(3):347-352.