

## A Brief Review on Rational Consideration of Fixed Dose Combinations.



## Medical Science

**KEYWORDS :** Fixed dose combination, Rationality, Risk benefit ratio, Essential medicine list.

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### ABSTRACT

*The irrational prescription of fixed dose combinations is a major health concern in our country. The Indian pharmaceutical market is flooded with fixed dose combinations. The production and sale of these products are increasing day by day. Few of such products have ethical and rational basis. Fixed dose combinations enhance the efficacy of product, decrease the chances of drug resistance and improve patient compliance. On the other hand, there are some disadvantages associated like, difficulty in dose adjustment of individual drug, complexity of dose rating, irrational prescription, ineffective and unsafe treatment, exacerbation or prolongation of illness, and higher treatment cost. The awareness regarding merits, demerits and rational aspect of fixed dose combinations among the physicians is very essential to prevent irrational prescribing practices. We have tried to consolidate important aspects of fixed dose combination with hope to improve awareness regarding this issue.*

Fixed dose drug combinations (FDCs) are products obtained by combination of two or more active pharmaceutical ingredients with a definite proportion in a single dosage form. The rationality of fixed dose combination (FDC) is one of the most controversial and debatable issue. The FDCs can be divided into rational and irrational based on rationality of the products. Rational use of drugs requires that patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements for an adequate period of time, at the lowest cost to them and their community. The criteria for rational use of drugs are appropriateness, safety and efficacy of drug and low cost of therapy. Irrational use of the drugs is the use in a way that does not follow the rationality as defined above (WHO, 2002).

Drugs acting on the same effect are known as homergic drugs while two drugs are called heterergic if they do not cause response of the same effect. Homergic drug combinations have benefit of reduced dose and increase in therapeutic action (e.g., amlodipine + enalapril) while heterergic drug combinations have advantages of decreased adverse effects (e.g., ramipril + hydrochlorothiazide, furosamide + spironolactone), increase in duration of action (e.g., probenecid + penicillin, Imipenem + cilastin), modified absorption (e.g., lignocaine + adrenaline), and decreased rate of degradation (e.g., levodopa + carbidopa) (Jadav & Parmar, 2011).

Combination products which are obtained by combining two or more active pharmaceutical ingredients in definite proportion in a single dosage form are known as FDCs. A new FDC is considered as 'New Drug' according to Drugs and Cosmetics Act, 1940 (Rule 122(E)); and hence it must undergo clinical trials before entering in the market (Prakash, 2007). It is universally accepted fact that a drug dosage form should have a single active compound. The combination of two or more active principles should only be considered in case when these have established benefit over each of single drugs individually. The FDCs should have a considerable positive risk benefit ratio, i.e. the combination products should have more benefit in terms of efficacy, cost, and compliance or fewer demerits in the form of adverse drug reactions and high cost in comparison to its constitutional ingredients separately (Gautam, & Saha, 2008). The FDCs should have certain criteria in order to fulfill its aspects of its rationality such as (Panda, et al., 2006; Amitava, 2002):

1. The drugs used for making the FDCs should follow different mechanism of action. This increases the possibility of synergistic effect.
2. The pharmacokinetics of the constituent drugs must not differ widely.
3. The combining drugs should not have supra-additive toxicity and drug interaction between the ingredients.
4. The FDCs should have favorable risk benefit ratio. The claim

of benefit should be supported by evidence based results obtained by ethically designed randomized clinical trials.

5. The safety of FDC is utmost importance. The ingredients should be stable in combination or should not react chemically.
6. The active pharmaceutical ingredients of FDCs should be enlisted in the WHO Essential Medicine List (EML) or in the National List of Essential Medicine (NLEM).
7. The dose of each active pharmaceutical ingredient should fulfill the requirement of population concerned.

As the two sides of coin, FDCs also have merits and demerits. Physicians should decide the prescription of FDC on the basis of evidence based medicine and clinical ground by evaluating the risk/ benefit of particular FDC. **Advantages of FDC are** (Jadav & Parmar, 2011):

1. Increase in efficacy of product due to synergistic effect, e.g., estrogen + progesterone, sulfamethoxazole + trimethoprim.
2. The FDCs increase compliance in the patients as this decrease the scheduled dosages. Adherence in the treatment is important issue in chronic infectious diseases where partial adherence can lead to the development of drug-resistant strains, treatment failure, and a threat to public health, e.g., treatment of TB and HIV.
3. Decreases the chances of development of antimicrobial resistance. This is the rational basis of combination of drugs in antitubercular treatment, FDCs of antiretroviral drugs and combination artemisinins and long acting antimalarials in treatment of malaria.
4. FDCs ensure that single drug will not be administered.
5. The adverse effects of one medicine can be reduced by combining it with another medicine in FDCs. e.g. levodopa + carbidopa and furosemide + spironolactone.
6. Psychological benefits as patients believe that they are taking less number of drugs.

Most FDCs have the following demerits (Jadav & Parmar, 2011):

1. Dosage modification and withdrawal of one drug cannot be done without altering the dose of the constituent drug.
2. The patients may not need all the drugs present in the FDCs.
3. Differences in pharmacokinetic properties of constituent drugs lead to difficulties in frequency of administration of the dosage forms.
4. Unsuitable pharmacodynamic profile which can make diagnosis and treatment more difficult.
5. There are increased likelihood of adverse drug reactions and drug interactions as compared to drug given separately, e.g., paracetamol and nimesulide.
6. Increase the development of antimicrobial resistance

among the bacterial strains, e.g., in case of FDCs of fluoroquinolones and nitroimidazoles.

7. It imposes increased economic burden on patient and society as a whole. FDCs increase the price of therapy as unnecessary drugs are also included, e.g. ibuprofen + paracetamol + caffeine.
8. Gives rise to unethical practice of polypharmacy. One of the drugs in the combination may not be required to the patient or wasteful, e.g., vitamins + iron.

The recent 18th model list of essential drugs prepared by the WHO (April 2013) includes 353 formulation of which 26 are FDCs (WHO model list of essential medicines 18th list, 2013).

1. Amoxicillin + Clavulanic acid
2. Efavirenz + Emtricitabine + Tenofovir
3. Emtricitabine + Tenofovir
4. Lamivudine + Nevirapine + Stavudine
5. Lamivudine + Nevirapine + Zidovudine
6. Lopinavir + Ritonavir
7. Lamivudine + Zidovudine
8. Ethambutol + Isoniazid
9. Ethambutol + Isoniazid + Pyrazinamide + Rifampicin
10. Ethambutol + Isoniazid + Rifampicin
11. Isoniazid + Pyrazinamide + Rifampicin
12. Isoniazid + Rifampicin
13. Artemether + Lumefantrine
14. Artesunate + Amodiaquine
15. Artesunate + Mefloquine
16. Sulfadoxine + Pyrimethamine
17. Sulfamethoxazole + Trimethoprim (Oral)
18. Sulfamethoxazole + Trimethoprim (Injection)
19. Imipenem + Cilastatin
20. Ethinylestradiol + Levonorgestrel
21. Ethinylestradiol + Norethisterone
22. Estradiol cypionate + Medroxyprogesterone acetate
23. Levodopa + Carbidopa
24. Ferrous salt + Folic acid
25. Lidocaine + Epinephrine (Adrenaline)
26. Oral rehydration salts (sodium chloride, trisodium citrate dehydrate, potassium chloride, glucose).

The National List of Essential Medicines (NLEM) of India has 348 essential drugs, including 16 drug combinations (National list of essential medicines, 2011):

1. Co-trimoxazole (Trimethoprim + Sulfamethoxazole)
2. Lamivudine + Nevirapine + Stavudine
3. Lamivudine + Stavudine
4. Lamivudine + Zidovudine
5. Amoxicillin + clavulanic acid
6. Artesunate + Amodiaquine
7. Sulfadoxine + Pyrimethamine
8. Neomycin + Bacitracin
9. Ethinylestradiol + Levonorgestrel
10. Ethinylestradiol + Norethisterone
11. Levodopa + Carbidopa
12. Lignocaine hydrochloride + Adrenaline
13. Acriflavin + Glycerin
14. Ferrous salt + Folic acid
15. Aluminum hydroxide + Magnesium hydroxide
16. Oral rehydration salts (sodium chloride, trisodium citrate dehydrate, potassium chloride, glucose)

There are numerous FDCs products available in the Indian pharmaceutical market. Unfortunately, most of the FDCs are irrational. The most important matter of concern with irrational FDCs is that they cause of unnecessary risk of adverse drug reactions. FDC of diclofenac + serratiopeptidase is very commonly used in clinical practice but it does not seem to offer any added advantage over the individual drugs. Serratiopeptidase in combination is promoted with the claim of more rapid resolution of inflammation, on the other hand, it exposes the patients to greater risk of gastrointestinal (GI) irritation and serious internal hemorrhage from peptic ulceration (Gautam & Saha, 2008).

FDCs of quinolones and nitroimidazoles like norfloxacin + metronidazole, ciprofloxacin + tinidazole, ofloxacin + ornidazole are also commonly used for GI infections, pelvic inflammatory disease, dental infections and other soft tissue infections. But it has not been recommended in WHO and Indian essential medicine list. Due to such an indiscriminate use of antibiotics, antimicrobial resistance has emerged as disaster of present century. The treatment and management of resistant strains are not only difficult but also very costly and full of adverse drug reactions (Jadav & Parmar, 2011; Gautam & Aditya, 2006).

In India, plentiful number of combination products of NSAIDs is available over the counter. This results in compulsion to take other drug when only one of them is needed by the patients. By these types of combination products, sale of the other drug increases. Hence these types of fixed dose combination are vigorously promoted by pharmaceutical companies. The combination products are dubiously promoted as "ibuprofen for pain and paracetamol for fever and ibuprofen for peripheral action and paracetamol for central action". Although this is irrational but unfortunately works in the market as physicians get entangled in this type of irrational prescription practices. Ultimately it is the patient who has to bear the disadvantage of irrational prescribing practices in terms of adverse drug reactions, drug interactions and extra economic burden. These combinations do not simply follow the criteria for FDC as both the drugs act by similar mechanism. Thus FDCs of two NSAIDs does not improve the efficacy. It only increases the cost of therapy (Gautam & Saha, 2008).

The FDCs of NSAIDs with one of the antispasmodic agents are also very commonly prescribed in India. These types of combinations are not only of questionable efficacy but also dangerous. The antipyretic promotes sweating and thereby helps in heat dissipation while the antispasmodic drug having anticholinergic activity inhibits sweating. Combination of these two can result in fatal rise of the body temperature (Amitava, 2002).

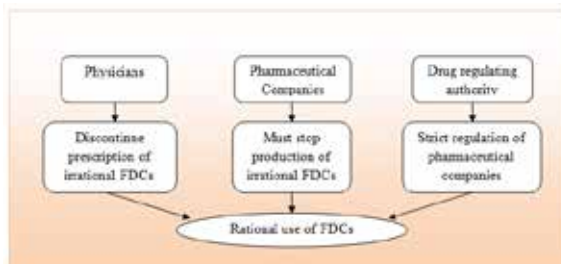
FDCs of antihypertensive drugs such as ramipril + telmisartan are associated with more adverse drug reaction without offering any increase in benefits thus lowering risk benefit ratio (Yusuf, 2008). FDCs of hypolipidemic drugs such as statins + nicotinic acid or fibrates enhance the probability of myopathy. FDCs of gastrointestinal drugs such as domperidone + rabeprazole found to have increased incidence of rhabdomyolysis. FDCs of cough and cold remedies such as cetirizine + phenylpropanolamine + dextromethorphan; any combination with phenylpropanolamine is banned in India as it causes stroke. FDCs of antimicrobials such as fluconazole + tinidazole are irrational as the patients require only single drug after an accurate diagnosis. FDCs of antimicrobials such as amoxycillin + cloxacillin are ineffective as most strains of staphylococcus produce  $\beta$ -lactamase and hence amoxycillin is ineffective against these and cloxacillin is not much active against streptococci. Therefore, for such type of FDCs, one of the components is useless and adds to extra cost and adverse drug effects. Further, since the dose of each drug is halved in combination, efficacy is reduced and chances of development of resistance are increased (Gautam & Aditya, 2006).

The awareness regarding advantage and disadvantage of FDCs is lacking in resident doctors. As patient's health is in the hands of physicians, awareness among the doctors regarding advantages, disadvantages and rational prescription of FDCs is very crucial. Awareness among the physicians can be increased by circulating drug bulletin, newsletters and also through continuous medical education. The basic awareness and training regarding this should be carried out from the undergraduate level of teaching and should be updated according to current scenario (Goswami et al, 2013).

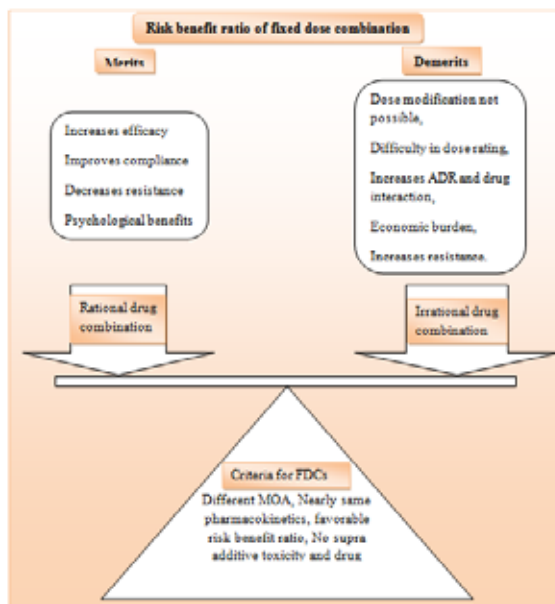
Over the years the Indian Drug Control Authority has banned many FDCs (Tripathi, 2013). But these measures seem to be insufficient. WHO is making all effort to rationalize the therapeutics and disseminate the concept of rational use of drug amongst consumers, prescriber and manufacturers throughout the world. India, being the second most populous country in the world, demands a more rationalization of therapeutics. Sensitization

towards authentic sources of information like Essential Medicine List, education programs about FDCs as well as day to day updates regarding banned FDCs are quite necessary to promote rational use of drugs. Irrational FDCs also impose unnecessary financial burden on consumers. In spite of all these efforts pharmaceutical companies continue to manufacture and supply FDCs in the market to gain profit and they will keep on manufacturing and marketing the FDCs in India till the regulating authorities ban it. Though it is the responsibility of drug regulatory authorities to keep a check on irrational FDCs, physicians must also discourage the practice of prescribing irrational FDCs.

**Figure-2: Factors affecting the risk benefit ratio of fixed dose combinations.**



**Figure-1: Ways to rationalize the use of FDCs.**



## REFERENCE

- Amitava, S. (2002). Indian market's fixation with fixed dose combinations (Editorial) Rational Drug Bulletin. 12:1. | Gautam, C. S., & Aditya, S. (2006). Irrational drug combinations: Need to sensitize undergraduates. Indian Journal Pharmacol, 38, 169-70. | Gautam, C. S., & Saha, L. (2008). Fixed dose drug combinations (FDCs): rational or irrational: a view point. British Journal of Clinical Pharmacology, 65(5), 795-796. doi: 10.1111/j.1365-2125.2007.03089.x. PMID: PMC2432494. | Goswami, N., Gandhi, A., Patel, P., & Dikshit, R. (2013). An evaluation of knowledge, attitude and practices about prescribing fixed dose combinations among resident doctors. Journal ListPerspect Clin Resv, 4(2), Apr-Jun 2013PMC3700327. | Jadav, S. P., & Parmar, D.M. (2011). Critical appraisal of irrational drug combinations: A call for awareness in undergraduate medical students. Journal of Pharmacology and Pharmacotherapeutics, 2 (1): 45-48. DOI: 4103/0976-500X.77117. | National list of essential medicines, (2003). Available from: [http://www.searo.who.int/t/LinkFiles/Essential\\_Drugs\\_and\\_Medicines\\_India.pdf](http://www.searo.who.int/t/LinkFiles/Essential_Drugs_and_Medicines_India.pdf). [last accessed on 2010 Aug 3]. | Panda, J., Tiwari, P., & Uppal, R. (2006). Evaluation of rationality of some FDCs: Focus on antihypertensive drugs. Indian Journal of Pharmaceutical Sciences, 68(5), 649-653. | Prakash, S. (2007). Irrational combinations: No consideration for patient safety. Indian Journal of Pharmacology, 39(5), 217. | Sreedhar, D., Subramanian, G., & Udupa, N. (2006). Combination drugs: are they rational? Curr Sci. 91:406. | Tripathi KD. Essentials of medical pharmacology. 7. New Delhi: Jaypee Brothers; 2013. Appendix 2. Drugs and fixed dose combinations banned in India; pp. 969-70. | WHO model list of essential medicines 18th list. (2013). Available from: [http://www.who.int/medicines/publications/essentialmedicines/Updated\\_sixteenth\\_adult\\_list\\_en.pdf](http://www.who.int/medicines/publications/essentialmedicines/Updated_sixteenth_adult_list_en.pdf). [Last updated on 2013, April 2013]. | WHO policy perspectives on medicines-promoting rational use of medicines: Core components. Geneva: World Health Organization, 2002. | Yusuf, S., Teo, K.K., Pogue, J., Dyal, L., Copland, I., et al. (2008). Telmisartan, ramipril, or both in patients at high risk for vascular events. New England Journal of Medicine, 358, 1547-59. |