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## Current Pattern of Use of Irrational Fixed Dose Combinations: A Prescription Audit Study

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### ABSTRACT

Despite of provision of toolkit by WHO expert committee for identification of Irrational Fixed Dose Combinations (IFDCs) and though number of measures are taken to weed out the menace of IFDCs, it hasn't been possible to completely stop their marketing. The present study is intended to document the prevailing pattern of use of IFDCs and discuss the probable measures that can be taken to curtail their use. To know the overall pattern of prescribing IFDCs by prescription audit. To know the percentage of total number of prescribed drugs prescribed as IFDCs, most commonly prescribed IFDCs and most commonly prescribed Irrational Antimicrobial combinations. Prescriptions copied and audited between 1<sup>st</sup> August 2011 to 31<sup>st</sup> August 2011. The results were analysed by using descriptive statistics. Out of total prescriptions 22% of prescriptions contained at least one IFDC. Out of this, 3% of prescriptions contained  $\geq 2$  IFDCs. 10.5% of all the brand names prescribed contained some IFDC. 26% of all the prescribed IFDCs were Irrational antibiotic combination. Most commonly prescribed IFDCs were multivitamin combinations, and 2<sup>nd</sup> most common were antipyretic- antiinflammatory combination. While the most commonly prescribed antimicrobial combination was antiprotozoal-antibacterial.

**Keywords:** Irrational, Prescription, FDC, audit.

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## INTRODUCTION

The prescribing, marketing, and use of Fixed dose combinations (FDC) is an important issue among the health service providers and service recipients. As per Editorial in Indian journal of Medical Ethics around 70 Irrational Fixed Dose Combinations (IFDCs) were being marketed and prescribed in India under more than 1000 of brand names in 2003. Many of them are still being marketed. Only 26 FDCs are included in the 16th edition of WHO model list of Essential Drugs. Obviously many irrational FDCs are being marketed, many of which don't have a well-documented safety.

According to WHO expert committee on specifications for pharmaceutical preparations (39th report, 2005) a FDC can be defined as "A combination of two or more actives in a fixed ratio of doses. This term is used generically to mean a particular combination of actives irrespective of the formulation or brand. It may be administered as single entity products given concurrently or as a finished pharmaceutical product [1].

Despite of provision of toolkit by WHO expert committee for identification of IFDCs and though number of measures are taken to weed out the menace of IFDCs, it has not been possible to completely stop their marketing . The present study is intended to document the prevailing pattern of use of IFDCs and discuss the probable measures that can be taken to curtail their use.

To know the overall pattern of prescribing IFDCs by prescription audit.

## OBJECTIVES

- 1.To know the percentage of total number of prescribed drugs prescribed as IFDCs.
- 2.To know most commonly prescribed IFDCs.
- 3.To know the most commonly prescribed Irrational antimicrobial Combinations.

## MATERIALS AND METHODS

**Study Design:** Present study is a Prescription audit study.

**Study site:** LN Medical College, Bhopal.

**Study duration:** 1 month (From 1<sup>st</sup> August 2011 to 31<sup>st</sup> August 2011 )

A total of 1000 randomly copied prescriptions were audited in 1 month duration from 1<sup>st</sup> Aug 2011 to 31 Aug 2011. The prescriptions were copied from original prescriptions of patients coming to 4 different Medical stores of Bhopal city. These were then entered in Microsoft excel sheets at LNMC, Bhopal in order to evaluate them directly. The study was specifically designed to evaluate pattern of use of IFDCs.

**Statistical analysis:** Descriptive statistics was applied to the data so obtained.



## RESULTS

Out of total prescriptions 22% of prescriptions contained at least one IFDC .Out of this 3% of prescriptions contained  $\geq 2$  IFDCs. 10.5% of all the brand names were of some or other IFDC were prescribed in the form of IFDCs. 26% of all the prescribed IFDCs were Irrational antimicrobial combination. Most commonly prescribed IFDCs were multivitamin combinations, and 2<sup>nd</sup> most common were antipyretic- antiinflammatory combination. While the most commonly prescribed antimicrobial combination was Antiprotozoal-antibacterial.

## DISCUSSION

IFDC is currently the hottest issue of debate for pharmaceuticals, physicians and regulatory authorities. For pharmaceuticals, they are major source of income from market. While for Physicians, it poses some advantages like ease if prescribing, saves time, increases patients compliance and adherence. Regulatory authorities are more concerned with the safety of the IFDCs, as IFDCs are associated with some drawbacks like difficulty in dose titration to meet individual needs, may increase the price as well as chances adverse drug reactions of unwanted component drugs, inability to find out the culprit drug in case of adverse effect. It is important to discuss here all the merits and demerits of the use of IFDCs.

### Advantages of IFDCs includes

1. Combination medicines have the advantages in disorders where combination therapy is required as well as advantages related to reducing the number of pills to be taken.
2. Reducing the number of pills diminishes the complexity of the regimen and therefore leads to improved patient adherence.
3. Reduced administration costs stem from simplified packaging, fewer prescriptions, and lesser dispensing time and cost.
4. FDCs can improve compliance in the treatment of chronic infectious disease, 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.
5. The side effects of one medicine can be reduced by combining it with another medicine in a FDCs, e.g. Combination of aluminium hydroxide and magnesium trisilicate counteracts the side effects of each other, atropine is combined with diphenoxylate to reduce the dependence liability of later.
6. The efficacy of one medicine can be synergistically increased by combining it with another, e.g., Levodopa + carbidopa, Sulfamethoxazole + Trimethoprim

### Disadvantages of IFDCs [3]

1. Titration of dose of medicine to suit individual patients is not possible, e.g., atorvastatin 10 mg + amlodipine 5 mg.

2. FDCs increase the price of the medication which poses unnecessary burden to the patient, if unnecessary drugs are included, e.g., ibuprofen + paracetamol + caffeine.
3. One of the drugs in the combination may be superfluous or wasteful, e.g., vitamins + iron.
4. The incidence of adverse effects increases, e.g., atorvastatin + nicotinic acid.
5. In FDCs, there is always a chance that individual medicines may not be present in adequate amounts, e.g., multivitamins.
6. Incompatible pharmacodynamics, e.g., combination of an antihistaminic with an antidiarrheal is dangerous as the antihistaminic action may mask other symptoms and make accurate diagnosis and treatment difficult.
7. It is difficult to identify which medicine in the FDCs has caused an adverse effect.

### **Some IFDCs which are being marketed include**

1. FDCs of cardiovascular drugs such as ramipril + telmisartan are associated with more adverse events without offering any increase in benefits.
2. FDCs of analgesic, anti-inflammatory and antipyretic like nimesulide + paracetamol having increased hepatotoxic adverse effects.
3. FDCs of hypolipidemic drugs such as atorvastatin + nicotinic acid combination having increased probability of myopathy [5].
4. FDCs of gastrointestinal drugs such as domperidone + rabeprazole having increased incidence of rhabdomyolysis [5].
5. FDCs of cough and cold remedies such as cetirizine + phenylpropanolamine + dextromethorphan; in this combination phenylpropanolamine is a banned drug which has potential to cause stroke [5].
6. FDCs of antimicrobials such as fluconazole + tinidazole are irrational because the patient may need only one drug after making a correct diagnosis [5].
7. FDCs of antimicrobials such as amoxicillin + cloxacillin; in this combination, amoxicillin is inactive against staphylococcus as most strains produce  $\beta$ -lactamase and cloxacillin is not so active against streptococci. Therefore, for any given infection, one of the components is useless and adds to cost and adverse effects. Further, since the amount of each drug is halved, efficacy is reduced and chances of selecting resistant strains are increased. [5]

A few of the known IFDCs which are clearly irrational are described below, which are widely used. Irrational FDCs of diclofenac + serratopeptidase do not offer any particular advantage over the individual drugs despite the claim that serratopeptidase promotes more rapid resolution of inflammation.

FDCs of quinolones and nitroimidazoles (e.g. norfloxacin + metronidazole, ciprofloxacin + tinidazole, ofloxacin + ornidazole) have not been recommended in any standard books but

continue to be heavily prescribed drugs in GI infections, pelvic inflammatory disease, dental infection, etc., to cover up for diagnostic imprecision and the lack of access to laboratory facilities. FDCs of quinolones and nitroimidazoles (e.g. norfloxacin + metronidazole, ciprofloxacin + tinidazole, ofloxacin + ornidazole) have not been recommended in any standard books but continue to be heavily prescribed drugs in GI infections, pelvic inflammatory disease, dental infection, etc., to cover up for diagnostic imprecision and the lack of access to laboratory facilities. Such injudicious use of antibiotic FDCs can rapidly give rise to resistant strains of organisms, which is a matter of serious concern to the health care situation in our resource poor country. A glaring example is the emergence of ciprofloxacin-resistant *Salmonella typhi* strains which have made treatment of typhoid fever a difficult and expensive proposition in India today [6].

According to Drug and cosmetic act 1940 (122E), every new FDC should be considered as a new drug and should be allowed for marketing only after submission of relevant Preclinical and clinical trial data. Rationality or irrationality of an FDC can be examined based on the provisions made in Schedule Y. The power of examination of an FDC lies with licensing authority mentioned under section 21(b) of Schedule Y. It has been argued that many pharmaceuticals have got marketing permission for IFDCs from state licensing authority, which are presently under the screening of DCGI. More importantly some banned FDCs are still being marketed. Broadly speaking it is difficult to stop the marketing of all the IFDCs but some measures should be taken to effectively prevent the same. To reduce the confusion of licensing the marketing of IFDCs, WHO has formed guidelines in the 39th Report, 2005 on specifications for pharmaceutical preparations (WHO technical report series 929). If used it can help to reduce the flood of IFDCs. However, According to Schedule Y Appendix VI (b), such FDCs where active ingredients are already approved/marketed individually, reports of clinical trials carried out in the country should be submitted. When ratio of ingredients in approved FDCs is to be changed then also manufacturers need to submit clinical trial data to DCGI. We recommend that special emphasis on demerits of use of IFDCs should be given by medical colleges.

### CONCLUSION

It is obvious from the above results that despite various measures from regulatory authorities, IFDCs are still being extensively used. Considering the advantages and disadvantages it is obligatory to understand the potentially dangerous IFDCs and avoid their use by clinicians.

### SUMMARY

Currently IFDCs (Irrational fixed dose combination) are being very commonly used by clinicians. Though marketing of some IFDCs have been banned, many of them are still being prescribed. In the present study, all advantages and disadvantages of IFDCs were discussed and an attempt has been made to evaluate, the most commonly prescribed IFDCs and reasons (as per the physicians) behind prescribing them. Our results document the high irrationality in prescribing drugs in the form of IFDCs. One of the important way to prevent prescribing

dangerous IFDCs is by educating students of medical colleges regarding merits and demerits of prescribing them.

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