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Rationality of Fixed Drug Dose combination for the management of Upper Respiratory Tract Infection.

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ABSTRACT

To study and evaluate the rationality of fixed drug dose combination (FDC) with various formulations available in the Indian market for the management of Upper Respiratory Tract Infection. A cross-sectional and observational study was conducted where drugs were selected using an annual Drug Compendium entitled "Indian Drug Review" (IDR) 2014 that enlists most of the medicines commercially available in India during a particular year and they were classified as irrational using the Rational Drug Bulletin criteria. A total of 1376 FDCs were studied out of which 785 (57%) FDCS were found to be irrational where majority belonged to the class of expectorants (76.09 %). The most common cause of irrationality was due to FDCs containing drugs with same mode of action (56.6%), second common being (36.05%) due to FDC drugs with opposite mode of action and 7.38% FDCs were banned by the government. Availability of such a large number of irrational FDCs for cough and cold requires serious review of the legal provisions in India for drug manufacturing and marketing as these act as a financial burden for the population.

Keywords: Irrational drug combinations, fixed dose combinations, Upper Respiratory Tract Infection.

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INTRODUCTION

A fixed-dose combination (FDC) is a drug that includes two or more pharmaceutical ingredients (to be administered simultaneously) made in fixed doses that meets the requirement of a defined group of population and is distributed in a single dosage form. [1- 3]

FDC products are acceptable only if the combination can be justified on therapeutic principles such as an increase in efficacy as compared to when each component is taken separately, counteracting the adverse reaction of one substance by the other and increasing safety or decreasing the pill burden of the patient and thus increasing compliance. [1, 2]

Now-a-days FDCs have become a huge part of routine medical practice. However not all FDCs manufactured in the market meet the acceptability criteria mentioned above and thus result in rampant production of irrational FDCs.

In India, Appendix VI FDC of Schedule Y (Drugs & Cosmetics Rules 1945, India) provides details about the requirements for manufacture/import approval and marketing of various types of FDCs which clearly state that a therapeutic justification is required to produce a FDC. [4] However these rules are clearly not being followed as several studies have shown the presence of irrational combinations in the market [5-9]. In addition the Indian laws too are not properly defined to grant marketing approvals of FDCs by the state or central drug controlling authorities. [10]

The pharmaceutical companies have vested interests in purporting the irrational FDCs as it means saving money and making profit as less funds are required as the cost of production of FDC is less than that of the individual products sold due to decrease in dispensing fees, the use of fewer bottles, label set c [11] On the other hand doctors either due to lack of knowledge or on account of receiving personal gains from the pharmaceutical companies prescribe these irrational FDCs under the pretext of increased patient compliance. All these factors have led to a boom in the production of irrational FDCs in the market.

The major cause of concern against irrational FDCs is the quantifiable increase in the probability of adverse drug effects and drug interactions as well as the antibiotic FDCs can increase the chances of resistance. [6, 12, 13]

The FDC drugs are perhaps most misused in upper respiratory tract infection (URTI) which is usually due to rhinovirus, para-influenza virus, corona virus and adenovirus and resolve without prescription drugs and tend to resolve without the need of any medication. [14]

Moreover the recent 19th Model of the list of essential drugs prepared by the WHO (April 2015) contains just 18 FDCs where none of them feature in the section on medicines acting on the respiratory tract. [10, 15]

A study conducted by Shah *etal [*16] which studied 209 FDCs showed that a majority were irrational and included mainly beta 2 agonists with antihistamines/expectorants/anticholinergics. Similar results were found in another study conducted by Roy et al. [17] Another study conducted in 2010 using the Current Index of Medical Specialties(CIMS) India in which 1297 formulations were studied, where 94% were FDCs and only 2% had pharmacologic rationale for their use in cough and cold. [18] Thus, the aim of our study is to evaluate the rationality of fixed drug dose combination with various formulations available in the Indian market using the Indian Drug Review for the management of URTI.

MATERIALS AND METHODS

This is a cross-sectional, observational study and was conducted at the Department of Pharmacology, Grant Government Medical College, Mumbai, Maharashtra. The drugs were selected using an annual Drug Compendium entitled "Indian Drug Review" (IDR) 2014that enlists most of the medicines commercially available in India during a particular year.

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Seven classes of drugs under the section for Upper Respiratory Tract Section were studied which included Antitussives, Antihistamines, Expectorants, Mucolytics, Decongestants, Bronchodilators and Analgesics.

The rationality of FDCs was studied by the Rational Drug Bulletin criteria [10] -

- 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

These were justified by using the standard textbook of pharmacology – Goodman and Gilman.

The FDCs were also assessed for the number of active pharmacological ingredients, mentioned in World Health Organization (WHO) essential medicine list (EML) as well as National List of Essential Medicine.

The irrational FDCs were then numbered and classified as per reason of irrationality as FDCs including drugs that were banned in India, multiple drugs with same mode of action and drugs with opposite mode of action.

RESULTS

A total of 1376 FDCs were studied from IDR 2013 Issue b (ISSN 0971-8125), according to the rational drug combination criteria, out of which 785 (57%) FDCS were found to be irrational. We found that the most common cause of irrationality was due to 444 FDCs containing drugs with same mode of action (56.6%), second common being 283 FDC drugs(36.05%) with opposite mode of action and 58(7.38%) FDCs were banned by the government.

On subcategorizing the FDC's into 7 groups as Antitussives, Antihistamines, Expectorants, Mucolytics, Decongestants, Bronchodilators, Analgesics, we found that nearly half or more of the generic combinations were found to be irrational in most subgroups.

As seen in Fig 1, Irrationality in generic combinations was found in maximum in expectorants (76.09%) which was closely followed by antitussives (73.47%). Least irrational generic combinations were found among bronchodilators (45.94%).

All the subgroups had same mechanism of action as the most common cause of irrationality except antitussives where the main cause of irrationality was due to opposite mechanism of action of individual drugs in the FDC (52.77%). Also this same mechanism of action was responsible for more than 50% of irrationality in all of the subgroups except antitussives. 100% of the irrational FDC's among bronchodilators were due to same mode of action.

Table 1: Subgroups of FDCs showing total generic combinations and formulations with their rationality available in the market along with the reason for irrational drug combinations

Analgesics

Total analgesics combinations for URTI

Rationality	No of Generic Combinations	No of Formulations
Rational	9 (52.94%)	38 (50%)
Irrational	8 (47.06 %)	38 (50%)
Total	17	66

Reasons for irrational combinations:

Rationality	Banned (Formulations)	Same (Formulations)	Opp(Formulations)
Irrational	1(5)	5(15)	2(8)
Percentage	12.5 %	62.5%	2.5%

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Bronchodilators

Total bronchodilators combinations for URTI

Rationality	No of Generic Combinations	No of Formulations
Rational	20 (54.04%)	56 (47.86%)
Irrational	17 (45.94%)	61 (52.13%)
Total	37	117

Reasons for irrational combinations:

Rationality	Banned (Formulations)	Same (Formulations)	Opp(Formulations)
Irrational	0	17(61)	0
Percentage		100%	

Decongestants

Total decongestants combinations for URTI

Rationality	No of Generic Combinations	No of Formulations
Rational	25 (42.37%)	92 (48.42%)
Irrational	34 (57.63%)	98 (51.58%)
Total	59	190

Reasons for irrational combinations:

Rationality	Banned (Formulations)	Same (Formulations)	Opp(Formulations)
Irrational	3(9)	20(45)	11(43)
Percentage	8.82%	58.82%	32.35%

Mucolytic

Total mucolytic combinations for URTI

Rationality	No of Generic Combinations	No of Formulations
Rational	13 (28.26%)	41 (29.28%)
Irrational	33 (71.74%)	99 (70.72%)
Total	46	140

Reasons for irrational combinations:

Rationality	Banned (Formulations)	Same (Formulations)	Opp(Formulations)
Irrational	1(2)	18(57)	14(40)
Percentage	3.03%	54.54%	42.42%

Expectorants

Total expectorants combinations for URTI

Rationality	No of Generic Combinations	No of Formulations
Rational	11 (23.91%)	45 (30.82%)
Irrational	35 (76.09%)	101 (69.17%)
Total	46	146

Reasons for irrational combinations:

Rationality	Banned (Formulations)	Same (Formulations)	Opp(Formulations)
Irrational	2(10)	22(49)	11(42)
Percentage	5.71%	62.85%	31.42%

Antihistamines

Total antihistamines combinations for URTI

Rationality	No of Generic Combinations	No of Formulations

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Rational	43 (32.82%)	194 (39.59%)
Irrational	88 (67.17%)	296 (60.40%)
Total	131	490

Reasons for irrational combinations:

Rationality	Banned (Formulations)	Same (Formulations)	Opp(Formulations)
Irrational	7(19)	48(173)	33(100)
Percentage	7.95%	54.54%	37.5%

Antitussives

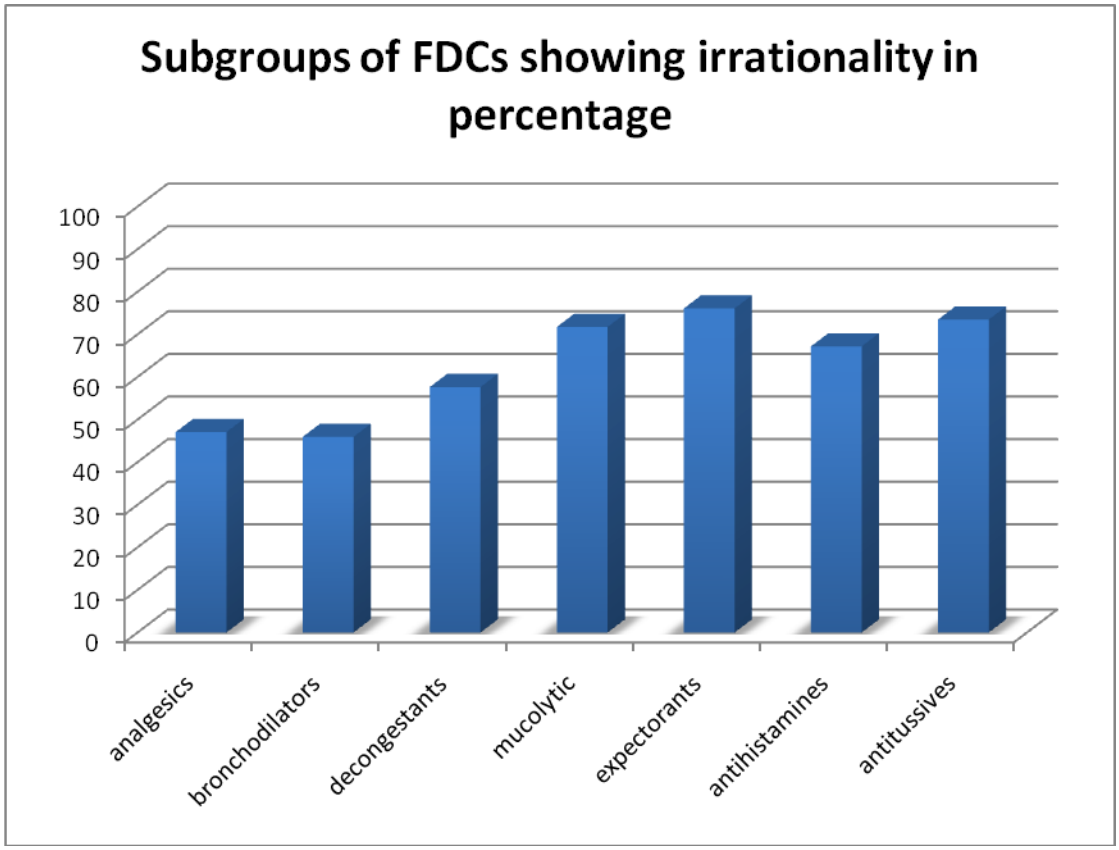
Total antitussives combinations for URTI

Rationality	No of Generic Combinations	No of Formulations
Rational	13 (26.53 %)	125 (55.06%)
Irrational	36 (73.47%)	103 (44.94%)
Total	49	227

Reasons for irrational combinations:

Rationality	Banned (Formulations)	Same (Formulations)	Opp(Formulations)
Irrational	3(13)	14(34)	19(56)
Percentage	8.33%	38.88%	52.77%

Figure 1: Subgroups of FDCs showing irrational combinations



Various formulations of drugs were analyzed and the maximum numbers of irrational formulation combinations were found in the subgroup of Mucolytics (70.72%), and the least being in Antitussives (44.94%). Bronchodilators had 52.13% of irrational formulations which were among the bottom 4 subgroups. Thus we observed that bronchodilators had least number of irrational generic combinations, less irrational formulations

as compared to other groups and no banned formulations were available. Expectorants on the other hand had maximum number of irrational generic combinations and a high (70.72%) number of irrational formulations. (Table 1)

DISCUSSION

India's pharmaceutical market is one of the largest markets in the world valued at more than US$12 billion in 2009 and is expected to exceed $55 billion in 2020. [19, 20]

Due to poorly enforced regulations and lack of laws for granting approval for new FDCs, India has a significant drug use problem. [10] A 2012 report by the Parliament of India emphasized that new drug approvals were granted by the Central Drugs Standard Control Organization (CDSCO- the Indian regulatory body to ensure drug safety), in the absence of evidence of efficacy and without the necessary clinical trials.10,20,21Such a pharmaceutical market is a fertile ground for irrational FDCs to flourish.

This study was designed specifically to identify the rationality of the drugs available in the market for URTI as it is usually viral in origin and is mostly self-limiting. These findings are corroborated by several studies. [16-18]

Furthermore, the recent 19th Model of the list of essential drugs prepared by the WHO(April 2015) contains just 18 FDCs out of which none are featured in the section on MEDICINES ACTING ON THE RESPIRATORYTRACT. [15]

We found that expectorants have the maximum number of irrational generic combinations and a high number of irrational formulations. The drug combination of Guaifenesin+ Bromhexine has been used earlier in several combinations with expectorants/decongestants/anti-tussives. Otherexamples include chlorpheniramine + cetirizine, ambroxol +guaifenesin/bromhexine, bromhexine+ chlorpheniramine+ paracetamol, dextromethorphan + codeine, dextromethorphan +guaifenesin/bromhexine, chlorpheniramine + guaifenesin/bromhexine. Drugs like mucolytics which increase mucus secretions should not be combined with chlorpheniramine which dries up the secretion. A fever may not accompany cold and cough so the patient is unnecessarily exposed to paracetamol induced hepatotoxicity.

This could be a result of the fact that they are so well known to the common public as they are used by almost everyone and are sold maximally over the counter without the need of any prescriptions or visiting a physician thus accumulating more revenue for the pharma company whereas drugs belonging to the classes like bronchodilators which are not commonly prescribed and are needed by selective populations. This also leads us to suggest that more legal emphasis should be placed on over the counter drugs with are sold without prescription and are common knowledge to the population as the chances of irrational combinations being sold are extremely high.

The uncontrolled growth of such combinations in India is also due to the brainwave of marketing heads of pharmaceutical companies. Gullible doctors are easily deceived by marketing ads like 'ibuprofen for pain and paracetamol for fever' and 'ibuprofen for peripheral action and paracetamol for central action'. [7]

Also in spite of issuing laws they are not being followed – For instance, certain FDCs like analgen + pitofenone, vitamins B1 + B6 +B12, cyproheptadine + lysine, etc. that were banned by the authorities continue to be readily available in the marketplace. [7]

The patient is the one who suffers amidst the problem created due to negligence on the account of doctors and the government. The patient has to not only pay in terms of money required to buy the FDCs but also terms of possible detriments to his or her health due to adverse drug interactions. The study conducted by Desai P et al showed that on comparing the retail prices of cough and cold irrational combinations showed that irrational FDCs led to increasing the financial burden on the consumer thus causing wasteful expenditure in the economy. [18]

Stringent laws are required to counter this explosion of irrational FDCs in the market. As per the Ranjit Roy Choudhury Expert Committee in 2013, an urgent review of the drugs in the Indian market was

recommended and suggested that majority of the 85 000 drug formulations available in India should not be marketed at all. [22]

However just recommendations are not enough. The current India Drug Act of 1945 has loopholes that pharma companies use to evade CDSCO approval for FDCs which needs to be reviewed immediately. [20, 23] A new Drug Act is the need of the hour.

As for our role in the fight against these irrational FDCs, hospitals should constitute drugs therapeutics review committees to rationalize prescribing by doctors and medical schools and postgraduate colleges must train students and young doctors how to assess new drug combinations more logically as opposed to prescribing them blindly. [24, 25]

The presence of irrational FDCs is not just limited to India. It is thus necessary that all medical practitioners raise this matter vociferously on all possible platforms to ensure that drug regulatory bodies take urgent action to mitigate this free flow of irrational FDCs.

A possible limitation of this study is that actual prescriptions were not taken from practicing physicians in the hospital as studies show physicians prescribing antibiotics for URTI with no evidence of bacterial infections [26, 27] which thus may not provide the exact situation which could be worse with the added load of the unnecessary antibiotics for viral URTIs.

CONCLUSION

Rationality assessment of the FDC preparations revealed that most of the preparations were irrational and had no documented benefit in the treatment of URTI. Expectorants on the other hand have maximum number of irrational generic combinations and a high number of irrational formulations whereas least irrational generic combinations were found among bronchodilators.

Availability of such a large number of irrational FDCs for cough and cold requires serious review of the legal provisions in Indiato ensure implementation of CDSCO guidelines on the industries for manufacture of well-known over the counter drugs which are commonly sold without prescriptions.

A rational approach needs to be adopted by key players (i.e., companies, regulatory agencies, academicians and physicians) to ensure that irrational FDCs never see the light of the day. We also lay emphasis over sensitizing the medical professionals to the magnitude of this problem so that they make a conscious effort to prescribe rational FDCs only as the irrational drugs have no support in any literature and legal action can be taken against them.

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