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Evaluation of Rationality of Selected Antimicrobial Fixed Dose Combination Used in Indian Population

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Abstract: ***To analyse the rationality of selected antimicrobial FDCs used in the Indian market and to find out irrational FDCs existing in Indian market. The rise in illogical fixed dosage combinations is causing considerable worry. They place an unwarranted financial burden on patients, raise the risk of negative drug reactions, and significantly lower quality of life. The patient must receive medication that is appropriate for their clinical needs, in a dose that meets their unique requirements, for an adequate amount of time, and at the least expensive cost to them and their community. FDCs are classified as new medications since the effectiveness, safety, and bioavailability profiles change when two or more pharmaceuticals are combined into a single formulation. In India prescribing rational FDC is very important in medical practice, reason being majority of them are available freely in Indian market. Since large number of FDC are being manufactured every year, knowledge and evaluation of FDC available in the market is becoming increasingly important for better health outcomes.***

Keywords: Antimicrobial, irrational, Rational

1. Introduction

Fixed Dose Combinations (FDCs) relate to medications having two or more active components used for a specified indication. As per Rule 122-E of Drugs & Cosmetics Rule, A fixed dose combination of two or more drugs, individually approved earlier for certain claims, which are now proposed to be combined for the first time in a fixed ratio, or if the ratio of ingredients in an already marketed combination is proposed to be changed, with certain claims, viz. indications, dosage, dosage forms (including sustained release dosage form) and route of administration are considered new drugs. Further, a new medicine shall continue to be classified as new drug for a period of four years from the date of its first approval or its inclusion in the Indian Pharmacopoeia.

When the combination outperforms a single medication provided independently in terms of therapeutic efficacy or safety, FDC is approved. More and more doctors favour FDCs due to increased patient compliance. As a result, pharmaceutical firms take advantage of this excellent opportunity and promote an increasing number of combinations, many of which are irrational.
Guidelines for approving FDCs were established by the Central Drug Standard Control Organization in August 2010, with an emphasis on the justification for combining medications in a certain ratio. Yet, there isn't a verified tool accessible to judge the reasonableness. The goal of the current study was to develop a technique to evaluate the efficacy of antimicrobial (AM) products offered on the Indian market.

2. Material and Methods

Study design: Observational and cross sectional

Sample: Data on FDC's available in the Indian market was collected from Current Index of Medical Specialties (CIMS), Monthly Index of Medical specialties and IDR (Indian Drug Review)

Active pharmacological ingredient along with strength……
……

2. API
A. Approved by DCGI Yes (+1) No (−1)
B. Ingredient: Bannedor controversial
Yes(−1) No(+1)
(API = Active pharmacological ingredient, DCGI = Drug controller general of India

3. Listing in EML WHO/National/Both/None
(+1) (0)

4. Efficacy (text book/reference book/pub med/Medline/ other)
1 API Yes (+1) No (0)
2 FDC Yes (+1) No (0)
(API = Active pharmacological ingredient, FDC = Fixed dose combination)

5. Safety (textbook/reference book/pub med/Medline/other)
1 API Yes (+1) No (0)
2 FDC Yes (+1) No (0)
(API = Active pharmacological ingredient, FDC = Fixed dose combination)

6. Pharmacokinetic (absorption/distribution/metabolism/ excretion/BA/BE/t ½)
•Interaction: Favorable/Unfavorable/Not affected
(+1) (−1) (0)

7. Pharmacodynamic-M/A of each ingredient Similar (0)/Different (+1)

8. Advantage of FDC
• Reduced Yes (+1)/No (0)
• Less ADR Yes (+1)/No (0)

•Convenient (frequencyor pill count)Yes (+1)/No (0)
Total score: 12 Score ≥7: Rational
FDC Score ≤6: Irrational FDC
Figure:1Tool to assess the rationality of fixed dose combinations available in Indian market

3. Methods

A pretested tool was used to analyses the rationality of FDCs based on their pharmacodynamic activity, pharmacokinetic parameters, and significant drug interactions caused by API (Active Pharmaceutical Ingredients) present in the product. These FDCs are listed in the WHO Essential List of Medicines and the National List of Essential Medicines (NLEM). The information was gathered from the "Indian Drug Review" (IDR), an annual Drug Compendium that lists the majority of the medications that were sold commercially in India that year, in both 2021and 2022. The WHO model list of the EML and the NLEM was used for the assessment of the first criteria. The dose of the individual APIs was verified from standard textbooks and Martindale Extra Pharmacopoeia.

The published data regarding clinical evidence of safety and efficacy were collected from databases such as clinical site of government of India, PubMed, Medscape, and the Cochrane library. The cost data of individual components, as well as the FDCs, were obtained from the Indian Drug Review, Jan 2021 and ref Rx (ref Rx is a drug information/ reference book published monthly basis just like CIMS, IDR (Indian Drug Review), July–October 2022. The information enter into an Excel spreadsheet.

By using common textbooks and reference books, it was possible to look for the proof of the individual ingredient's safety and effectiveness for a set dose combination.

The criteria were rated using follows: plus (+1) for positive, minus (-1) for negative or unfavorable conditions. If the score was greater than 7, it was deemed to be reasonable; otherwise, it was deemed to be irrational.

4. Result

86 FDCs are antimicrobial include. There were a total of 51 irrational, with 35 being rational. The average antimicrobial FDC had a logic score of **6.360**. The majority of antimicrobials (68) included two active pharmacological components, 16 contained three, and four contained two.20 antimicrobial FDCs mentioned in the WHO EML, the rationality score was > 10 [Table 3]. There were also 2 other antimicrobial FDCs that, according to the tool, scored below 8.

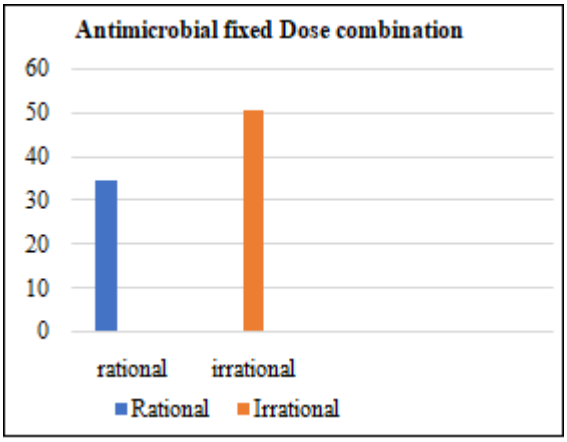

Figure 2: Rational and irrational fixed dose combination in both categories

51 of the 86 AM FDCs were irrational, while 35 were sensible. 20 rational FDCs were mentioned in the WHO EML 2021.18 FDCs mention in the NLEM. Antibiotic and antiretroviral drugs made up the majority of the rational AM FDCs (13, 18). Only 17 of reasonable FDCs showed advantages of less adverse drug reactions (ADRs) when combined compared to the individual ingredients in terms of favourable pharmacokinetic interactions.

Table 1: Assessment of antimicrobial FDCs using Rationality tool

S. no	Parameters	Antimicrobials FDCs (n=86)
1	Mean rationality score	6.36
2	Minimum score	2
3	Maximum score	12
4	Number of rational FDCs	35
5	Number of irrational FDCs	51
6	Number of API in Each FDCs	
	2	68
	3	16
	4	2
7	FDCs enlisted in WHO EML	20

Table 2: List of FDCs scored ⩾ 7(rational) as per tool and not enlisted in WHO EML2021(n=7)

S. No	Medication name
1	Cefuroxime + clavulanic acid
2	Ceftriaxone + tazobactam
3	Cefpodoxime +clavulanic acid
4	Albendazole + Ivermectin
5	Trimethoprim + sulphadoxine
6	Tenofovir + emtricitabine
7	Levofloxacin + ambroxol

Table 1 show: Assessment of antimicrobial FDCs using Rationality tool is 6.360
Table 2 Show: List of FDCs scored ≥ 7(rational) as per tool and not enlisted in WHO EML2021(n=7)
Table 3 Show: List of FDCs scored ≥ 7 (rational) as per tool and enlisted in WHO EML 2021 (n=20)

Table 3: List of FDCs scored ≥ 7 (rational) as per tool and enlisted in WHO EML 2021 (n=20)

S. No	Medication name
1	abacavir + lamivudine
2	atazanavir + ritonavir
3	ceftazidime + avibactam
4	daclatasvir + sofosbuvir
5	dolutegravir + lamivudine + tenofovir
6	meropenem + vaborbactam
7	piperacillin + tazobactam
8	levodopa + carbidopa
9	sofosbuvir + velpatasvir
10	Lopinavir + ritonavir
11	zidovudine + lamivudine
12	Levodopa + carbidopa
13	sulphadoxine + pyrimethamine
14	Rifampicin + Isoniazid + Pyrazinamide
15	ferrous salt + folic acid
16	ticarcillin + clavulanic acid
17	Zidovudine +Lamivudine+Nevirapine
18	tenofovir + emtricitabine +efavirenz
19	efavirenz +Lamivudine +tenofovir
20	ledipasvir +sofosbuvir

The majority of unreasonable AM FDCs (51, 51%) were combinations of antibiotics (25), antivirals (17), cephalosporin plus beta-lactamase inhibitor, anti-amoebic, anti-fungal, and antiparkson, as well as antibacterial with lactobacilli or serratiopeptidase.

5. Discussion

In our study, 51 irrational antimicrobial as FDCs. 35 of the FDC contained rational FDCs. The rational AM FDCs were antiretroviral and antibacterial class of drugs with proven efficacy, safety, pharmacokinetic and pharmacodynamic advantages. While 51% of AM FDCs were irrational, with no justification of combining the ingredients .The most serious issue with irrational FDCs was their illogical antibacterial and corticosteroid combination, which lowers immunity and makes people more susceptible to infections. Moreover, combining cephalosporin with a beta lactamase inhibitor is not justified because the latter broadens the antibacterial spectrum of the former by preventing the degradation of the beta lactam ring in the penicillin family of medicines. They, however, are ineffective against cephalosporins with a broader spectrum, such as ceftazidime, ceftriaxone, and cefotaxime. Many AM FDCs included antibacterial, antiamoebic, and/or antifungal drugs in trendy combinations. Seldom do amoebic and bacterial infections overlap, and this promotes resistance while also putting patients at unnecessary risk for negative treatment effects.

The availability of such items lessens attempts to make an accurate diagnosis and only raises the price of treatment. It is common knowledge that lactobacilli can treat diarrhoea on their own. Possessed the necessary dose (5–10 billion) to reduce antibacterial-induced diarrhoea. Several FDCs also contained serratiopeptidase, an enzyme that was said to hasten the healing of inflammation. Data gathering and information about formulations offered in the Indian market came from a commercial and widely utilised annual drug compendium among prescribers. It is impossible to completely rule out the potential of incomplete information. Yet, the compendium still accurately depicts the situation regarding the country's marketed drug products.

The majority of the FDCs were judged to be cost-effective using published studies as a guide, however many of them lacked safety and efficacy. For those combinations' safety and effectiveness, more studies need to be done. In the case of antimicrobial drugs, irrational FDCs unnecessarily increase expense, side effects, and resistance. Hence, rational FDCs should be encouraged and drug regulatory bodies should take urgent action to stop the free flow of irrational FDCs. Standard criteria should be formed with the help of regulatory bodies, health-care professionals, researchers, and pharmaceutical companies for evaluating the rationality of the FDCs on an individual basis. More studies need to be conducted to evaluate rationality of the FDCs present in India by using these standard criteria.

6. Conclusion

Most of the FDCs were irrational according to criteria used only 35 FDCs were found to be rational considering safety and efficacy as most important criteria for rationality. So drug regulatory bodies should take urgent action stop the free flow of irrational FDCs.

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