International Journal of Basic & Clinical Pharmacology
*Srivastava R et al. Int J Basic Clin Pharmacol. 2022 Mar;11(2):128-131*
http://www.ijbcp.com
pISSN2319-2003 | eISSN2279-0780

DOI: https://dx.doi.org/10.18203/2319-2003.ijbcp20220411

**Original Research Article**

# Evaluation of rationality of fixed dose combinations of antimicrobials available in Indian market

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**Received:** 22 December 2021
**Accepted:** 13 January 2022

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## ABSTRACT

**Background:** The antimicrobial resistance is alarming at present. One of the important factors for resistance is use of irrational fixed dose combinations. Thus, objective was to critically analyze the rationality of FDCs of antimicrobial agents currently available in India.
**Methods:** The FDCs of AMAs enlisted in Indian Drug Review 2019 were analyzed by 8 point criteria tool. Analysis includes number of active pharmacological ingredients, approval by central drug standard control organization, listing in world health organization model list of essential medicines (2019) or Government of India national list of essential medicines (2015). Literature search was used for assessing efficacy, safety, pharmacokinetic and pharmacodynamic interactions and advantages of each FDC. Each criterion was assigned score one, if positive and minus one, if negative leading to total score of 12. FDC with score of ≥7 was considered as rational.
**Results:** The FDCs of AMA available in Indian market were 116 while FDCs included in WHO model list, 2019 were 24. Majority of FDCs available were irrational that include combination of antibacterial with bromhexine, carbocisteine, ambroxol, serratiopeptidase, antiamoebic and antifungal etc. Most of the rational FDCs belong to antiretroviral, antitubercular and antimalarial drugs.
**Conclusions:** Most of the FDCs of AMAs available in Indian market are irrational. These needs educating the prescribers including resident doctors. There is need to critically review such FDCs by drug regulators with strict action regarding manufacturing and marketing.

**Keywords:** Antimicrobial agents, Resistance, Fixed dose combination

## INTRODUCTION

Antimicrobial agents (AMAs) are the cream of therapeutic armamentarium as most of infections are curable in comparison to other diseases. Antimicrobial resistance is alarming at present due to various reasons. One of the important factors is use of irrational fixed dose combinations (FDCs). Guidelines for registration of fixed dose combination of medicinal products including AMAs have been introduced by world health organization, Geneva, 2005.[1] Guidelines for Industry on Fixed dose combinations in India have been issued.[2] Subsequently, Antibiotic policy was introduced by WHO; and subsequently in India to overcome antimicrobial resistance & promote rational use of AMAs. In March, 2017 (20th ed.) onwards WHO Model list categorized the antibacterial into three categories; the access, watch and reserve group to develop tools for antibiotic stewardship and to reduce antimicrobial resistance.[3] Thus, present study was undertaken to critically analyze the rationality of FDCs of AMAs currently available in the Indian market.

## METHODS

Current study is a cross sectional observational study. The FDCs of AMAs listed in Indian drug review (2019) were analyzed by 8 points criteria tool based on WHO guidelines to consider as rational FDC.[4]

Analysis includes 8 points as follows: no. of active pharmacological ingredients (API), approval by CSDSCO (DCGI), listing in WHO model list (2019)/ Government of India NLEM (2015), efficacy, safety, pharmacokinetic interactions, pharmacodynamic interactions and advantages of each FDC. Literature search using standard textbooks, reference books, websites such as Pubmed; and also opinion from experts and academician as per the requirement was used for assessment of above mentioned parameters as applicable.

### *Details of WHO 8 points criteria tool to assess rationality*

Active pharmacological ingredient (API) and strength, API approved by CDSCO; (+1) if yes, (-1) if no, banned ingredient; (-1) if yes, (+1) if no, whether listed in either WHO model list or NLEM or both; (+1) if yes, (0) if no, efficacy API, (+1) if yes, (0) if no, FDC; (+1) if yes, (0) if no, safety API; (+1) if yes, (0) if no, FDC; (+1) if yes, (0) if no, pharmacokinetic (A/D/M/E/BE/BA/t½) interaction; (+1) if favourable, (-1) if unfavourable and (0) if no change, pharmacodynamic mechanism of action of each ingredient, advantage of FDC, dose of individual ingredient reduced; (+1) if yes, (0) if no, less adverse effect; (+1) if yes, (0) if no, reduced frequency (convenient); (+1) if yes, (0) if no, each criterion was scored one for positive; minus one for negative and zero as appropriate. Total maximum score (12); score ≥7: rational; score ≤ 6: irrational.

## RESULTS

The numbers of FDCs of AMAs available were 116 out of which 92 (79.3%) FDCs were having two active pharmacological ingredient and 23 (19.8%) with 3 active pharmacological ingredients. Based on WHO criteria, 31 (26.7%) FDCs were rational and 85 (73.3%) were irrational (Table 1). The minimum rationality score was 02 and mean rationality score was 4.25 (Table 1). Rational FDCs included only in WHO MLEM (2019) were ten while FDCs included only in NLEM (2015) were 2 (Table 3). Out of 31 rational FDCs twenty-two rational FDCs were included in both WHO- MLEM (2021) and NLEM (2015) (Table 2); while nine FDCs though rational but were not included in either of essential list and these include antibacterial FDCs, antiHIV FDC and FDCs of anthelmintic drugs (Table 4). Some of the FDCs of antibacterial, antiviral and antimalarial drugs though included in WHO-MLEM (2021) and NLEM (2015) but not marketed in India (2015). Most of rational FDCs were penicillins, cephalosporins, antitubercular and antiretroviral drugs.

**Table 1: Rationality assessment of antimicrobials available in the Indian market.**

| Parameters | FDCs |
|---|---|
| **Total number available** | 116 |
| **With 2 API in each FDC, N (%)** | 92 (79.3) |
| **With 3 API in each FDC, N (%)** | 23 (19.8) |
| **With 4 or more API in each FDC** | 01 (antitubercular included in WHO list) |
| **Rational, N (%)** | 31 (26.7) |
| **Irrational, N (%)** | 85 (73.3) |
| **Minimum rationality score** | 02 |
| **Maximum rationality score** | 12 |
| **Mean rationality score** | 4.25 |

**Table 2: Rational FDCs available in Indian marked and included in essential drug list.**

| Parameters | Observation |
|---|---|
| **Total rational FDCs included in WHO MLEM (2019)/NLEM (2015)** | 22 |
| **Rational FDCs included in both WHO MLEM (2019) and NLEM (2015)** | 10 |
| **Rational FDCs included in WHO MLEM (2019) only** | 10 |
| **Rational FDCs included in NLEM (2015) only** | 2 |
| **Total rational FDCs not listed in WHO MLEM (2019)/NLEM (2015)** | 9 |

**Table 3: List of rational FDCs (score ≥7) of AMAs available in Indian market and listed in WHO-MLEM and NLEM India**

| FDCs listings | |
|---|---|
| **FDCs listed in both WHO-MLEM and NLEM India (N=10)** | **FDCs listed only in WHO MLEM (N=10)** |
| Amoxicillin+clavulanic acid, sulphamethoxazole+ trimethoprim, piperacillin+tazobactam, atazanavir+ritonavir, lopinavir+ritonavir, efavirenz+lamivudine+ tenofovir,lamivudine+nevirapine+zidovudine, lamivudine+zidovudine, artemether+lumefantrin, sulfadoxine+pyrime-thamine | Imipenem+cilastatin, ethambutol+isoniazid, ethambutol+isoniazid+ pyrazinamide+rifampicin, ethambutol+isoniazid+rifampicin,isoniazid+pyrazinamide+rifampicin, Isoniazid+rifampicin, efavirenz+emtricitabine+tenofovir, emtricitabine+tenofovi, artesunate+amodiaquie artesunate+mefloquine |
| **FDCs listed only in NLEM India (N=2 )** | |
| Lamivudine+nevirapine+stavudine, lamivudine+ stavudine | |

Irrational FDCs include combination of antibacterial with other antibacterial such as ampicillin/amoxicillin with cloxacillin, antibacterial with bromhexine/carbocisteine/ ambroxol and antibacterial with antiamoebic/antifungal agents.

**Table 4: List of rational FDCs (score ≥7) of AMAs not included in WHO-MLEM/NLEM.**

| Rational FDCs |
|---|
| **Ampicillin+sulbactam** |
| **Ticarcillin+clavulanic acid** |
| **Cefotaxime+sulbactam** |
| **Cefoperazone+sulbactam** |
| **Ceftriaxone+sulbactam** |
| **Lamivudine+stavudine+efavirenz** |
| **Ivermectin+albendazole** |
| **Clindamycin+isotretinoin** |
| **Albendazole+ivermectin** |

**Table 5: List of FDCs not manufactured in India though included in WHO-MLEM and NLEM India.**

| List of FDCs |
|---|
| **Both in WHO and National list** |
| Abacavir+lamivudine |
| **Only in WHO list** |
| Isoniazid+pyridoxine+sulphamethoxazole+ trimethoprim, artesunate+pyronaridine, dihyroartemisinin+piperaquine |
| **Only in National list** |
| Lamivudine+ tenofovir, artesunate+sulfadoxine+ pyrimethamine |

## DISCUSSION

Fixed dose combinations of antimicrobial agents are the formulations of two or more drugs combined as one product. The advantages of FDCs are increased efficacy synergistically, broadening of spectrum and reduction is development of resistance. However, FDCs of AMAs may contribute to subtherapeutic concentration of one or both components of AMAs. The clinical effectiveness is reduced due to resistant strain arising because of use of such irrational FDCs.

The present study reveals that most of the FDCS of antimicrobial agents marketed in India were irrational and these were not compatible with WHO-MLEM and NLEM of India. Their mean rationality score was 4.5 (poor). The irrational FDCs were 73.3% and there was no justification of combing the ingredients in such FDCs and there was no pharmacological basis. The rational antimicrobial FDCs were antibacterial penicillins and cephalosporins with beta lactamase inhibitors, antitubercular drugs and antiretroviral drug. These are also included in WHO model list of essential medicines (MLEM) as well as National List of Essential Medicines (NLEM).[5]

Similar results were show by study of prescribing pattern of FDCs among practitioners by Rayasam et al and Shah et al.[3,6,7] Irrational FDCs include combination of antibacterial with other antibacterial drugs such as ampicillin/amoxicillin with cloxacillin, antibacterial with mucolytics such as ampicillin/ amoxicillin with bromhexine/carbocisteine/ambroxol. Moreover, antibacterial were also combined with antiamoebic drugs and antifungal drugs which are irrational. Serratiopeptidase is enzyme not effective orally and literature search including standard textbooks have not shown its absorption by oral route in human beings except one study that showed that the orally administered serratiopeptidase gets absorbed from the gut of rat and entered into the circulation in active form; thus, it is of doubtful utility.[8] This enzyme is also included in FDC with antibacterial agents such as amoxicillin+ cloxacillin+serratiopeptidase, roxithromycin+serration-peptidase, clarithromycin+serratiopeptidase.[10] These FDCs are neither mentioned in NLEM of India nor in latest edition of WHO-MLEM.

These FDCs increase the cost of treatment and expose the patient to adverse effects without any significant benefit. Further, FDCs of more than 3 drugs is usually not required and considered irrational based on US-FDA except some FDCs of antitubercular drugs such as ethambutol+isoniazid+ pyrazinamide+rifampicin which is approved and listed in MLEM (2019).

## CONCLUSION

Based on the present analysis, it is concluded that most of the FDCs of AMAs are available in India are irrational. Thus, there is need to educate prescribers including resident doctors, to critically review the marketing of such FDCs by drug regulators in India; and take appropriate action to prevent mushrooming of irrational formulations and ultimately the AMA resistance.

## ACKNOWLEDGEMENTS

The authors would like to thank all the staff, department of Pharmacology and general medicine, government medical college, Surat for their constant valuable support and suggestions to successfully complete this study.

*Funding: No funding sources*
*Conflict of interest: None declared*
*Ethical approval: The study was approved by the Institutional Ethics Committee*

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**Cite this article as:** Srivastava R, Kantharia ND. Evaluation of rationality of fixed dose combinations of antimicrobials available in Indian market. Int J Basic Clin Pharmacol 2022;11:128-31.