ASIAN JOURNAL OF PHARMACEUTICAL AND CLINICAL RESEARCH

INNOVARE ACADEMIC SCIENCES
Knowledge to Innovation

Vol 17, Issue 6, 2024

Online - 2455-3891
Print - 0974-2441

Research Article

AN ANALYSIS OF ANTIMICROBIAL AND ANTIDIABETIC FIXED DOSE COMBINATIONS BANNED IN INDIA

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Received: 25 February 2024, Revised and Accepted: 10 April 2024

ABSTRACT

Objective: National regulatory authority reviewed various fixed-dose combinations (FDCs) in view of doubtful rationality status and subsequently 349 FDCs were banned in 2018. This study was conducted to analyze the antimicrobial and antidiabetic FDCs banned by the Central Drugs Standard Control Organization in India.

Methods: Data were collected from the report of drugs technical advisory board subcommittee. Banned antimicrobial and antidiabetic FDCs were assessed for the following parameters – number of active pharmacological ingredients, routes of administration and dosage forms, indications for marketing, reasons for banning, and pharmacological group of FDCs.

Results: Seventy antimicrobial and 25 antidiabetic FDCs were analyzed. These FDCs contained 2–7 drugs, available mostly as tablets (51.42%, 100%) in antimicrobial and antidiabetic groups, respectively. Antimicrobial FDCs were marketed most for respiratory tract infections and infection and inflammatory conditions of the skin (17, 24.28% each) while antidiabetic FDCs were marketed for Type 2 diabetes mellitus (14, 56%). The reasons for ban were pharmacodynamic (68.57%, 16%) and pharmacokinetic (20%, 40%) mismatches, lack of evidence of efficacy (7.14%, 36%), and safety concerns (4.28%, 8%) in antimicrobial and antidiabetic groups, respectively. In antimicrobial FDCs, the most common combination was that of an antibacterial with other miscellaneous drugs (like zinc, Vitamin E, serratiopeptidase, etc.) (19, 27.14%) whereas antidiabetic FDCs most commonly had biguanide with thiazolidinedione and sulfonylurea (7, 28%).

Conclusion: There is a need for scrutiny of other FDCs in larger interests of patient care and prescribers should be made aware about recently banned FDCs to promote rational pharmacotherapy.

Keywords: Central drugs standard control organization, Banned drugs, Rational pharmacotherapy, Drugs technical advisory board subcommittee.

 DOI: http://dx.doi.org/10.22159/ajpcr.2024v17i6.50741. Journal homepage: https://innovareacademics.in/journals/index.php/ajpcr

INTRODUCTION

A combination of more than one drug at a fixed ratio in a single dosage form prescribed for a particular indication is considered as a fixed-dose combination (FDC) [1]. Central Drugs Standard Control Organization (CDSCO) defines FDCs as products containing two or more active ingredients used for a particular indication(s) [2]. The FDCs provide some advantages such as potentiating therapeutic efficacy, decreasing the incidence of adverse effects and resistance to drugs, convenience to the patients and better compliance amongst them, and cost-saving as compared to the individual drugs. Unfortunately, these FDCs have some disadvantages such as increased side effects and cost of treatment when patient does not need all the drugs present in a combination, pharmacokinetic mismatch, dose titration of individual drugs is not possible, and drug interactions, leading to a decrease in therapeutic efficacy [3].

The manufacturing and marketing of FDCs have been flourishing in Indian pharmaceutical market in the last few years. More than 6300 FDCs are available in India until date [1]. The reason behind such huge availability of FDCs and their rampant usage is liberal licensing system [4]. In India, the Drugs and Cosmetics Rules, 1945 under the Drugs and Cosmetics Act, 1940 regulate the manufacture, sale, and distribution of FDCs. CDSCO approves the FDCs after checking for rationality, safety, and efficacy data. Then the state licensing authority (SLA) grants permission for marketing [1].

However in the past, SLA issued the license without seeking approval from CDSCO which led to questioning of rationality of such FDCs and increase in irrational prescriptions. Hence, the Central government constituted an expert committee headed by Professor C. K. Kokate to examine the safety and efficacy of such FDCs. In accordance with the report submitted by the Kokate committee and the judgment given by the Hon. Supreme court, CDSCO formed a drugs technical advisory board (DTAB) subcommittee for in-depth analysis of these FDCs which led to banning of 349 FDCs in 2018 [5].

The most popular and highly profitable FDCs marketed in India are analgesics, antimicrobials, cough, and cold preparations, drugs for hypertension, diabetes, dyslipidemias, etc, multivitamins, and antacids [4]. As per the World Health Organization, antimicrobial resistance (AMR) is one of the top 10 global public health threats; its main drivers being misuse and overuse of antimicrobials [6]. About 422 million people worldwide have diabetes, a chronic metabolic disease usually associated with some comorbidity and majorly prevalent in low and middle-income countries. This requires combination therapy of oral hypoglycemic agents with or without insulin along with drugs for treating comorbidities [7]. Furthermore as per the American diabetes association, the risk of Type 2 diabetes mellitus increases as age increases and geriatric patients generally suffer from multiple diseases which ultimately leads to polypharmacy [8]. Irrational FDCs increase the development of AMR, risk of adverse effects, unnecessary financial burden, and decrease therapeutic efficacy and the quality of life.

Hence, the present study was done with the objective to analyze the antimicrobial and antidiabetic FDCs banned by CDSCO in India.

METHODS

Data were collected from the report of DTAB subcommittee obtained from the official website of CDSCO. From this data, banned antimicrobial and antidiabetic FDCs were assessed for the following parameters:

1. Number of active pharmacological ingredients
2. Routes of administration and dosage forms
3. Indications for marketing
4. Reasons for banning and
5. Pharmacological group of FDCs.

Data was analyzed using descriptive statistics on Microsoft Excel 365. Additional information regarding FDCs was obtained from the standard textbooks of pharmacology and articles published and available on authentic online sources of drug information such as PubMed and Google Scholar.

RESULTS

A total of 349 FDCs were banned by CDSCO. Out of these, we analyzed 70 (20.05%) and 25 (7.16%) FDCs belonging to antimicrobial and antidiabetic groups, respectively.

The number of active pharmacological ingredients in these groups of FDCs ranged from two to seven. The majority of antimicrobial FDCs (28, 40%) contained two ingredients whereas 13 (52%) antidiabetic FDCs had the highest of three drug combinations (Fig. 1).

The banned antimicrobial FDCs were available in different dosage formulations administered through various routes of administration (Fig. 2). All antidiabetic FDCs (n=25) were available as tablet formulations.

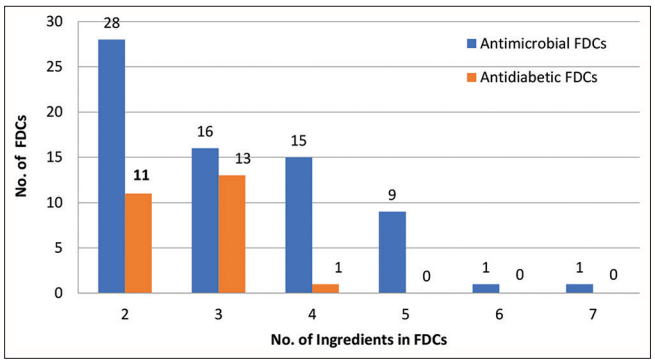

Fig. 1: Number of ingredients in antimicrobial and antidiabetic group of fixed-dose combinations

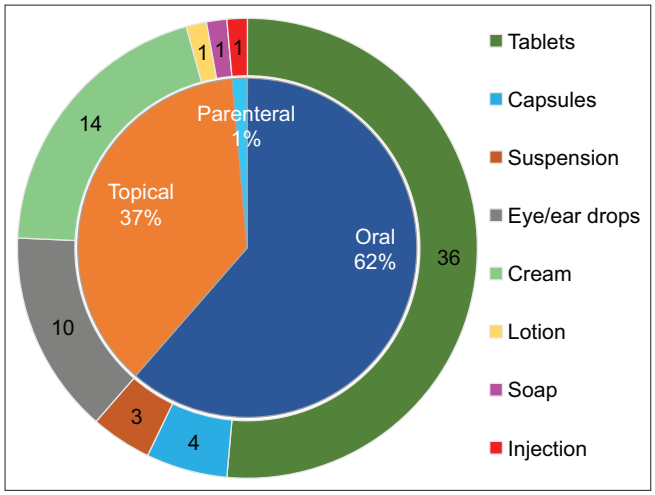

Fig. 2: Routes of administration with dosage forms of banned antimicrobial fixed-dose combinations

Antimicrobial FDCs were marketed most commonly for respiratory tract infections and Infection and inflammatory conditions of the skin (17, 24.28% each) followed by gastrointestinal tract infections (14, 20%) (Fig. 3). 14 out of 25 antidiabetic FDCs (56%) were indicated for the treatment of Type 2 diabetes mellitus whereas 5 (20%) were used as second-line therapy for Type 2 diabetes mellitus (Fig. 4).

The most common reason for banning antimicrobial FDCs was pharmacodynamic mismatch (48, 68.57%) whereas only four FDCs (16%) from the antidiabetic group were banned for this reason. Out of 25, 10 antidiabetic FDCs (40%) were banned due to pharmacokinetic mismatch and this was the second most common reason for banning antimicrobial FDCs i.e., (14, 20%). The other reasons for ban of FDCs were lack of evidence of efficacy and safety concerns (Fig. 5).

As shown in Tables 1 and 2, different drug groups were combined in the formulations of banned antimicrobial and antidiabetic FDCs.

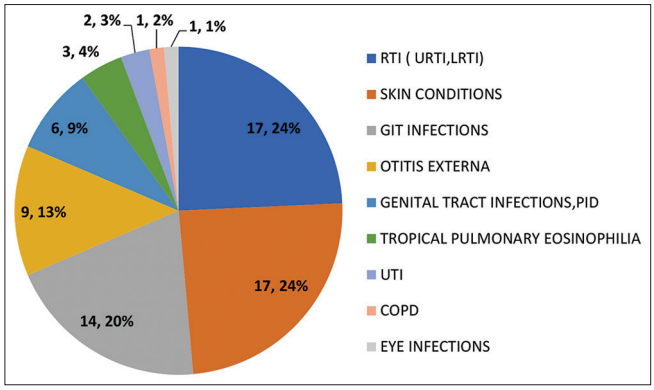

Fig. 3: Indications for marketing of antimicrobial fixed dose combinations

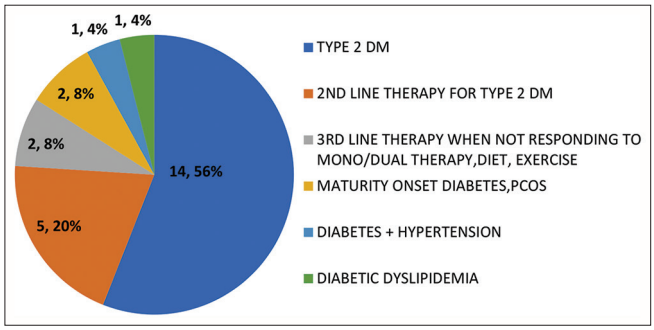

Fig. 4: Indications for marketing of antidiabetic fixed dose combinations

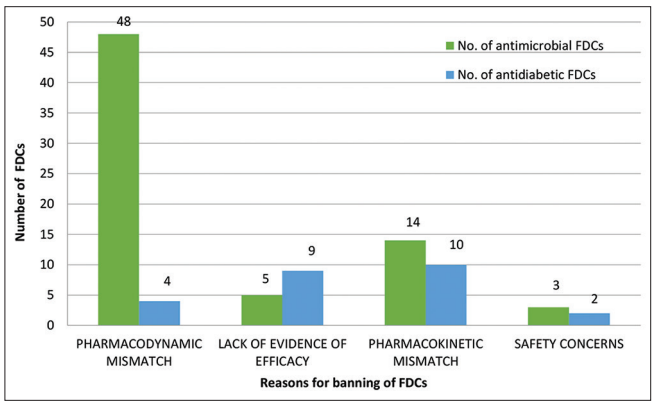

Fig. 5: Reasons for banning of antimicrobial and antidiabetic group of fixed dose combinations

Table 1: Combination of different pharmacological drug groups in banned antimicrobial FDCs

Sr. no.	Pharmacological Group of FDCs in antimicrobial group	No. of FDCs with %
1.	Antibacterial+Others	19 (27.14)
2.	Antibacterial+Antifungal+Steroid+Others	17 (24.28)
3.	2 Antibacterials	11 (15.71)
4.	Antibacterial+Antifungal+Steroid	7 (10.00)
5.	Antibacterial+Mucolytic	6 (8.57)
6.	Antibacterial+Antifungal+Others	3 (4.28)
7.	Antifilarial+Others	3 (4.28)
8.	Antibacterial+Steroid	2 (2.85)
9.	Antiprotozoal+Antimotility+Others	2 (2.85)

Others – Zinc, Chlorocresol, Vitamin E, Serratiopeptidase, Lactic acid bacillus, nonsteroidal anti-inflammatory drugs, Urinary analgesic, Local anesthetic, angiotensin receptor blockers, Anti-amoebic, Demulcents, Antihistaminic, Expectorants. FDCs: Fixed-dose combinations

Table 2: Combination of different pharmacological drug groups in banned antidiabetic FDCs

Sr. no.	Pharmacological group of FDCs in antidiabetic group	No. of FDCs with %
1.	Biguanide+Thiazolidinedione+Sulfonylurea	7 (28)
2.	Biguanide+Others	5 (20)
3.	Thiazolidinedione+Biguanide	4 (16)
4.	Sulfonylurea+Biguanide	3 (12)
5.	Biguanide+Sulfonylurea+Others	2 (8)
6.	Biguanide+Sulfonylurea + α-glucosidase inhibitor	1 (4)
7.	α-glucosidase inhibitor+Biguanide+Others	1 (4)
8.	α-glucosidase inhibitor+Thiazolidinedione+Biguanide	1 (4)
9.	Biguanide+Thiazolidinedione+ Sulfonylurea+Others	1 (4)

Others - Angiotensin receptor blockers, Vitamin B1, Chromium Picolinate, Vitamin B12, Dopamine D2 agonist, Statin. FDCs: Fixed-dose combinations

In antimicrobial FDCs, most common combination was that of an antibacterial with other miscellaneous drugs (like zinc, Vitamin E, non-steroidal anti-inflammatory drugs [NSAIDs], etc.) (19, 27.14%) followed by the combination of antibacterials with antifungal, steroid and other miscellaneous drugs (17, 24.28%). In antidiabetic FDCs, the most common combination was that of three different classes of oral hypoglycemic agents, that is, Biguanide + Thiazolidinedione + Sulfonylurea (7, 28%) followed by the combination of a biguanide with other miscellaneous drugs (like angiotensin receptor blockers [ARBs], Vitamin B_1, Vitamin B_{12}, dopamine D_2 agonist etc.) (5, 20%).

DISCUSSION

The evaluation of efficacy, safety, and rationality of a drug or combination of drugs (FDCs) is done by the national regulatory authority of India, that is, CDSCO. A drug or an FDC is banned if its benefits do not outweigh the risks and is found to be irrational. Our study analyzed antimicrobial and antidiabetic FDCs banned by CDSCO on the basis of various parameters mentioned.

In our study, we analyzed 95 FDCs out of which 70 (20.05%) were antimicrobial and the rest 25 (7.16%) were antidiabetic FDCs. In antimicrobial group of FDCs, the number of ingredients ranged from two to seven. The majority of them (28, 40%) contained two ingredients followed by three ingredients in 16 (22.85%) FDCs and 4 in 15 (21.42%) FDCs. The most common combination of two ingredients were that of two different antibacterials such as azithromycin with levofloxacin/ofloxacin, cefixime with linezolid, etc. This causes unnecessary exposure to antibacterials increasing the risk of developing resistance. We also found antimicrobial FDCs with six and seven ingredients having bizarre combinations like antibacterials along with antifungal, steroid, NSAID, and a local anesthetic agent, that is, Chloramphenicol + Lignocaine + Betamethasone + Clotrimazole + Ofloxacin + Antipyrine. More the number of ingredients more are the chances of drug-drug interactions. Although there is no rule stating the maximum number of active ingredients in an FDC, US FDA does not recommend a combination of >3 ingredients [9]. In antidiabetic FDCs, there were 13 combinations (52%) having three ingredients followed by 11 FDCs (44%) having 2 and only 1 FDC (4%) having four ingredients, that is, Metformin + Gliclazide + Pioglitazone + Chromium Polynicotinate.

The banned antimicrobial FDCs were available in oral, topical, and parenteral preparations. These were a combination of different groups of drugs marketed for various indications. The most common oral dosage form was tablets (36, 51.42%) and this can be correlated to the indications for which the FDCs were marketed such as respiratory tract infections (17, 24.28%) and gastrointestinal tract infections (14, 20%), etc. Many patients of respiratory tract infections are treated with largely antibiotics, although the majority of them are caused due to viruses. The probable reason could be the treating physician adds the antibiotic for the prevention of secondary bacterial infections which can cause increase in bacterial resistance and unwanted side effects [10]. Topical dosage forms like cream (14, 20%) and eye/ear drops (10, 14.28%) were marketed for Infection and inflammatory conditions of the skin (17, 24.28%) and conjunctivitis/otitis externa (9, 12.85%), respectively. Details about other dosage forms and marketing indications are depicted in Figs. 2 and 3. As shown in Table 1, many different groups of drugs were combined with antimicrobials. We have shortlisted some examples giving explanation for their irrational combination. FDCs of topical preparations containing combinations of antibacterial with antifungal and steroids are irrational and are similar to the findings of Rayasam *et al*. [11]. Patients almost never need all of these drugs together as the infections are either bacterial fungal or viral and not likely to be mixed. Furthermore, routine use of potent steroids should be restricted to severe or unresponsive inflammatory conditions of the skin such as eczema and psoriasis. [3]. Another example is that of combinations containing serratiopeptidase. The claim behind adding this enzyme to FDC was that it could promote rapid resolution of inflammation. The DTAB subcommittee experts disapproved this claim and also no such evidence in support of this was found in the standard textbooks [12,13].

Antidiabetic FDCs were marketed most for the treatment of Type 2 diabetes (14, 56%) followed by 2nd line (5, 20%) and 3rd line therapy (2, 8%), respectively. The other indications for marketing of antidiabetic FDCs are depicted in Fig. 4. Combination of three differents oral hypoglycemic agents was indicated as a second-line therapy, that is, when single drug therapy along with diet and exercise does not attain glycemic goal. Most common combination was that of biguanide with thiazolidinedione and sulfonylurea. Standard treatment guidelines for Type 2 diabetes recommend a stepwise approach [14,15]. Dual combinations of a biguanide with either sulfonylurea or thiazolidinedione or with other miscellaneous drugs like ARBs, chromium picolinate, Vitamin B_{12} etc., were present in the banned FDCs. We could not find any evidence in standard textbooks or scientific journals supporting the antidiabetic combinations containing chromium picolinate, Vitamins B_{12} and B_1. Furthermore, the standard treatment guidelines of Type 2 diabetes do not recommend these drugs as first, second, or third-line agents in combination with other oral hypoglycaemic drugs [15,16]. Instead, we found a drug interaction between metformin and Vitamin B_{12} using Medscape drug interaction checker which mentions that metformin on long-term treatment could decrease the levels of Vitamin B_{12} leading to its deficiency [17].

The antimicrobial and antidiabetic FDCs were banned by CDSCO based on the grounds of pharmacokinetic (dosing – frequency schedule) and pharmacodynamic (different therapeutic uses or antagonistic actions) mismatch, lack of evidence of efficacy, and safety concerns. The majority of the antimicrobial FDCs were banned due to pharmacodynamic mismatch (48, 68.57%). For example, the combination of furazolidone

(anti-protozoal) with metronidazole (anti-amoebic) and loperamide (anti-motility) is irrational. This is because the individual drugs have different indications. Furthermore, loperamide is contraindicated in invasive diarrheas caused by salmonella, and shigella due to the risk of toxic megacolon [16]. Only four antidiabetic FDCs had pharmacodynamic mismatch. One such example is addition of Vitamin B_{12} to oral hypoglycemic drugs which is irrational as it does not provide any additive effect for the given indication [16]. Pharmacokinetic mismatch could lead to over-dosing or under-dosing of one or more ingredients in a FDC. For example, in antimicrobial group, extended-spectrum penicillin was combined with a 3rd generation cephalosporin wherein penicillin requires TDS/QDS dosing and cephalosporin requires BD dosing. In the antidiabetic group, combinations of sulfonylurea with biguanide were noted. As per literature evidence, sulfonylureas are administered before meals while metformin is to be administered after meals to avoid gastrointestinal side effects [18].

As discussed earlier, a lack of evidence of efficacy was seen in both groups of FDCs such as combinations of antimicrobials containing serratiopeptidase and antidiabetics with Vitamin B_{12}. Fortunately, safety concerns were found to be very less among both the groups which is of utmost importance before marketing the drug for use in patients.

Limitation

We did not include the 80 FDCs banned by the Central government vide gazette notification dated 11.01.2019 into our study as only the list of drugs and not their details were available on the CDSCO website. We have analyzed only the antimicrobial and antidiabetic group of FDCs. Pre-1988 approved FDCs were not analyzed as the expert committee is still examining the rationality of those FDCs.

CONCLUSION

Our findings indicate the marketing of these FDCs for common indications, their availability in almost all dosage forms, and the reasons for their banning. Many more FDCs are available in the Indian market and their critical evaluation is necessary. There is a need to increase awareness about the recently banned FDCs amongst the medical fraternity. This corrective action taken by CDSCO, Government of India toward banning of 349 FDCs is a step toward promoting rational pharmacotherapy.

ACKNOWLEDGMENT

We acknowledge Dr. Rajan Nerurkar, Professor and Head, Department of Pharmacology, T. N. Medical College and B. Y. L. Nair Ch. Hospital, Mumbai, and Dr. Ashwini Karve, Associate professor, Department of Pharmacology, T. N. Medical College and B. Y. L. Nair Ch. Hospital, Mumbai for agreeing to be potential reviewers of our study.

AUTHORS CONTRIBUTION

Conceptualization, literature review, acquiring the data, analysis, and drafting the primary manuscript were done by: Dr. Ankita Rao. Conceptualization, reviewing and corrections, and final approval of the manuscript were done by: Dr. Jitendra Hotwani.

CONFLICTS OF INTEREST

The authors have no conflicts of interest to declare.

AUTHORS FUNDING

No funding sources.

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