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Original Article

Pharmacology Section

Evaluation of Adverse Drug Reactions Due to Fixed-dose Combinations at a Tertiary Care Hospital: An Observational Retrospective Study

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ABSTRACT

Introduction: The mushrooming of Fixed-dose Combinations (FDCs) has been observed in the past decade in the Indian market. The majority of these FDCs are irrational and put patient safety at risk.

Aim: To evaluate Adverse Drug Reactions (ADRs) due to rational as well as irrational FDCs available in India.

Materials and Methods: This was an observational, retrospective study where recorded data of ADRs reported over a period of 10 years (January 2011-December 2021) at the Regional Training Centre and ADR Monitoring Centre (B.J. Medical College and Civil Hospital, Ahmedabad, Gujarat, India) was analysed. The data evaluation was carried out from May 1, 2022, to December 15, 2022. Any ADR where FDC(s) was the suspected causal drug was included in the analysis. Out of a total of 8,218 reported ADRs in the ten-year duration, 1,575 ADRs were reported to have occurred due to FDCs. The data were analysed for age, gender, System Organ Class (SOC), suspected drug, seriousness of the ADRs, causality assessment, and outcome of ADRs, and presented in terms of numbers or percentages.

Results: A total of 1,575 ADRs occurred due to 1,649 FDC(s). The most common SOC class of ADRs was Gastrointestinal (GI) disorders in 359 (23%) cases, followed by skin and subcutaneous disorders in 317 (20%). The common suspected groups were Anti-Retroviral (ARV) drugs in 787 (50%) ADRs, followed by antitubercular drugs in 298 (19%). Out of a total of 1,649 FDCs as the suspected drug, 1,551 (94%) were rational, and 98 (6%) were irrational. A total of 169 (11%) serious ADRs were reported, of which seven ADRs were due to irrational FDCs (prescribed for cold and cough). Causality assessment using the World Health Organisation-Upsala Monitoring Centre (WHO UMC) classification showed a possible causal association with the suspect FDCs for 1,385 (84%) ADRs.

Conclusion: FDCs contribute to a significant proportion of ADRs, which could be prevented by avoiding the use of irrational FDCs and monitoring the patients for the possible development of ADRs.

Keywords: Anti-retroviral drugs, Antitubercular drug, Gastrointestinal disorders, Serious adverse drug reaction, Skin and subcutaneous disorders, System organ class

INTRODUCTION

Fixed-dose Combinations (FDCs) are defined by the World Health Organisation (WHO) as combinations of two or more active ingredients in a fixed ratio of doses [1]. FDCs are used in the treatment of a wide range of conditions, such as Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome (HIV/AIDS), malaria, and tuberculosis, which are considered to be the foremost infectious disease threats in the world today [2]. An FDC is considered rational according to WHO guidelines if it meets the following criteria: the Active Pharmaceutical Ingredients (APIs) have complementary mechanisms of action, decrease the occurrence of resistance for antimicrobial agents, increase the efficacy of the combination, decrease the occurrence of Adverse Drug Reactions (ADRs) or toxicity, increase the compliance of drug therapy by reducing pill burden, and decrease the total cost of therapy. Therefore, the dose of each API should be appropriate for defining or larger groups of populations [3]. However, the majority of FDCs do not fulfill these criteria, making them irrational for usage.

Multiple studies have shown that FDCs, including irrational ones, are popular among physicians and patients, possibly due to better patient compliance and reduced pill burden [4-6]. Pharma companies also opt for FDCs to expand their portfolio of drugs as they are cheaper and quicker to combine existing active ingredients into new products. However, in their rush to deliver new and unique FDCs, manufacturers often overlook the generation of clinical safety and efficacy data, resulting in the availability of many irrational FDCs in the market [7]. The Central Drugs Standard Control Organisation (CDSCO), under the aegis of the Ministry of Health and Family Welfare, Government of India, has taken several steps to control this issue and has banned several FDCs due to their irrationality and unproven safety and efficacy [7].

On the recommendations of the Expert Committee of the Drugs Technical Advisory Board (DTAB), the Government of India confirmed the prohibition of manufacture for sale and distribution for human use of 327 FDCs through their notification dated September 7, 2018. They also revoked the ban on the FDC of Paracetamol+Caffeine+Phenylephrine+Chlorpheniramine through notification no. 697(E) dated February 5, 2019. Therefore, the current tally stands at 327 banned FDCs, primarily consisting of Non Steroidal Anti-inflammatory Drug (NSAID) combinations, FDCs for oral anti-diabetic drugs, and drugs used in the treatment of cold and cough [7]. In cases where patients are treated with these irrational FDCs, one or more drug contents of the FDCs are not relevant to the disease. This not only places a financial burden on the patient but also puts them at risk of toxicity, serious adverse effects, and drug interactions [6,8-10].

Thus, FDCs are highly popular in the Indian pharmaceutical market and have particularly flourished in recent years [11]. FDCs are expected to be preferred for the treatment of various diseases in the coming years due to their pharmacological mechanisms of action, pharmacokinetic compliance, reduction in the number of drugs, additive effects, reduced side effects, superior efficacy and tolerability, bioavailability profiles similar to monotherapy, and acceptable stability criteria [12]. Many unapproved and irrational formulations of FDCs are still available in India, with analgesics, antibiotics, multivitamins, and cough and cold preparations being the most popular and highly profitable. However, they impose unnecessary financial burden, increase the occurrence of ADRs, and ultimately reduce the quality of life [2].

There are very few studies that elaborate on ADRs due to FDC use [9,13]. ADRs due to rational as well as irrational FDCs are well-documented individually, but there is a lack of information related to ADRs specifically due to FDC use in the Indian context. This formed the basis for conducting the present study, with the aim of evaluating ADRs due to rational as well as irrational FDCs.

MATERIALS AND METHODS

This was an observational, retrospective study carried out at the Department of Pharmacology, B.J. Medical College and Civil Hospital, Ahmedabad, Gujarat, India. The department serves as a Regional Training Centre (RTC) and ADR Monitoring Centre for the Pharmacovigilance Programme of India (PvPI). The study utilised 10 years of retrospective data of ADRs reported at the centre from January 2011 to December 2021. Data evaluation was conducted from May 1, 2022 to December 15, 2022.

Inclusion and Exclusion criteria: Out of a total of 8,218 ADRs, 1,575 ADRs were reported due to prescribed FDCs and were included for analysis in the present study, excluding the rest.

Study Procedure

The ADRs were reported by resident doctors of the Pharmacology Department at the Out/In Patient Department (O/IPD) of Medicine, Surgery, Obstetrics and Gynaecology, Paediatrics, Psychiatry, Anti-retroviral (ARV) Treatment Centre, Ear Nose and Throat (ENT), Ophthalmology, Respiratory Medicine, and Skin and Venereal Disease at the affiliated tertiary care Civil Hospital over a period of ten years. This was part of the pharmacovigilance activity under the PvPI programme [13,14]. Data for each ADR was collected and filled out in an ADR reporting form [15], along with the causality assessment based on the WHO Upsala Monitoring Centre (WHO-UMC) criteria [16]. Each ADR was also reported in VigiFlow. The data was analysed for different demographic parameters, such as age, gender, and System Organ Class (SOC) [17], suspected drug group, rationality of FDCs, serious reactions (any event leading to death, life-threatening situations, prolonged hospitalisation, disability, interventions to prevent permanent impairment/damage, congenital anomalies), causality assessment as per WHO-UMC criteria [16], and outcome due to ADRs (fatal, recovering, recovered, unknown, continuing, or other) as recommended by PvPI [18]. In accordance with the 2nd WHO Essential Medicines List (EML) (2021) [19,20] and WHO guidelines [3], FDCs were also characterised as rational or irrational.

STATISTICAL ANALYSIS

An Excel sheet was maintained, which included all the details from each ADR reporting form under appropriate headings. The data was analysed and presented as whole numbers or percentages.

RESULTS

A total of 8,212 ADRs were reported during the period of ten years (2011-2021). Out of these, a total of 1,575 ADRs (19%) were found to be associated with FDCs. The majority of the ADRs were observed in the age group between 21-40 years, with 740 cases (47%), followed by 519 cases (33%) in the 41-60 years age group. Out of these, 897 cases (57%) were seen in males and 677 cases (43%) in females.

The most common SOC associated with ADRs was GI disorders, with 359 cases (23%), followed by skin and subcutaneous disorders with 317 cases (20%) [Table/Fig-1].

A total of 1,649 FDCs were found to cause 1,575 ADRs. The most common suspected drug groups included ARV drugs with 787 cases (48%), followed by antitubercular drugs with 298 cases (18%), and penicillin+beta-lactamase inhibitors with 268 cases (16%). Other suspected FDCs are listed in [Table/Fig-2]. Out of the 1,649 FDCs, 1,551 (94%) were rational FDCs and 98 (6%) were irrational FDCs, as shown in [Table/Fig-2].

SOC classification	Number
GI disorders	359 (23%)
Skin and subcutaneous disorders	317 (20%)
Nervous system disorders	183 (12%)
Blood and lymphatic disorders	157 (10%)
Kidney and urinary system disorders	152 (10%)
Cardiac disorders	111 (7%)
Metabolism and nutritional disorders	63 (4%)
Body as a whole general disorders	53 (3%)
Musculoskeletal and connective tissue disorders	38 (2%)
Psychiatric disorders	38 (2%)
Reproductive system and breast disorders	26 (2%)
Others*	78 (5%)
Total	1575 (100%)

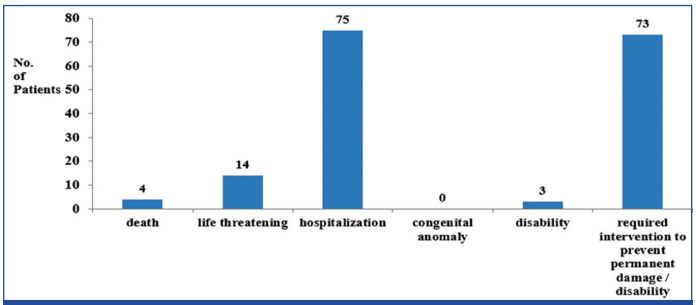
[Table/Fig-1]: System Organ Class (SOC) distribution of ADRs (N=1575).
*Eye disorders/vision disorders, Application site disorders, Respiratory, Thoracic and Mediastinal disorders, Ear and labyrinth disorder, Infections and infestations, Immune disorders, and endocrine disorders

Suspected drugs/group	Suspected FDCs	Number (%)
ARV drugs	Zidovudine+lamivudine+nevirapine, Tenofovir+lamivudine+efavirenz, Atazanavir+ritonavir	787 (48%)
Antitubercular drugs	Isoniazid+rifampicin+pyrazinamide+ethambutol	298 (18%)
Penicillin+Beta lactamase inhibitors	Amoxicillin+clavulanic acid Piperacillin+tazobactam	268 (16%)
Cotrimoxazole	Sulfamethoxazole+trimethoprim	73 (4%)
Drugs used in respiratory disorders (COPD** and asthma, cold and cough medication)	Ambroxol hydrochloride+terbutaline sulphate+guaiphenesin (I*) Dextromethorphan hydrobromide+chlorpheniramine maleate+phenylephrine hydrochloride (I*) Paracetamol+chlorpheniramine maleate+ambroxol+guaiphenesin (I*) Paracetamol+chlorpheniramine maleate+phenylephrine hydrochloride+caffeine (I*) Montelukast+desloratadine Indacaterol+glycopyronium Levosalbutamol+ipratropium Salmeterol+fluticasone Salbutamol+ipratropium bromide Etophylline+theophylline	33 (2%)
Vaccines	MMR** and DPT** vaccine	29 (2%)
NSAIDs** combinations (I*)	Paracetamol+ibuprofen, Paracetamol+diclofenac, Paracetamol+tramadol, Paracetamol+caffeine, Paracetamol+aceclofenac	25 (1.50%)
Drugs for GI disorders (I*)	Ofloxacin+ornidazole Ciprofloxacin+tinidazole Metronidazole+norfloxacin Oral rehydration solution Oxetacaine+aluminium hydroxide+magnesium+simethicone Pancreatin+dimethicone Pantoprazole+domperidone Domperidone+ranitidine	25 (1.51%)

Drugs for ophthalmic use	Brimonidine+timolol Dorzolamide+timolol Atropine/tropicamide+phenylephrine	21 (1%)
Oral contraceptive pills	Norgestril+oestradiol Norethisterone+ethynyloestradiol	16 (1%)
Vitamin supplements	Multivitamin multimineral preparations (I*) Ferrous calcium citrate+folic acid	14 (1%)
Cephalosporin+Beta lactamase inhibitors	Cefoperazone+sulbactam	13 (1%)
Drugs for dysmenorrhoea	Mefenamic acid+dicyclomine (I*)	11 (1%)
Topical drugs used for treatment of skin disease (acne)	Isotretinoin+clindamycin, Isotretinoin+adapalene, Hydroquinone+tretinoin+mometasone (I*), Clobetasol propionate+salicylic acid (I*), Beclomethasone+gentamicin+miconazole (I*)	10 (0.6%)
Antihypertensive drugs	Amlodipine+losartan Lisinopril+hydrochlorothiazide Losartan+hydrochlorothiazide Amlodipine+atenolol Telmisartan+hydrochlorothiazide Furosemide+spironolactone	9 (0.50%)
Antidiabetic drugs (I*)	Metformin+glimepiride Metformin+glipizide Pioglitazone+glimepiride	6 (0.30%)
Anticancer	Paclitaxel+carboplatin Doxorubicin+cyclophosphamide Cisplatin+etoposide	5 (0.30%)
Antimalarial	Sulfadoxine+pyrimethamine	4 (0.20%)
Antipsychotics	Risperidone+trihexyphenidyl	1 (0.06%)
Anticoagulants	Heparin sodium+benzyl nicotinate	1 (0.06%)
Total		1649 (100%)

[Table/Fig-2]: Suspected drug groups of the Fixed Dose Combinations (FDC).
{*:Irrational FDCs; **: COPD: Chronic obstructive pulmonary diseases; MMR: Measles, mumps and rubella; DPT: Diphtheria, pertussis and tetanus; NSAIDs: Non-steroidal anti-inflammatory drugs}

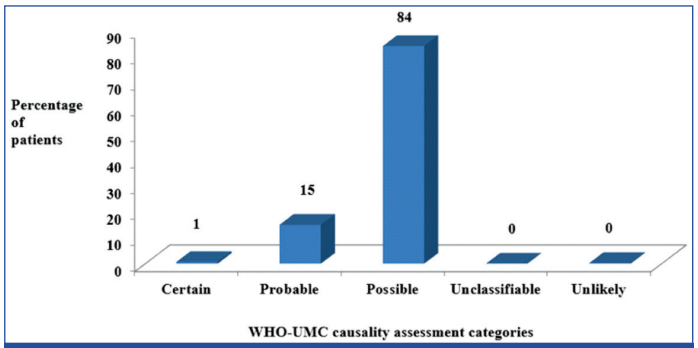
Out of the 1,575 ADRs, 169 cases (11%) were serious in nature. In 75 cases (44.4%), ADRs led to hospitalisation, while in 73 cases (43.2%), some intervention was necessary to prevent permanent damage/disability. Other types of serious ADRs observed in the study are shown in [Table/Fig-3].



[Table/Fig-3]: Types of serious ADRs (n=169).

Two individuals faced disabilities due to ADRs from FDCs, including restriction of lower limb movement (pentavalent vaccine) and optic neuritis due to isoniazid, rifampicin, pyrazinamide, ethambutol (HRZE). Four deaths were reported to be related to ADRs during this ten-year period. These include hyperkalaemia due to piperacillin+tazobactam (two cases), acute bronchospasm due to NSAIDs combination of paracetamol+diclofenac, and toxic epidermal necrolysis due to amoxicillin+clavulanic acid. Life-threatening ADRs include anaemia (four cases), lactic acidosis (one case), Stevens-Johnson syndrome (two cases), and toxic epidermal necrolysis (one case) due to zidovudine+lamivudine+nevirapine (ZLN); hypokalemia (three cases) due to piperacillin+tazobactam, depression with suicidal thoughts (two cases) due to tenofovir+lamivudine+efavirenz (TLE); anaphylaxis due to cefoperazone+sulbactam; and Stevens-Johnson syndrome (ofloxacin+ornidazole). Out of the 169 serious ADRs, about seven ADRs occurred due to the use of irrational FDCs (treatment of cold and cough, metformin+glimepiride, paracetamol+diclofenac, ofloxacin+ornidazole).

Causality assessment of ADRs using the WHO-UMC scale showed that 1,385 cases (84%) of FDCs were possibly related to the ADRs, as shown in [Table/Fig-4].



[Table/Fig-4]: Types of serious ADRs (n=169).

The outcome due to ADRs was categorised as fatal, recovering, recovered, unknown, continuing/not recovered, and recovered with sequelae, as recommended by PvPI, as shown in [Table/Fig-5]. The majority of the ADRs, 534 cases (34%), were reported as not recovered, followed by 452 cases (29%) with an unknown outcome. 18% of the ADRs were reported as recovered, and 18% were reported as recovering.

Outcome	Number of patients (%)
Recovered	286 (18.16)
Fatal	4 (0.25)
Recovering	290 (18.41)
Recovered with sequelae	9 (0.57)
Not recovered	534 (33.90)
Unknown	452 (28.70)
	1575 (100)

[Table/Fig-5]: Outcome of ADRs due to FDCs.

DISCUSSION

ADRs always accompany drug use, especially when drugs are combined unscientifically in FDCs. It is astonishing to find thousands of such FDCs being routinely marketed and prescribed in India currently. The irrational prescribing of these FDCs can jeopardise the health of patients and lead to fatal ADRs, which often go unreported

[13,21]. This study was undertaken to analyse the pattern of ADRs caused by the use of FDCs.

Out of a total of 8,212 ADRs reported during a ten-year period, 1,575 (19%) ADRs were caused by FDCs. These ADRs were mainly seen in male patients (57%) within the age group of 21-40 years (47%). The majority of the ADRs (43%) were related to GI disorders and skin and subcutaneous disorders. The most common suspected drug groups were ARV drugs (48%), antitubercular drugs (18%), and penicillin+beta-lactamase inhibitors (16%). Out of the 1,649 FDCs causing ADRs, 1,551 (94%) FDCs were found to be rational. ARV drugs (50.7%), antitubercular drugs (19.2%), penicillin+beta-lactamase inhibitors (17.3%), and cotrimoxazole (4.7%) accounted for approximately 92% of the rational FDCs. On the other hand, different NSAID combinations (25.5%), cold and cough medicines (23.5%), and drugs for GI disorders (19.4%) constituted the majority of the irrational FDCs. About 169 cases (11%) of ADRs and four deaths were reported. Seven serious ADRs were caused by irrational FDCs, which are preventable.

In the present study, 19% of ADRs were found to be caused by FDCs, while a study conducted by Khjauria V et al., reported only 4% of ADRs being due to FDCs, and a study by Tandon VR, reported around 58% of ADRs occurring due to FDCs [8,9]. In the present study, the majority of ADRs were seen in males (57%) and in the adult age group (47%). Khjauria V et al., reported similar findings to the present study, while Tandon VR, reported a higher number of ADRs due to FDCs occurring in females and the geriatric age group [8,9]. This variation could be due to differences in the duration of the study, the demographic profile at the study site, and the types of patients coming to the hospital.

In the present study, the most common SOC was GI disorders, followed by skin and subcutaneous disorders. Similar results were reported by Khjauria V et al., [8]. In the present study, the most common suspected drugs were ARV and antitubercular drugs (AKT-4), while in the study by Tandon VR, it was NSAIDs [9]. All of these drugs are known to be associated with the aforementioned common SOCs [11,20]. SOCs are standardised medical terms for each human body system, derived from the Medical Dictionary for Regulatory Activities (MedDRA®) [17].

In the present study, the most common suspected drug group was ARV, followed by antitubercular drugs and penicillin+beta-lactamase inhibitors. These are rational FDCs according to the WHO Essential Medicines List (EML), 2021 (22nd list) [18], and WHO guidelines [3] for evaluating the rationality of FDCs. However, we have also reported ADRs due to irrational FDCs such as combinations of NSAIDs, cold and cough medicines, and drugs for GI disorders. In the study conducted by Tandon VR, the majority of ADRs were due to irrational FDCs of antimicrobial agents and combinations of NSAIDs [9]. They also reported ADRs due to rational FDCs such as antitubercular drugs and cotrimoxazole. Similarly, Khjauria V et al., found that the majority of ADRs were due to irrational FDCs such as combinations of NSAIDs and muscle relaxants, and antimicrobial combinations [8]. Safety is a major concern for irrational FDCs, in addition to cost, drug-drug interactions, and polypharmacy. Prescribers should be aware of the hazards of such irrational FDCs, and regulatory agencies should take regulatory steps to prevent the approval of such irrational FDCs.

In the present study, 11% of ADRs were serious in nature, with four ADRs reported as deaths and fifteen ADRs reported as life-threatening. Tandon VR, reported approximately 3% of serious ADRs, while Radhika MS et al., reported 23% of serious ADRs [9,13]. Serious ADRs require hospitalisation, increasing the burden on government hospitals and patients in terms of costs. Clinicians should be aware of such serious ADRs associated with FDCs.

Causality assessment, according to the WHO-UMC, helps to determine whether the reported adverse drug event is associated with the drugs prescribed to a patient [17]. In the present study, 84% of the FDCs were possibly related to the ADRs, and our findings were similar to studies conducted by Khjauria V et al., and Tandon VR [8,9]. This is a drawback of FDCs, as it is difficult to ascertain which drug in the combination has caused the ADRs. Additionally, in many cases, dechallenge is not applicable, and sometimes the disease itself can contribute to the reported ADRs. All of these factors lead to a higher number of FDCs being possibly related to the reported ADRs.

Thus, FDCs affect causality assessment and increase the risk of drug-drug interactions and polypharmacy. However, the development of FDCs is important for public healthcare as they carry advantages, particularly in the management of chronic diseases where compliance plays a crucial role in the final therapeutic outcome. FDCs also offer other clinical benefits such as increased efficacy, reduced financial burden, potentially lower manufacturing costs, compared to producing separate products administered concurrently, and simpler distribution logistics [19].

The results of the present study highlight the importance of safety data on FDCs and call for serious reviews by drug regulatory authorities to assess the rationality of FDCs before allowing their marketing. These results can significantly raise awareness among physicians that the majority of ADRs can be prevented by avoiding the use of at least irrational FDCs.

Limitation(s)

There was a lack of follow-up, which resulted in the unknown exact outcome of the majority of reported ADRs.

CONCLUSION(S)

Both rational and irrational FDCs can cause serious and non-serious ADRs. It is important to make stakeholders, such as prescribers and pharmacists, aware of these findings. These results can significantly raise awareness among physicians that ADRs can be prevented by avoiding the use of at least irrational FDCs. Therefore, there needs to be a serious review by drug regulatory authorities to assess the rationality of FDCs before allowing their marketing.

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