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## EDITORIAL

# Prevalence Of Fixed Dose Drug Combinations In Nepal: A Preliminary Study

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### ABSTRACT

**Background:** Though fixed dose combinations (FDCs), offer certain advantages in terms of patient compliance, their use is highly debatable. Studies from Nepal have documented a high prevalence of prescribing FDCs. However, there are no extensive studies on FDCs. Hence, we aimed to study the registration status, availability and utilization pattern of FDCs in the Western region of Nepal.

**Methods And Findings:** Primary, secondary and tertiary healthcare centers (one each) and ten retail pharmacies were randomly selected. Initially, the registration status of 50 FDCs in the national drug regulatory authority was evaluated. The availability of these 50 FDCs in ten retail pharmacies was studied following which, a total of 25, 50 and 75 prescriptions were collected from primary, secondary and tertiary health care (PHC, SHC, and THC) centers, respectively, from October 18<sup>th</sup> to December 15<sup>th</sup> 2008 and were studied. Among the 50 registered FDCs at the Nepal Department of Drug Administration, only 5 were listed in either the Nepalese National Formulary (NNF), the Essential Drug list of Nepal, or the WHO model list of Essential medicines (15<sup>th</sup> Edition). Four FDCs which were not registered in the national drug regulatory authority were found in the market. We found that seventy seven percent of FDCs were prescribed in PHC as 'antimicrobials'. Twenty nine and 35 percent of FDCs prescribed in SHC and THC respectively were for respiratory diseases. We found that 68% and 73% of the total FDCs prescribed in secondary and tertiary health care centers were in the range of 'less than NRs 100 (US\$1.33)'.

**Conclusions:** Although some FDCs are not registered in the national drug regulatory authority of Nepal, they are still available in the market. Large proportions of FDCs are widely utilized in different health care settings of Nepal. A study on the availability, utilization pattern and rationality of FDCs in different cities and health care centers of Nepal are urgently needed.

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### Introduction

Irrational prescription of a drug is a common occurrence in clinical practice [1]. It is well documented that safe and effective drug therapy is possible only when patients are well informed about the medications and their use. It has become a very common practice for the physicians to prescribe polypharmacy including many irrational fixed dose combinations (FDCs) [2]. Several pharmaceutical companies manufacture generic preparations using different brand names, which leads to the formulation of several irrational FDCs. The presence of

these multi-drug combinations results in the prescription of drugs that are not necessary and drug combinations that are irrational [3]. Extensive studies and inspections are required in South Asian countries with respect to prescribing habits [4],[5],[6]. These studies conclude that the quality of drug prescription is poor and that there is overuse of antimicrobials along with the irrational use of FDCs, particularly in private sectors [4]. The FDCs are extensively utilized and their use is a highly debatable issue [2].

A FDC is a combination of two or more than two drugs in a single pharmaceutical formulation [7]. More than one-third of all the new drug products introduced worldwide during the last decade were FDCs [8]. The 15<sup>th</sup> edition of the WHO model list of Essential Drugs contain 25 (7%) FDCs out of 352 medicines in total. The National Drug list of Nepal (Third revision-2002) contains 14 (4%) FDCs out of 302 medicines in total. Although only a handful of essential FDCs have been recognized by WHO [7] and the National essential drug list of Nepal, a wider variety of FDCs are available in the market today [9]. Combination drugs increase the risk of side effects, lead to an ineffective dosage and liability to abuse, potential for drug resistance and may also needlessly increase cost with reduction in the quality of drug therapy [10]. Studies from Nepal have identified the use of FDCs [11],[12]. However, there is no extensive study on FDCs beyond this. Hence, a preliminary study was conducted with the objective of assessing the registration status, availability and utilization pattern of FDCs in Pokhara, Western Nepal.

## Methods

### Study Design

A prospective and cross sectional study was carried out for a period of two months starting from October 18<sup>th</sup> to December 15<sup>th</sup>, 2008.

### Setting

Selected primary, secondary and tertiary healthcare centers (one each) in Western Nepal and ten randomly selected retail pharmacies from Nepal.

Sub-health post at Hemja Village Development Committee (VDC) of the Kaski district was selected as a primary health care center. This healthcare centre is located about 12 km away from the main city, Pokhara, with an average patient flow of 20 patients per day. This healthcare centre caters the primary healthcare need of the patients of Hemja VDC. Fishtail hospital, a private hospital in Pokhara, was selected as a secondary healthcare centre, which has an average bed occupancy of about 70 patients and an average outpatient attendance of about 150 patients per day. Manipal Teaching Hospital (MTH), Pokhara, was selected as a tertiary healthcare centre. MTH is a 700 bedded tertiary care hospital with an average outpatient attendance of about 500 patients per day. The hospital caters to the healthcare needs of the patients from the Western and Mid-western region of Nepal.

The survey was conducted at ten retail pharmacies from Pokhara, western Nepal, to assess the availability of FDCs that are not registered in the national drug regulatory authority. Five retail pharmacies were selected from rural areas and five from urban areas.

### Method Of Data Collection

Initially, the registration status of 50 FDCs in the national drug regulatory authority (Department of Drug Administration, drug list of Nepal) was studied. The list of registered drugs was accessed through the website [www.dda.gov.np](http://www.dda.gov.np) [9]. The presence of these 50 FDCs was checked in the Nepalese National Formulary [13] (Information on drugs and their dosages available in Nepal can be obtained from this formulary), 15<sup>th</sup> version of the WHO model list of essential medicines [14] and in the Essential drug list of Nepal (National list of essential drugs Nepal, third revision 2002) [15]. FDCs of topical and injectable

products were excluded from the study. The available unregistered FDCs were purchased and the information was noted on the data collection form. The utilization pattern of FDCs in different healthcare settings was also analyzed. The prescription behaviour was evaluated in the selected primary, secondary and tertiary healthcare centers (one each) of Pokhara, Western Nepal. A total of 25 prescriptions were collected from primary health care centers. Five prescriptions on every alternate day of visit were collected from a time period of 12<sup>th</sup> to 21<sup>st</sup> November, 2008. A total of 50 prescriptions were collected from a time period of 11<sup>th</sup> to 20<sup>th</sup> November, 2008, from secondary health care centers. Similarly, a total of 75 prescriptions were collected from a time period of 5<sup>th</sup> to 25<sup>th</sup> November, 2008, from a tertiary health care center. For each prescription, information was noted on the data collection form. Data analysis was carried out as per the study objectives. The data were analyzed using a Microsoft Excel spreadsheet. SPSS version 15 was used to carry out the descriptive statistical analysis.

## Results

### A) Registration Status

The first 50 FDCs were selected from the DDA drug list of Nepal. Among the 50 FDCs, 4 (8%) were present in NNF, 2 (4%) were present in the Essential Drug list of Nepal (3<sup>rd</sup> Revision 2002), and 4 (8%) were present in the WHO model list of Essential medicines (15<sup>th</sup> Edition). The details regarding the registration status of FDCs are listed in [Table/Fig 1].

(Table/Fig 1) Registration Status of FDCs (n=50)

SN	FDC Product	Presence in		
		Nepalese National Formulary (NNF)	Essential Drug List of Nepal (3 <sup>rd</sup> Revision 2002)	WHO Model List of Essential Medicines (15 <sup>th</sup> Edition)
1.	Diloxanide Furoate+Metronidazole	+	-	-
2.	Sulphamethoxazole+Trimethoprim	+	+	+
3.	Pyrimethamine + Sulfadoxine	+	+	+
4.	Amoxicillin+Clavulanate Potassium	-	-	+
5.	Ethinylestradiol + Levonorgesterol	+	-	+
	Total	4 (8%)	2 (4%)	4 (8%)

\* '+ ' Denotes Presence, '- ' Denotes Absence

### B) Product Availability

Altogether, 10 retail pharmacies were randomly selected from Pokhara, the Western part of Nepal. Five were from the urban areas and the remaining five were from the rural areas. We visited these ten retail pharmacies and gathered information on the data collection form. Most of the pharmacies did not have the FDCs that were not registered in DDA, the drug list of Nepal. The details regarding some of the FDCs that are not registered in the DDA drug list of Nepal, but still have been available in the market, are listed below.

1. *Tab. Diphenoxylate 2.5 mg + Atropine Sulphate 0.025 mg + Furazolidone 50 mg:* The combination of antimotility drugs with antiamoebic drugs cannot be justified. Furazolidone has been banned in several countries as it was shown to have carcinogenic potential following long-term administration to experimental animals [3]. This product is also not registered by the DDA.

2. *Tab. Diclofenac 50 mg + Paracetamol 500 mg + Chlorpheniramine maleate 4 mg:* Diclofenac and Paracetamol have the same mechanism of action. Therefore, there is no synergism. NSAID combinations are known to cause direct damage to the kidney.

3. *Norfloxacin 400 mg + Tinidazole 600 mg + Lactic acid bacillus 60 msp:* The combination of antimicrobial drugs with antiamoebic drugs cannot be justified.

4. *Diclofenac 50 mg + Chlorzoxazone 250 mg + Paracetamol 325 mg:* Diclofenac and Paracetamol have the same mechanism of action. Therefore, there is no synergism. NSAID combinations are known to cause direct damage to the kidney.

### C) Evaluation Of Prescription Behaviour

#### a) Primary Healthcare Center

Altogether, 25 prescriptions were encountered. Among them, 12 (48%) were males and 13 (52%) were females. A higher number of patients were within the age group of up to 10 years. The professional qualification of the prescriber was found to be that of CMA (Community medical assistant), followed by AHW (Auxiliary health worker). Out of the total 25 prescriptions encountered, only 13 prescriptions contained FDC formulations. The total number of FDCs prescribed, were 13. The details regarding the presence of FDCs in different formularies and the essential drug list are given in [Table/Fig 2].

**(Table/Fig 2) Details Of FDC Products (n=13)**

Presence of FDC in	Number	Percentage
WHO Model List of Essential Medicines (15 <sup>th</sup> Edition)	11	84.6
Essential Drug List of Nepal (3 <sup>rd</sup> Revision 2002)	13	100
Nepalese National Formulary (NNF)	13	100

### b) Secondary Healthcare Center

Altogether, 50 prescriptions were encountered. Among them, 14 (28%) were males and 36 (72%) were females. A higher number of patients were within the age group of more than 50 years. Out of the total 50 prescriptions collected, 45 (%) prescriptions contained FDC formulations. The details regarding the presence of FDCs in different formularies and the essential drug list are given in [Table/Fig 3].

**(Table/Fig 3) Details Of FDC Products (n=62)**

Presence of FDC in	Number	Percentage
WHO Model List of Essential Medicines (15 <sup>th</sup> Edition)	5	8.6
Essential Drug List of Nepal (3 <sup>rd</sup> Revision 2002)	1	1.6
Nepalese National Formulary (NNF)	1	1.6

The total number of FDCs prescribed was 62. Out of the total 62 FDCs, it was identified that 29% of drugs were prescribed for respiratory problems, followed by antimicrobial combinations (11%). The details are listed in [Table/Fig 4].

**(Table/Fig 4) Therapeutic Category Of FDCs Prescribed (n=62)**

SN	Therapeutic classification	No. of drugs	Percentage
1	Cough and cold remedies	18	29.0
2	Antimicrobials	11	17.7
3	Analgesics/antipyretics	9	14.5
4	Vitamins, minerals and dietary supplements	9	14.5
5	Muscle relaxants	6	9.6
6	Antifungal	4	6.4
7	Others	5	8.0

The cost of FDCs was also assessed in the study. The median (interquartile range) cost of the medications during a single visit was 305.25 (145.87 - 521.76) NRs. It was found that 68% of FDCs were between the ranges of up to NRs 100, followed by 10% of FDCs between the ranges of NRs 101-200. The details of the cost analysis are listed in [Table/Fig 5].

**(Table/Fig 5) Cost Analysis For The FDCs Prescribed (n= 62)**

SN	Cost (NRS)	Number of prescriptions	Percentage
1	Up to 100	42	67.7
2	101-200	6	9.6
3	201-300	4	6.4
4	301-400	2	3.2
5	401-500	1	1.6
6	501-600	4	6.4
7	>600	3	4.8

### c) Tertiary Healthcare Center

Altogether, 75 prescriptions were encountered. Among them, 41 (54.66%) were males and 34 (45.33%) were females. A higher number of patients were within the age group above 50 years of age. Out of the total 75 prescriptions encountered, 39 (%) prescriptions contained FDC formulations. The details regarding the presence of FDCs in different formularies and the essential drug list are given in [Table/Fig 6].

**(Table/Fig 6) Details Of FDC Products (n=51)**

Presence of FDC in	Number	Percentage
WHO Model List of Essential Medicines (15 <sup>th</sup> Edition)	7	13.7
Essential Drug List of Nepal (3 <sup>rd</sup> Revision 2002)	5	9.8
Nepalese National Formulary (NNF)	7	13.7

The total number of FDCs prescribed was 51. Out of the total 51 FDCs, it was recognized that 35% of drugs were prescribed for respiratory problems, followed by analgesic/antipyretics

combinations. The details are listed in [Table/Fig 7].

**(Table/Fig 7) Therapeutic Category Of FDCs Prescribed (n= 51)**

SN	Therapeutic classification	No. of drugs	Percentage
1	Cough and cold remedies	18	35.2
2	Analgesics/antipyretics	10	19.6
3	Antimicrobials	7	13.7
4	Muscle relaxants	6	11.7
5	Sedatives and anxiolytics	4	7.8
6	Vitamins, minerals and dietary supplements	2	3.9
7	Others	4	7.8

The cost of FDCs was also assessed in the study. The median (interquartile range) cost of the medications during a single visit was 338.35 (157.73 - 632.90) NRs. It was found that 73% of FDCs were in the range of up to NRs 100, followed by 10% of FDCs between the ranges of NRs 101-200. The details of the cost analysis are listed in [Table/Fig 8].

**(Table/Fig 8) Cost Analysis For The FDCs Prescribed (n= 51)**

SN	Cost (NRS)	Number of prescriptions	Percentage
1	Up to 100	37	72.5
2	101-200	5	9.8
3	201-300	-	-
4	301-400	2	3.9
5	401-500	2	3.9
6	501-600	-	-
7	>600	5	9.8

## Discussion

Most of the essential drugs should be formulated as single compounds. FDCs are used only when the dosage of each ingredient meets the requirement of the defined population and should have defined advantage over single compounds which are administered separately [16]. The present study evaluated the registration status, availability and utilization pattern of FDCs in Pokhara, Western Nepal. The study found that large amount of FDCs are registered and widely utilized in Nepal, but their presence in the WHO essential drug list, the Nepalese national formulary and the National essential drug list of Nepal was quite low. In spite of the existence of regulatory guidelines, the WHO essential drug list and the National essential drug list of Nepal which include only 11 and 25

combinations respectively, FDCs are used widely. Almost 61.3% of the FDCs prescribed at a tertiary care hospital in India were in accordance with those listed in the WHO's recommended list of FDCs [17], but it is evident from the present study, that there are only 8.65% and 13.72% of FDCs respectively in secondary and tertiary health care centers which are in accordance with the WHO's recommended list of FDCs.

In contrast to the secondary and tertiary health care centers, primary health care centers account for 84.6% of the prescribed FDCs, which were in accordance to the WHO's recommended list of FDCs and 100% of the prescribed FDCs were in accordance with the Essential drug list of Nepal (3<sup>rd</sup> Revision 2002) and the Nepalese National Formulary (NNF). Adherence with the guidelines may be because in primary healthcare centers, 24 drugs from the essential drug list of Nepal are supplied by the government.

The most widely prescribed FDCs in secondary health care centers were cough and cold remedies, followed by antimicrobials. Similarly, in tertiary health care centers, cough and cold remedies were the most commonly prescribed FDCs, followed by analgesics/antipyretics. A study by Das B et al. in the paediatric outpatient department (OPD) at Central Referral Hospital (CRH), Gangtok, Sikkim, found that 59.2% of medicines were FDC products and two-thirds of FDCs were respiratory medicines [18]. A similar study was conducted by Hazra et al, which accounts for the use of antibiotics (72.8% of encounters) and irrational FDCs (45.6% of prescribed drugs) in the health facilities of non-government organizations [19]. Several studies from Nepal also reported the use of FDCs. One of the studies done in a tertiary care teaching hospital of Western Nepal reports that 21.67% of the drugs which were used, were FDCs [11]. Inappropriate and irrational prescribing patterns of antimicrobial fixed dose combinations was seen in one of the district hospitals of Nepal

[20]. A similar type of study in North India also reported a higher value of 45% of FDCs [21].

The average cost per prescription was found to be NRs 373.24 (US\$ 4.97) and NRs 463.82 (US\$ 6.18) in secondary and tertiary health care centers, respectively. The present study found that 68% and 73% of the total FDCs prescribed in secondary and tertiary health care centers were in the range of up to NRs 100 (US\$1.33).

During our market survey in Pokhara, we came across several irrational fixed dose combinations which are considered to be of harmful/doubtful therapeutic value, but still are registered and marketed in Nepal. Our findings are similar to those carried out by Pharmaceutical horizon of Nepal (PHON), which identified some of the combinations which are irrational and are of doubtful efficacy, such as the ampicillin and cloxacillin combination, the atropine and diphenoxylate combination, several cough and cold preparations etc which are registered and are available in Nepal [22].

### Conclusion

Although some FDCs are not registered in the national drug regulatory authority of Nepal, they are still available in the market. Large proportions of FDCs are widely utilized in different health care settings of Nepal. Availability, utilization pattern and rationality of FDCs in different cities and health care centers of Nepal are urgently needed.

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