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Adherence of Drug Promotional Literatures Distributed by Pharmaceutical Companies to World Health Organization Ethical Criteria for Medicinal Drug Promotion

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ABSTRACT

Background: Drug Promotional Literatures are usually relied upon for drug promotion, however studies have shown them to contain several pitfalls. World Health Organization has time and often revised the guideline to address the issue and World Health Organization Ethical Criteria for Medicinal Drug Promotion was established. Based on this guideline, several regional as well as national guidelines have been formulated. Though laws to regulate drug promotion is existent, studies have shown problems with drug promotional literatures in Nepal also. This study was carried out to analyse the drug promotional literatures distributed by pharmaceutical companies in Nepal as per World Health Organization Ethical Criteria for Medicinal Drug Promotion.

Methods: A cross-sectional study over a period of one year was conducted at our department. Pharmaceutical companies registered in Department of Drug Administration, Kathmandu and consenting for the study were requested to provide ten unique drug promotional literatures of their products. Collected drug promotional literatures were analysed for inclusion of essential information as per World Health Organization Ethical Criteria for Medicinal Drug Promotion, level of biasness. Different drug promotional literatures were also classified and compared for these aspects.

Results: A total of 48 pharmaceutical companies were included in the study. Drug promotional literatures (n = 372) were analysed during the study. Adherence to criteria concerned with positive attributes of the promoted medicine was found to be higher, most of the drug promotional literatures adhered to 5-8 criteria of World Health Organization Ethical Criteria for Medicinal Drug Promotion and were categorised into grade B. Difference in adherence as well as number of biased drug promotional literatures was also seen when drug promotional literatures were compared on different basis.

Conclusions: Adherence to World Health Organization Ethical Criteria for Medicinal Drug Promotion was found to vary when drug promotional literatures were classified as per pharmaceutical company, type of formulation being promoted, type of drug promotional literatures.

Keywords: Drug act Nepal 1978; drug promotional literatures; WHO-ethical drug criteria for medicinal drug promotion.

INTRODUCTION

All informational and persuasive activities by manufacturers and distributors, the effect of which is to induce the prescription, supply, purchase and /or use of medicinal drugs are considered as drug promotion.[1] Information thus disseminated, using printed or electronic materials, should be in accordance with the information contained in the package insert and address both the therapeutic claims and unwanted effects of the promoted drug.[2,3] Drug promotional literatures (DPLs) should be compliant with national health policies and regulations if existent, or with the voluntary standards like WHO Ethical Criteria for Medicinal Drug Promotion (WHO-ECMDP).[1] In Nepal, Department of Drug Administration (DDA) is authorised to screen DPLs as per

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Drug Act, 1978 and attempts to tailor and adopt WHO-ECMDP.[4,5]

DPLs missing information related to negative aspects of a drug has been reported by several studies.[6-8] This study was conducted to analyse the DPLs distributed by pharmaceutical companies in Nepal as per WHO-ECMDP.

METHODS

A cross-sectional study was conducted from 17 September 2016 to 16 September 2017. The study was conducted at our department. List of all the pharmaceutical companies with active registration in DDA, Kathmandu, Nepal as of 1 January 2017 was obtained, segregated into Nepal Based pharmaceutical companies and International-Multinational pharmaceutical companies.

All the Nepal based pharmaceutical companies (49) were attempted to be contacted by e-mail (expected response rate of 80%). Similar number of International pharmaceutical companies (40) were selected by simple random sampling by lottery method and were contacted initially. If the selected international pharmaceutical company (A) did not participate in the study, the consecutive company in the list that was not selected earlier (B), was included in the study. If thus selected company (B) did not participate, the company listed immediately before the initial company (A) that was not selected earlier (C) was included in the study and so on, unless the desired sample size was attained.

Using the prevalence of 48% from previous study, the required number of DPLs was calculated to be 400.[7] Pharmaceutical companies were requested to submit ten DPLs of their best-selling product belonging to different therapeutic classes. If a company submitted more than one copy of a DPL, only one copy was included in the study.

The inclusion criteria for the study were: company should be actively registered in DDA as of 1 January 2017 and should provide written informed consent. The exclusion criteria were: DPLs related to pharmacological products related to animal care, reminder advertisements, DPLs related to herbal products related to human use and promotional literatures related to medical devices.

In our study, there was one dependent variable (biasness of DPLs) and 11 independent variables (all the criteria laid by WHO-ECMDP) coded as E1-E11 as summarized in table 1. DPLs were considered biased if they did not contain any information related to at least 3 out of 4 WHO-ECMDP (coded as E4, E7, E8 and E9) criteria related to negative attributes of the promoted drugs. As reported in a study, DPLs adhering to any 1-4 criteria, 5-8 criteria and 9-11 criteria were also graded as A, B and C respectively.[9]

Table 1. Independent variables (as per WHO Ethical Criteria for Medicinal Drug Promotion) and their assigned codes (for this study)

Code	Criteria
E1	The names of the active ingredients using either international non-proprietary names or the approved generic names of the drug
E2	The brand name of the drug
E3	Content of the active ingredient per dosage form or regimen
E4	Name of other ingredients known to cause problems
E5	Approved therapeutic uses
E6	Dosage form or regimen
E7	Side effects and major adverse drug reaction
E8	Precautions, contraindications and warnings
E9	Major interactions
E10	Name and address of the manufacturer or distributor
E11	Reference to scientific literature as appropriate

The received DPLs were evaluated as per study proforma sheet and data was entered using EpiData. Statistical analysis was done using Statistical Package for Social Sciences (SPSS) version 16. Results were presented using descriptive statistics. Comparison of adherence to each criterion between Nepal based pharmaceutical companies and International/Multinational based pharmaceutical companies were done using chi-square test. A p-value of less than 0.05 was considered significant. The ethical approval was obtained from Institutional Review Board of our institute.

RESULTS

There were 49 Nepal based pharmaceutical companies and 393 International-Multinational based pharmaceutical companies with active registration in DDA as of 1 January 2017. Of them, 110 companies were contacted by e-mail (42 and 68 companies respectively). Response was obtained from 70 companies (40 and 30 respectively, response rate 63.63%). Because some of the companies from national based and international/multinational based pharmaceutical companies did not consent (1 and 4 respectively), did not participate (7 and

3 respectively), and did not meet inclusion criteria (6 and 1 respectively), DPLs from 48 (26 and 22 respectively) companies were utilized in the study. A total of 539 DPLs (329 and 210 respectively) was received out of which 372 DPLs met the inclusion criteria. The characteristics of DPLs included in the study is summarized in table 2. DPLs promoting 12 different therapeutic categories of drugs were received among which DPLs promoting antimicrobial agents were most common (70, 20.43%) followed by DPLs promoting drugs used in nervous system disorder (49, 13.17%), gastrointestinal tract disorder (42, 11.29%), miscellaneous (35, 9.41%), musculoskeletal system (34, 9.14%), endocrine system (30, 8.06%), cardiovascular system (28, 7.53%) and respiratory system (28, 7.53%).DPLs promoting drugs acting on reproductive system (16, 4.30%), drugs affecting blood and blood formation (15, 4.03%), drugs acting on urinary tract (10, 2.69%) and for cancer therapy (9, 2.42%) were also received. Though there were 65(17.47%) DPLs promoting fixed drug combination formulations, only 17(26.15%) of those DPLs were promoting FDCs included in WHO Model Formulary-Essential Medicines, 20th edition.[10]

Table 2. Types of DPLs received, basis of their categorization with number and percentage of each type of DPLs.

Basis of categorization	Categories	Number (%)
By type of pharmaceutical company	Nepal based pharmaceutical companies	232 (62.37)
	Multinational/ International based pharmaceutical companies	140 (37.63)
By intended route of administration	Oral formulation	275 (73.92)
	Injectable	48 (12.90)
	Topical	37 (9.95)
	Inhalational	3 (0.81)
	Others	9 (2.42)
By number of Active pharmaceutical ingredients (API)	Single drug formulation	307 (82.53)
	Fixed drug combination formulation	65 (17.47)
Type of DPL	Advertisements	189 (50.81)
	General Information	148 (39.78)
	Reprints	33 (8.87)
	Others	2 (0.54)

Adherence of DPLs to WHO-ECMDP criteria was found to be variable with mean of 7.52± 2.026 (range 2-11) as shown in table 3. It was seen that 17 (4.57%), 207 (55.64%) and 148(39.78%) of DPLs were categorized into grade A, B and C respectivelyas mentioned above.

Table 3. Number of criteria met by DPLs as per WHO-ECMDP.

WHO Criteria		Present	Absent
Code	Description		
E1	The name of active ingredients using either INN or approved generic names of the drug	369 (99.19)	3 (0.81)
E2	The brand name of the drug	372 (100.00)	0 (0.00)
E3	Content of API per dosage form or regimen	346 (93.01)	26 (6.99)
E4	Name of other ingredients known to cause problems	6 (1.61)	366 (98.39)
E5	Approved therapeutic uses	350 (94.09)	22 (5.91)
E6	Dosage form or regimen	356 (95.70)	16 (4.30)
E7	Side effects, and major adverse drug reactions	154 (41.40)	218 (58.60)
E8	Precautions, contraindications and warnings	156 (41.94)	216 (58.06)
E9	Major interactions	146 (39.25)	226 (60.75)
E10	Name and address of manufacturer or distributor	330 (88.71)	42 (11.29)
E11	Reference to scientific literature as appropriate	211 (56.72)	161 (43.28)

Difference in adherence to each criterion was also analyzed by categorizing the DPLs on different basis. It was found that difference in adherence to some of the criteria were statistically significant as is shown in table 4 and table 5.

Table 4. Difference in adherence to each criterion of WHO-ECMDP when DPLs categorised on different basis (only statistically significant differences shown).

DPL Categories	WHO-ECMDP Criteria	DPLs adherent (%)	p-value
Based on type of pharmaceutical company			
Nepal Based vs International/ Multinational based pharmaceutical companies	E5	96.55 vs 90.00	0.009
	E11	50.43 vs 67.14	0.002

Based on type of formulation being promoted (by intended route of administration)			
Oral vs Non-oral formulation being promoted	E4	0.36 vs 4.12	0.042
Based on type of formulation being promoted (by number of active pharmaceutical ingredient)			
Single drug formulation vs Fixed dose combination formulation being promoted	E1	100 vs 95.38	0.005
	E3	97.39 vs 72.31	0.000
	E5	95.44 vs 87.69	0.036
	E6	97.07 vs 89.23	0.011
	E11	59.61 vs 43.08	0.015

Table 5.Difference in adherence to each criterion of WHO-ECMDP according to type of DPLs(only statistically significant differences shown).

DPL Categories	WHO-ECMDP Criteria	DPLs adherent(%)	p-value
Reprints vs Non-reprints type of DPL	E7	84.85 vs 37.17	0.000
	E8	84.45 vs 37.76	0.000
	E9	81.82 vs 35.10	0.000
Advertisements vs Non-advertisements type of DPL	E3	87.83 vs 98.36	0.000
	E5	89.42 vs 98.91	0.000
	E6	92.59 vs 98.91	0.003
	E7	2.65 vs 81.42	0.000
	E8	3.17 vs 81.97	0.000
	E9	2.12 vs 77.60	0.000
	E10	82.01 vs 95.63	0.000
	E11	38.62 vs 75.41	0.000
General information vs Non-general information type of DPL	E3	98.65 vs 89.29	0.001
	E5	100 vs 90.18	0.000
	E6	98.65 vs 93.75	0.033
	E7	81.08 vs 15.18	0.000
	E8	81.76 vs 15.63	0.000
	E9	77.03 vs 14.29	0.000
	E10	95.95 vs 83.93	0.000
	E11	81.08 vs 40.63	0.000

When adherence to four criteria of WHO-ECMDP related to the negative attributes (coded as E4, E7, E8, E9) were assessed, it was found that only three (0.81%) and 143 (38.44%) DPLs contained information related to all four and any three of these criteria respectively and were found not be biased. DPLs adherent to less than three out of these four criteria were found to be 226 (60.75%) and were labelled biased. Statistically significant differences were seen when DPLs were categorized as advertisement and non-advertisement, general information and non-general information, reprints and non-reprints as shown in table 6. Statistically significant difference was not seen in level of biasness when DPLs were categorized based on pharmaceutical company (Nepal based vs International-Multinational based pharmaceutical company) and based on formulation being promoted (single drug formulation vs fixed dose formulation; formulation intended for oral, injectable, topical administration).

Table 6. Difference in biasness in DPLs when categorised according to their types (only statistically significant differences shown).

Type of DPL	Bias category		p-value
	Biased (%)	Not biased (%)	
Advertisement	185 (81.86)	4 (2.74)	0.000
Non-advertisement	41 (18.14)	142 (97.26)	
General Information	34 (15.04)	114 (78.08)	0.000
Non-general information	192 (84.96)	32 (21.92)	
Reprint	6 (2.65)	27 (18.49)	0.000
Non-reprint	220 (97.35)	119 (81.51)	

DISCUSSION

The response rate from the pharmaceutical companies was lower than expected which could be due to difference in methodology utilized in this study. Studies assessing promotional literatures were found utilizing materials distributed during conferences andin outpatient departments, published in journals and that are already available to them.[7-12] In this study, we contacted the companies and requested their participation to collect DPLs. Cooper et. al. reported that only 42% pharmaceutical companies responded to the request to avail the reference material cited in DPLs by them.[12] Tedious approval process for the international/ multinational pharmaceutical companies and lack of immediate monetary gain from the study could have caused low response rate from the companies. Printed materials received for the study were heterogenous, including company profile book, promotional materials related to medical devices, reminder advertisements and in multiple copies. These resulted in 30.98% DPLs meeting exclusion criteria which is similar to the rate reported by previous study.[13] This could have occurred due to limited number of products being manufactured

or registered in DDA (in case of Multinational companies) by pharmaceutical companies.

Proportion of DPLs promoting FDC formulations was lower in our study as compared to other studies.[11,13,14] Smaller proportion of these DPLs were promoting FDC formulations included in WMF-EM, 20th edition.[10] Study reporting lower proportion of DPLs promoting FDC formulations included in WMF-EM has been seen.[11] As formulations intended for oral formulation is preferred whenever longer duration of therapy is required, this could have induced pharmaceutical companies to develop and distribute DPLs promoting oral formulations. Similar to findings from other studies, analysis of DPLs based on therapeutic category of medicine being promoted showed that 20.43 % promoted antimicrobial agents.[7,11,13] Though antimicrobial agents are scheduled drugs and require prescription to be dispensed, their irrational use is common.[15,16] These could have lured pharmaceutical companies to promote drugs belonging to this therapeutic category drug more often. Almost half of the DPLs received for the study were of advertisement type, similar to findings reported by another study.[17] Commercially driven drug promotions activities, easy to design, less resource demanding (manpower, finance) nature of advertisement type of DPLs could also have resulted them to be circulated in higher number.

When analysed, number of criteria met by DPLs as per WHO-ECMDP varied greatly, from two to all eleven. A study from Nepal reported none of the DPLs studied contained all information related to criteria mentioned by WHO-ECMDP.[8] Most of the DPLs were graded into grade B, which is in accordance to the finding of Nath et. al.[9] Difference in adherence to criteria E5 (approved therapeutic uses) and E11 (reference to scientific literature as appropriate) was found to be statistically significant when DPLs were grouped according to the pharmaceutical companies. This difference could have been because of heterogeneity in type of DPLs (reprints, advertisements, general information, others), organizational structure of the pharmaceutical companies and membership to various pharmaceutical associations and targeted audiences. In our study, three of the DPLs were found not adherent to criterion E1 (name of active ingredient(s) in the drug formulation). These DPLs promoted multivitamin-antioxidant FDC, emollient and electrolyte solution. Similarly, 26 DPLs were found not adherent to criterion E3 (content of API per dosage form or regimen) and 23 of them were of advertisement type. This finding was also reported by a study from India and could have occurred because advertisements type of DPLs are focused more on promotional characteristics.[9,17] In contrast to this, several studies have reported that all the DPLs studied by them were adherent to criteria E1 and E3.[11,13,14,18]

Only three DPLs were found to contain information related to all four criteria coded as E4, E7, E8 and E9. Similarly, higher proportion of DPLs lacking information related to these criteria were reported by numerous studies.[6,7,11-13,19,20] Majority of the DPLs that were labelled biased in this study were of advertisement type, promoted single drug formulation and promoted oral formulations. Though proportion of biased DPLs received from Nepal based companies were higher, the difference seen was not found to be statistically significant. Lower proportion of biased DPLs were expected from international/ multinational pharmaceutical companies because of existence of industry self-regulatory codes, drug promotion guidelines/laws, membership criteria for pharmaceutical associations. Similar proportion of biased DPLs suggests that promotional strategies of international/ multinational companies in Nepal could have caused this result to be seen. Higher number of biased DPLs of advertisement type was found as anticipated because the sole purpose of this type of DPLs is to attract attention by highlighting the positive attributes. Similar to our finding, Styrer et. al. reported advertisement type of DPLs containing higher proportion of promotional characteristics than educational characteristics when compared to other type of printed materials.[17]

In our opinion, we have categorised and compared DPLs in numerous ways for adherence to WHO-ECMDP and level of biasness. Due to smaller number of DPLs in each therapeutic category, comparison on this basis could not be done. Smaller proportion of the contacted companies (43.64%) and of the received DPLs (69.02%) were included in the study which could have been avoided by clearer communication with the participating companies.

CONCLUSIONS

It was found that information contained in DPLs varies with its characteristics. Most of the DPLs were found to be adherent to 5-8 criteria mentioned by WHO-ECMDP. Statistically significant difference in adherence to criteria varied when DPLs were grouped as type of pharmaceutical company, type of DPL, type of formulation being promoted by DPL. Of the DPLs studied, it was seen that only three DPLs contained information related to all the negative attributes specified by WHO-ECMDP. Statistically significant, higher proportion of advertisement type of DPLs were found to be biased.

It is recommended that all the stakeholders (pharmaceutical companies, prescribers (consultants, residents), to be prescribers (undergraduate medical students) are made aware about the WHO-ECMDP criteria. It would also be appreciable if screening of DPLs at multiple levels (institutional, national) are carried out. Additionally, a mechanism to report biased DPLs to institute's drug and therapeutic committee, pharmaceutical companies, national regulatory authority could be established to check the dissemination of biased drug information. It is also recommended that we have ours laws reviewed and enforce ethical criteria for drug promotion, complemented with industry self-regulated codes.

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