January 2006

Critical evaluation of the claims made by pharmaceutical companies in drug promotional material in Pakistan

Dileep Kumar Rohra
Aga Khan University

Anwarul Hassan Gilani
Aga Khan University, anwar.gilani@aku.edu

Ismail Kamal Memon
Aga Khan University

Ghazala Perven
Dow University of Health Sciences, Karachi, Pakistan

Muhammad Talha Khan
Dow University of Health Sciences, Karachi, Pakistan

See next page for additional authors

Authors
Dileep Kumar Rohra, Anwarul Hassan Gilani, Ismail Kamal Memon, Ghazala Perven, Muhammad Talha Khan, Hina Zafar, and Rakesh Kumar

Critical evaluation of the claims made by pharmaceutical companies in drug promotional material in Pakistan

Dileep Kumar Rohra[a], Anwarul Hassan Gilani[a], Ismail Kamal Memon[a], Ghazala Perven[b], Muhammad Talha Khan[b], Hina Zafar[b], Rakesh Kumar[c]

[a]Department of Biological and Biomedical Sciences, the Aga Khan University, Karachi, Pakistan
[b]Dow University of Health Sciences, Karachi, Pakistan
[c]Jinnah Postgraduate Medical Centre, Karachi, Pakistan

Received 30 August 2005, Revised 18 January 2006, Accepted 23 January 2006, Published 14 February 2006

ABSTRACT Background. In Pakistan, there is no mechanism to monitor the drug promotional campaign by pharmaceutical industry despite the fact that there is enough evidence that irrational pharmacotherapy is increasingly encountered even in the developed countries due to unethical practices of pharmaceutical promotion. **Objectives**. To audit the drug promotional claims made by the pharmaceutical companies in Pakistan. **Methods**. Drug promotional pamphlets and brochures containing claims for the drugs, which were circulated by the pharmaceutical representatives were collected from 122 general practitioners (GPs) from Karachi and Larkana cities of the Sindh Province. The claims were critically analyzed and audited with the help of currently available evidence in the medical literature. **Results**. 345 distinct advertisements covering 182 drugs from different manufacturers were critically analyzed for information content. Sixty two out of 345 (18%) of the reviewed advertisements were adjudged to be misleading / unjustifiable, which were again classified as, exaggerated (32%), ambiguous (21%), false (26%), and controversial (21%). The primary source of information (approximately 78%) about the newly launched drugs for the GPs was found to be the pharmaceutical representatives followed by hospital doctors (5%) and colleagues (5%). Furthermore, 110 (90%) GPs were of the view that the drug promotion has definitely an influence on their prescribing pattern. **Conclusions**. Since GPs in Pakistan rate pharmaceutical companies as their primary source of information regarding drugs, it can be anticipated that inappropriate advertisement claims would lead to irrational prescribing if physicians had no any other information to follow.

Corresponding Author: Dileep K. Rohra, Department of Biological and Biomedical Sciences, Faculty of Health Sciences, The Aga Khan University, Stadium Road, P.O. Box 3500, Karachi 74800, Pakistan. dileep.rohra@aku.edu

INTRODUCTION

The accuracy and usefulness of drug advertisements has been the subject of debate for more than a century now (1). According to World Health Organization's (WHO) criteria for medicinal drug promotion, "promotion refers to all the informational and persuasive activities of manufacturers and distributors, the effect of which is to induce the prescription, supply, purchase and / or use of medicinal drugs" (2). Drug promotion and marketing make up a very large part of the activities of pharmaceutical companies in Pakistan. For the drug promotion, in addition to other activities, companies usually use the written material supposedly showing all the good and bad aspects about the concerned drug. These advertisements can be highly informative as long as they are critically appraised (3). However, when these are accepted without any question, can contribute to irrational prescribing. Ideally, drug promotional literature should provide health care professionals with substantial information. However, the information contained in promotional material may be inadequate (4) or altogether inaccurate (5). Undoubtedly, the pharmaceutical promotional activities have powerful influences on prescribing behavior of the clinicians although this influence may be more subliminal rather than overt (6, 7).

In an attempt to support and encourage the improvement of health care through the rational use of drugs, WHO has published ethical criteria for medicinal drug promotion and has recommended their implementation to its member states. As recommended in this document, all promotion-making claims concerning medicinal drugs should be reliable, accurate, truthful, informative, balanced and up to date, capable of substantiation and in good taste. These should not contain misleading or unverifiable statements or omissions likely to induce medically unjustifiable drug use or to give rise to undue risks.

Being a member state of the United Nations Organization, efforts to regulate drug promotions in Pakistan were also initiated with the promulgation of the Drug Licensing, Registering and Advertising Rules by the Ministry of Health, Government of Pakistan. However, there is no mechanism to monitor the drug promotional campaign by pharmaceutical industry in Pakistan despite the fact that there is

enough evidence that rational drug utilization problems are increasingly encountered even in developed countries due to unethical practices of pharmaceutical promotion (8, 9).

Since promotional activities influence the prescribing behavior of the health care providers (10), it is of utmost importance to critically analyze the claims made in the promotional material of the drugs. Internationally, aspects of contents in pharmaceutical advertising pertinent to evidence-based decision-making have been studied (11-13). The extent to which pharmaceutical companies promote the merits of their products and whether such claims are supported by evidence, has not been studied in Pakistan. The results of the present analytical study show that unethical and biased claims regarding the medicinal products are rampant in Pakistan. These drug promotions influence the prescribing behavior of the General Practitioners (GPs) thus accounting for one of the potentially major causes of irrational prescription.

METHODS

This was a descriptive study based on critical appraisal of drug promotional brochures, and on a questionnaire administrated from the GPs.

Drug promotional pamphlets and brochures containing claims for the drugs, which were circulated by the pharmaceutical representatives were collected from the clinics of 122 GPs. Since in Pakistan, we do not have a data base of the practicing GPs, randomization was not possible, therefore, the sampling units consisted of convenient areas of one big city (Karachi) and one relatively smaller town (Larkana) of the Sindh Province. The claims, which were written on those brochures were critically analyzed and audited by one Physician/Pharmacologist (DKR) with the help of currently available evidence in the medical literature. The medical literature consisted of published research articles retrievable from the Pubmed. Literature search was done for each claim by putting appropriate key words. All claims were adjudged misleading / unjustifiable, which were not supported by available evidence. The misleading / unjustifiable claims were further classified as follows:

1. Exaggerated: when a minor advantage of a drug was unnecessarily magnified showing exaggerated applications.

2. Ambiguous: when a merit of a drug in a particular circumstance was extrapolated erroneously to other situations.

3. False: when the claim in question was totally wrong.

4. Controversial: when the claim in question was supported by some scientific evidence. However, contradictory reports were also found challenging the validity of the claim. Overall, those claims were placed in this category, which are yet to be proven.

A structured questionnaire was also administered from the GPs from where the promotional material was collected. Questionnaire was developed and piloted before the study was started and the amended version was used in the main study. The questionnaire was designed to gather data about the sources of information regarding the drugs and the knowledge, attitude and beliefs of the GPs regarding medicinal drug promotion.

RESULTS

A. Appraisal of drug advertisements

Three hundred and forty five distinct advertisements covering 182 drugs from different manufacturers were randomly collected from the GPs and critically analyzed for information content. The total number of claims in all 345 advertisements was 1035. This study focused mainly on the authenticity of the claims made by the pharmaceutical companies. Sixty two out of 345 (18%) reviewed advertisements were adjudged to be misleading / unjustifiable, which were again classified as:

1. Exaggerated claims (32% of the unjustifiable claims): As shown in Table 1, many pharmaceutical companies in Pakistan, local as well as multinationals were found having the tendency to exaggerate certain facts about their products. One example of such exaggerated claim was made for a brand of loratadine, which states that this drug "provides alertness without sedation all day long" or "provides quick relief without sedation thus ensures the high activity of performance". These are false as well as exaggerated claims. Admittedly, loratadine is relatively less sedating than some of the conventional anti-histamines but not absolutely non-sedating (14). Furthermore; we can not think of any mechanism by which loratidine can provide alertness or ensure the high activity of performance. In yet one more claim for a drug, which is a calcium supplement, it is stated that this product "controls and prevents typical disorders of pregnancy: low back pains, leg cramps, lower abdominal pain". This claim is merely made on assumptions and there is no study and clinical evidence available to support such a claim.

Table 1: List of exaggerated promotional claims by pharmaceutical companies in the light of scientific evidence.

Drug	Pharmacological Class	Claim	Anti-claim statement	Remark
Alphacalcidol	Vitamin D3 precursor	For the treatment and prevention of osteoporosis	Only tried in corticosteroid-induced osteoporosis (15)	Exaggerated / ambiguous
Amoxicillin	Penicillin	Absence of side effects	Although relatively safer, this drug is not devoid of side effects	Exaggerated
Bromazepam	Anxiolytic	Restores confidence	It is anxiolytic. Has nothing to do with the lack of confidence associated with personality	Exaggerated
Buclizine	Anti-histamine	For anorexic child	Appetite stimulation and weight gain have been reported as side effects in few studies (16), but we could not find the anorexia in children as the approved use of this drug.	Exaggerated/ controversial
Domperidone	Anti-emetic	Indicated in non-specific abdominal pain	Only useful in abdominal pain associated with diabetic gastropathy (17)	Exaggerated
Domperidone	Anti-emetic	Provides relief in flatulence	Effective in flatulence in a subset of patients with irritable bowel syndrome (18)	Exaggerated
Duxil	Neuroprotective	Improves memory	Limited data in a subset of aged population (19)	Exaggerated
Glibenclamide	Sulfonylurea anti-diabetic	Prevents diabetic complications	Not directly. May delay the complications through optimum blood glucose control	Exaggerated
Glimepiride	Sulfonylurea anti-diabetic	Restores physiological insulin release pattern during meals and exercise	The study quoted by the advertisement has shown only the effect of drug after meals not during or after exercise (20)	Exaggerated
Hydrocortisone sodium succinate	Corticosteroid	Life saving in anaphylactic reaction	Steroids are never life saving in anaphylaxis. They are used once the condition has stabilized with other agents (21)	Exaggerated
Lactulose	Laxative	Indicated as a first line treatment of all types of constipation	Lack of evidence	Exaggerated
Loratadine	H_1-receptor antagonist	Provides quick relief without sedation thus ensures the high activity of performance	Causes less but definite sedation (14)	Exaggerated
Losartan	Angiotensin 1 receptor antagosist	Better tolerability than other anti-hypertensives	In what respect? No evidence	Exaggerated/ False
L-ornithine L-aspartate	Hepatoprotective	A scientifically proven therapy for all liver disorders and more…..	Has role in hepatic encephalopathy but not all liver disorders (22)	Exaggerated
Mecobalamin		The most effective treatment for peripheral neuropathy	Mildly effective in only diabetic peripheral neuropathy (23)	Exaggerated

Mediforte	Multivitamin preparation	Improves quality of life in general weakness	Can help if weakness is due to some vitamin deficiency	Exaggerated
Methotrexate	Anti-metabolite	Works through its anti-metabolite and anti-neoplastic actions	How these two actions are different from each other is not clarified.	Exaggerated
Metronidazole+ furazolidone	Anti-protozoal/anti-bacterial	The magic combination for all kinds of diarrhoea	All kinds of diarrhoea can not be treated by this combination for example travelers' diarrhoea or diarrhea associated with irritable bowel syndrome	Exaggerated
Nimodipine	Ca^{2+} channel antagonist	The effective treatment for senile dementia	Although little benefit has been observed in selected patients, its use is not justified as anti-dementia drug (24)	Exaggerated
Vitamin E	Vitamin supplement	Scientific approach to treat muscle cramps	Limited role in non-specific muscle cramps (25)	Exaggerated

Table 2: List of ambiguous promotional claims by pharmaceutical companies in the light of scientific evidence.

Drug	**Pharmacological Class**	**Claim**	**Anti-claim statement**	**Remark**
Bromazepam	Anxiolytic	Normalizes blood pressure	Limited data in a subset of hypertensive population (26)	Ambiguous
Bromazepam	Anxiolytic	Most effective in the treatment of anxiety states without affecting intellectual functions	Lack of evidence	Ambiguous / exaggerated
Famotidine	H_2 receptor antagonist	The H_2 receptor antagonist with predictable response	This is true for other H_2 receptor antagonists as well	Ambiguous
Fosfomycin	Antibiotic	First line for all kinds of infections	Strange claim. No evidence	Ambiguous
Lansoprazole	Proton pump inhibitor	Supreme in its class	In what respect??	Ambiguous
Lisinopril	ACE inhibitor	No prodrug	Then what? Is it a benefit?	Ambiguous
Losartan	Angiotensin 1 receptor antagosist	More effective control of blood pressure	More effective than what??	Ambiguous
Mecobalamin	Vitamin B12 analogue	Effective in all kinds of nerve disorders	Which disorders??	Ambiguous
Mecobalamin	Vitamin B12 analogue	Helps repair the damaged nerves	How? No evidence	Ambiguous
Methotrexate	Anti-metabolite	Works more quickly than commonly known drugs in rheumatoid arthritis	Compared to what?	Ambiguous
Metoclopramide	Anti-emetic	Specific behavioural effect on digestive system	Incomprehensible claim	Ambiguous
Mupirocin	Anti-bacterial	More effective that other topical and systemic antibiotics in the treatment of skin infections	Lack of evidence	Ambiguous / exaggerated
Ranitidine	H_2 receptor antagonist	The most comprehensive treatment of duodenal and gastric ulcer	In what terms??	Ambiguous

2. Ambiguous claims (21% of the unjustifiable claims): During analysis, we encountered some very vague statements about the drugs as presented in Table 2. These statements may be only half of the truth resulting in the misleading and misguiding of the physicians. For instance, there was an interesting claim about the use of bromazepam, which was being promoted for the normalization of blood pressure. To support the claim, a paper was quoted (26). This study was conducted on a limited number of patients with mild hypertension. We could not find any other study complementing the findings of this report. Based on a single isolated study, hypertension can not be claimed as an approved use of bromazepam.

Table 3: List of false promotional claims by pharmaceutical companies in the light of scientific evidence.

Drug	Pharmacological Class	Claim	Anti-claim statement	Remark
Atenolol	β-adrenergic blocker	No risk of bronchoconstriction	Risk of bronchoconstriction is there (27)	False
Betahistine	H_3-receptor antagonist	Improves neurotransmission in brain	The study quoted by the advertisement shows the characterization of histamine receptors in vascular tissue (28)	False
Betahistine	H_3-receptor antagonist	Does not sedate	The study quoted by the advertisement does not support the claim (29)	False
Calcium supplement	Nutritional supplement	Controls and prevents typical disorders of pregnancy: low back pains, leg cramps, lower abdominal pain	Lack of evidence	False
Famotidine	H_2 receptor antagonist	The most economical anti-ulcer in Pakistan	Cimetidine and ranititidine are more economical in Pakistan	False
Fosfomycin	Antibiotic	No drug interaction	Significant drug interactions (30)	False
Lisinopril	ACE inhibitor	The real ACE inhibitor	Are captopril or enalapril etc. fake inhibitors of ACE?	False
Liv. 52 DS	A food supplement	FDA approved for hepatoprotection	We could not find any approval on the website of FDA	False
Loratadine	H_1-receptor antagonist	Provides alertness	Lack of evidence	False
Mecobalamin		Recommended in low back pain	Lack of evidence	False
Methotrexate	Anti-metabolite	Rarely associated with side effects like bone marrow suppression and acute disturbances of liver functions	Frequently associated with bone marrow suppression and hepatotoxicity (31-34)	False
Micronized purified flavonoidic fraction		A decisive therapeutic benefit in acute hemorrhoidal attacks	Lack of evidence	False
Naproxen	NSAID	Is about 20 times more effective than aspirin, ibuprofen	Lack of evidence	False / exaggerated
Nimesulide	COX 2 inhibitor	No drug interactions	Although few but significant drug interactions have been described (35)	False
Promethazine + pholcodine cough suppressant	Anti-histamine/opioid	Reduces bronchial congestion and spasm of whooping cough	Lack of evidence	False
Terazosin	α-adrenergic blocker	The only selective blocker of α_1-receptors	Prazosin and doxazosin are other selective blockers	False

3. False Claims (26% of the unjustifiable claims): As depicted in Table 3, certain companies were found to promote their products on statements that were entirely false. For example, we observed a claim on a promotional material that methotrexate is rarely associated with side effects like bone marrow suppression and acute disturbances of liver functions. Contrary to this claim, there are various reports, which have shown that long term treatment with this drug is frequently associated with bone marrow suppression and hepatotoxicity (31-34).

Table 4: List of Controversial promotional claims by pharmaceutical companies in the light of scientific evidence.

Drug	Pharmacological Class	Claim	Anti-claim statement	Remark
Cefradine	Cephalosporin	Resistance to β-lacatamases is unmatched by any other cephalosporin	Many other cephalosporins are more resistant (36)	Controversial
Cetirizine	H_1-receptor antagonist	Remarkable mast cell stabilizing effect	No such effect has been observed in many studies (37)	Controversial/False
Citalopram	Anti-depressant	No drug interactions	Although few but significant drug interactions have been described (38)	Controversial
Citicoline	Neuroprotective	improves neurocognition	Efficacy of long term treatment still under investigation (39, 40)	Controversial
Dihydroergocryptine	Dopamine agonist	Effective in impotence	Lack of evidence	Controversial/False
Famotidine	H_2 receptor antagonist	Prevents recurrence of peptic ulcer	Lack of evidence	Controversial
Glibenclamide + metphormin	Sulfonylurea + biguanide anti-diabetic	A winning combination	Higher incidence of mortality when treated with the combination (41, 42)	Controversial
Glucosamine sulphate	Natural product	Stimulates biosynthesis of chondroitin sulphate	Exogenous glucosamine does not stimulate biosynthesis of chondroitin sulphate (43)	Controversial
Losartan	Angiotensin 1 receptor antagosist	Better anti-hypertensive response as compared to valsartan	Valsartan has been shown to be more efficacious (44)	Controversial
Mebeverine	Anti-spasmodic	A safe treatment for Irritable Bowel Syndrome	Hospitalization increased after use of mebeverine (45)	Controversial
Methotrexate	Anti-metabolite	Drug of choice for the treatment of rheumatoid arthritis	Lack of evidence	Controversial
Nimesulide	COX 2 inhibitor	Well tolerated by kidneys	Death due to nimesulide-induced renal failure has been reported (46)	Controversial
Silver sulphadiazine	Antibiotic	Accelerates wound healing	Impairment of wound healing has been shown in many studies (47)	Controversial

4. Controversial claims (21% of the unjustifiable claims): As shown in Table 4, we found that some of the promotional material contained claims that have not been proven yet. These claims are still under investigation. For example, some manufacturers of oral hypoglycemic drugs are promoting glibenclamide and metformin as a "Winning combination". But the other side of the story is that not enough studies have been conducted to prove the efficacy of the combination. As a matter of fact few of the studies that we came across showed higher incidence of mortality in patients treated with the combination compared to sulfonylurea alone (41, 42).

B. Source of information for medical practitioners about the drugs

A total of 150 GPs were contacted personally for filling a questionnaire. Out of which 122 GPs responded positively (response rate; 81.3%), while the rest refused to participate in the study due to one or other reasons. All the GPs selected were solo private practitioners not affiliated with any hospital or group. The characteristics of the GPs, who participated in this study, are shown in Table 5.

Table 5: Characteristics of General Practitioners who participated in the study (n = 122)

Characteristics	
Males	82.0% (100)
Females	18.0% (22)
Age	39.2 ± 4.5 years
Years since last degree	10.1 ± 2.4 years
Mean years of practice	13.3 ± 3.6 years
No of patients seen per week	132 ± 7.7

The area of study included the cities of Karachi and Larkana of the Sindh Province. Since the response of GPs from the two cities was not different, the answers from all the doctors belonging to both cities were pooled together. The doctors were asked to identify the primary source of information of the drugs for them. As shown in Table 6, the primary source of information (approximately 78%) about the newly launched drugs for the GPs was found to be the pharmaceutical representatives followed by hospital doctors (5%) and colleagues (5%) as stated by them. Furthermore, 110 (90%) GPs were of the view that the drug promotion has definitely an influence on their prescribing pattern. Interestingly, although 54% of the GPs did not believe completely in the advertised claims by the pharmaceutical companies, they continued to follow their version and prescribed their medications based on the information provided by them.

Table 6: Percentage of family physicians' rating for the source of information about the new drugs prescribed by him / her

Source of information about the drugs	**% (n = 122)**
Medical journal articles	0.8
Medical books	1.6
Newspapers	0
Drug bulletins	0
Pakistan National Formulary	0
PharmaGuide / Quick index of medical products	1.6
Colleagues	4.9
Consultants	4.9
Pharmaceutical Representatives	77.9
Sponsored meetings	3.3
Direct mail	0
Journal advertisements	0.8
Hospital doctors – Discharge letters, patients etc.	4.1
Internet	0

DISCUSSION

This is the first analytic survey of pharmaceutical advertising claims in Pakistan. Previous studies have shown that medical practitioners are reliant on the pharmaceutical industry for much of their drug information in Pakistan (48) or elsewhere (49). We also observed that despite the apprehensions about the truthfulness of the advertised claims, the GPs rate the pharmaceutical advertisement as the most important source of information about the drugs. Furthermore, a majority of physicians are of the view that drug marketing has undoubtedly an influence on their prescribing practices. The drug promotional practices carried out by the pharmaceutical industry would have undergone a sea-change from the early days. Initially it began as a genuinely informative exercise to keep the doctors informed about the company's products. Today it has become more like a commercial relationship. Although assessment of the truthfulness of the drug promotional claims is very complex, we tried to analyze this keeping in mind the objectives of the evidence-based medicine. Each claim was appraised objectively with the help of available evidence in the medical literature.

The international pharmaceutical industry is

rightly proud of advances made in quality control of pharmaceutical production and chemical purity. Unfortunately, as many examples in the present survey indicate flaws in drug promotional claims, it has much less to be proud of in the quality of the promotional information. Many of the claims made by them were not supported with data. When the text of the advertisements was critically evaluated, we found a significant ratio (18%) of claims to be unjustified or misleading. This carries a marked impact on the overall health delivery system. Since GPs in Pakistan rate pharmaceutical companies as their primary source of information regarding drugs, it can be anticipated that inappropriate advertisement claims would lead to improper prescribing if physicians had no other information on which to depend. The outcome of the irrational prescription may be that the drugs can be used when these are not needed or new, more expensive products are prescribed, when these bring no clear advantage over cheaper alternatives. The potential health consequences for the consumers are not benign; for instance, treatment failures from the use of the wrong drugs, patients suffering unnecessary adverse effects, increase in antibiotic-resistant microorganisms; and the waste of patients' money and national health resources.

In such a scenario immediate remedial measures need to be taken. Starting from the root cause of this malpractice, we need to have well-defined and updated ethical criteria for the marketing of medicinal drugs by the pharmaceutical companies. These criteria need to be enforced by a public institution, preferably the Ministry of Health. In order to ensure that the ethical criteria are being implemented, there is a need for screening of printed promotional material and active monitoring of other forms of promotion. In cases of non-compliance or malpractices, effective sanctions and mechanisms to correct misinformation should be well-defined.

Secondly, we need to teach our doctors the art of critical appraisal of medicinal drug promotion possibly during their undergraduate training so that they would be able to write rational prescriptions. Another step towards improvement could be reassessing the knowledge of all practicing doctors regarding drugs available in the market. This assessment should be according to the international standards and should be compulsory for the doctor to have an attempt after a specified time. This would compel the doctors to look up to the authentic medical literature for reference instead of relying solely on the promotional material.

Concluding, the results of the present study show that unethical practices regarding the medicinal drug promotion are rampant in Pakistan and it is suggested that physicians should be cautious and critical in assessment of advertised claims of greater efficacy, safety or convenience made by the pharmaceutical companies. Furthermore, it is high time that efforts directed towards an institutionalized implementation of ethical criteria for the promotion of drugs be made.

REFERENCES

[1] Anonymous., Can the advertisements in a reputable medical journal promote quackery? *J. Am. Med. Assoc*, 22: 958, 1894.

[2] Criteria for Medicinal Drug Promotion, World Health Organisation. Endorsed by the 33rd World Health Assembly, May 1986, Resolution No. WHA21.41.

[3] Levy, R., The role and value of pharmaceutical marketing. *Arch. Fam. Med*, 3(4): 327-332, 1994.

[4] Gutknecht, D.R., Evidence-based advertising? A survey of four major journals. *J. Am. Board Fam. Pract*, 14(3): 197-200, 2001.

[5] Villanueva, P.; Peiró, S.; Librero, J. and Pereiró, I., Accuracy of pharmaceutical advertisements in medical journals. *Lancet*, 361(9351): 27-32, 2003.

[6] Avorn, J.; Chen, M. and Hartley, R., Scientific versus commercial sources of influence on the prescribing behavior of physicians. *Am. J. Med*, 73(1): 4-8, 1982.

[7] Lober, C.W.,Ethics in pharmaceutical marketing. *Dermatol. Clin*, 11(2): 285-288, 1993.

[8] Caudill, T.S.; Johnson, M.S.; Rich, E.C. and McKinney, W.P., Physicians, pharmaceutical sales representatives, and the cost of prescribing. *Arch. Fam. Med*, 5(4): 201-206, 1996.

[9] Haayer, F., Rational prescribing and sources of information. *Soc. Sci. Med*, 16(23): 2017-2023, 1982.

[10] Jones, M.I.; Greenfield, S.M. and Bradley, C.P., Prescribing new drugs: qualitative study of influences on consultants and general practitioners. *Br. Med. J*, 323(7309): 378-381, 2001.

[11] Lexchin, J., How patient outcomes are reported in advertisements: review of Canadian medical journals. *Can. Fam. Physician*, 45: 1213-1216, 1999.

[12] Loke, T.W.; Koh, F.C. and Ward, J.E., Pharmaceutical advertisement claims in Australian medical publications. *Med. J. Aust*, 177(6): 291-293, 2002.

[13] Waxman, H.A., Ensuring that consumers receive appropriate information from drug ads: what is the FDA's role? *Health Aff (millwood)*, W4: 256-258, 2004.

[14] Verster, J.C. and Volkerts, E.R., Antihistamines and driving ability: evidence from on-the-road driving studies during normal traffic. *Ann. Allergy Asthma Immunol*, 92(6): 294-303, 2004.

[15] Richy, F.; Ethgen, O.; Bruyere, O. and Reginster, J.Y., Efficacy of alphacalcidol and calcitriol in primary and corticosteroid-induced osteoporosis: a meta-analysis of their effects on bone mineral density and fracture rate. *Osteoporos Int*, 15(4): 301-310, 2004.

[16] Lamy, F., Appetite stimulation and weight increase with buclizine. *Brux. Med*, 51(4): 287-290, 1971.

[17] Barone, J.A., Domperidone: a peripherally acting dopamine2-receptor antagonist. *Ann. Pharmacother*, 33(4): 429-440, 1999.

[18] Milo, R., Use of the peripheral dopamine antagonist, domperidone, in the management of gastro-intestinal symptoms in patients with irritable bowel syndrome. *Curr. Med. Res. Opin*, 6(9): 577-584, 1980.

[19] Poitrenaud, J.; Piette, F.; Malbezin, M.; Sebban, C. and Guez, D., Duxil and cognitive deficiency in the elderly. Results of a 6-month controlled multicenter study. *Ann. Med. Interne (Paris)*, 141(Suppl 1): 31-35, 1990.

[20] Sonnenberg, G.E.; Garg, D.C.; Weidler, D.J.; Dixon, R.M.; Jaber, L.A.; Bowen, A.J.; DeChemey, G.S.; Mullican, W.S. and Stonesifer, L.D., Short-term comparison of once- versus twice-daily administration of glimepiride in patients with non-insulin-dependent diabetes mellitus. *Ann. Pharmacother*, 31(6): 671-676, 1997.

[21] Ellis, A.K. and Day, J.H., Diagnosis and management of anaphylaxis. *Can. Med. Assoc. J*, 169(4): 307-312, 2003.

[22] Kircheis, G.; Wettstein, M.; Dahl. S. and Haussinger, D., Clinical efficacy of L-ornithine-L-aspartate in the management of hepatic encephalopathy. *Metab. Brain. Dis*, 17(4): 453-462, 2002.

[23] Zhu, X.P. and Zhou, Z.G., Clinical observation of combined therapeutic effect of prostaglandin E1 and mecobalamin on diabetic peripheral neuropathy. *Hunan. Yi. Ke. Da. Xue. Xue. Bao*, 26(4): 343-344, 2001.

[24] Lopez-Arrieta, J.M. and Birks, J., Nimodipine for primary degenerative, mixed and vascular dementia. *Cochrane. Database Syst. Rev*, 3: CD000147, 2002.

[25] Riley, J.D. and Antony, S.J., Leg cramps: differential diagnosis and management. *Am Fam Physician*, 52(6): 1794-1798, 1995.

[26] Mabadeje, A.F. and Adebayo, G.I., Comparative effects of labetalol and bromazepam on ambulatory blood pressure of Nigerians with labile and stress hypertension. *Clin. Exp. Hypertens. A*, 11(Suppl 1): 441-447, 1989.

[27] van Zyl, A.I.; Jennings, A.A.; Bateman, E.D. and Opie, L.H., Comparison of respiratory effects of two cardioselective beta-blockers, celiprolol and atenolol, in asthmatics with mild to moderate hypertension. *Chest*, 95(1): 209-213, 1989.

[28] Ottosson, A.; Jansen, I. and Edvinsson, L., Characterization of histamine receptors in isolated human cerebral arteries. *Br. J. Pharmacol*, 94(3): 901-907, 1988.

[29] Fujino, A.; Tokumasu, K.; Yosio, S.; Naganuma, H.; Yoneda, S. and Nakamura, K., Vestibular training for benign paroxysmal positional vertigo. Its efficacy in comparison with antivertigo drugs. *Arch, Otolaryngol, Head Neck Surg*, 120(5): 497-504, 1994.

[30] Morikawa, K.; Nonaka, M.; Yoshikawa, Y. and Torii, I., Synergistic effect of fosfomycin and arbekacin on a methicillin-resistant Staphylococcus aureus-induced biofilm in a rat model. *Int. J. Antimicrob. Agents*, 25(1): 44-50, 2005.

[31] Haustein, UF. and Rytter, M., Methotrexate in psoriasis: 26 years' experience with low-dose long-term treatment. *J. Eur. Acad. Dermatol. Venereol*, 14(5): 382-388, 2000.

[32] Themido, R.; Loureiro, M.; Pecegueiro, M.; Brandao, M. and Campos, MC.,. Methotrexate hepatotoxicity in psoriatic patients submitted to long-term therapy. *Acta. Derm. Venereol*, 72(5): 361-364, 1992.

[33] Hoekstra, M.; van Ede, A.E.; Haagsma, C.J.; van de Laar, M.A.; Huizinga, T.W.; Kruijsen, M.W. and Laan, R.F., Factors associated with toxicity, final dose, and efficacy of methotrexate in patients with rheumatoid arthritis. *Ann. Rheum. Dis*, 62(5): 423-426, 2003.

[34] Lewis, J.H., The rational use of potentially hepatotoxic medication in patients with underlying liver disease. *Expert Opin, Drug Saf*, 1(2): 159-172, 2002.

[35] Perucca, E., Drug interactions with nimesulide. *Drugs*, 46 Suppl 1: 79-82, 1993.

[36] Phillips, I. and Shannon, K., The activity of cephalosporins on beta-lactamase-producing Neisseria gonorrhoeae. *Scand. J. Infect. Dis*, 13: 23-26, 1978.

[37] Nielsen, P.N.; Skov, P.S.; Poulsen, L.K.; Schmelz, M. and Petersen, L.J., Cetirizine inhibits skin reactions but not mediator release in immediate and developing late-phase allergic cutaneous reactions. A double-blind, placebo-controlled study. *Clin. Exp. Allergy*, 31(9): 1378-1384, 2001.

[38] Kukoyi, O.; Argo, T.R. and Carnahan, R.M., Exacerbation of panic disorder with rifampin therapy in a patient receiving citalopram. *Pharmacotherapy*, 25(3): 435-437, 2005.

[39] Cohen, R.A.; Browndyke, J.N.; Moser, D.J.; Paul, R.H.; Gordon, N. and Sweet, L., Long-term citicolin (cytidine diphosphate choline) use in patients with

vascular dementia: neuroimaging and neuropsychological outcomes. *Cerebrovasc. Dis*, 16(3): 199-204, 2003).

[40] Zweifler, R.M., Membrane stabilizer: citicoline. *Curr. Med. Res. Opin*, 18 (Suppl 2): s14-17, 2002.

[41] Mannucci, E.; Monami, M.; Masotti, G. and Marchionni, N., All-cause mortality in diabetic patients treated with combinations of sulfonylureas and biguanides. *Diabetes Metab. Res. Rev*, 20(1): 44-47, 2004.

[42] Olsson, J.; Lindberg, G.; Gottsater, M.; Lindwall, K.; Sjostrand, A.; Tisell, A. and Melander A., Increased mortality in Type II diabetic patients using sulphonylurea and metformin in combination: a population-based observational study. *Diabetologia*, 43(5): 558-560, 2000.

[43] Mroz, P.J. and Silbert, J.E., Effects of [3H]glucosamine concentration on [3H]chondroitin sulphate formation by cultured chondrocytes. *Biochem. J*, 376(Pt 2): 511-515, 2003.

[44] Nishimura, T.; Hashimoto, J.; Ohkubo, T.; Kikuya, M.; Metoki, H.; Asayama, K.; Totsune, K. and Imai, Y., Efficacy and duration of action of the four selective angiotensin II subtype 1 receptor blockers, losartan, candesartan, valsartan and telmisartan, in patients with essential hypertension determined by home blood pressure measurements. *Clin. Exp. Hypertens*, 27(6): 477-489, 2005.

[45] Goettsch, W.G.; van den Boom, G.; Breekveldt-Postma, N.S.; Smout, A.J. and Herings, R.M., Treatment patterns and health care costs of mebeverine-treated IBS patients: a case-control study. *Pharmacoepidemiol. Drug Saf*, 13(11): 803-810, 2004.

[46] Schattner, A.; Sokolovskaya, N. and Cohen, J., Fatal hepatitis and renal failure during treatment with nimesulide. *Intern. Med*, 247(1): 153-155, 2000.

[47] Cho Lee, A.R.; Leem, H.; Lee, J. and Park, K.C., Reversal of silver sulfadiazine-impaired wound healing by epidermal growth factor. *Biomaterials*, 26(22): 4670-4676, 2005.

[48] Ahmad, S.R. and Bhutta, Z.A., A survey of paediatric prescribing and dispensing in Karachi. *J. Pak. Med. Assoc*, 40(6): 126-130, 1990.

[49] Gambrill, J. and Bridges-Webb, C., Use of sources of therapeutic and prescribing information by general practitioners. *Aust. Fam. Physician*, 9(7): 482-484, 1980.