

EXPERT REPORT JL

THE ROLE OF MARKETING IN THE PHARMACEUTICAL INDUSTRY

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QUESTION 1.

DOES MARKETING LEAD TO NEGATIVE HEALTH CARE DECISIONS

1. Patients

In most countries patients receive information only indirectly from the pharmaceutical industry through disease information awareness ads and leaflets given out with the purchase of prescription medications. In the United States and New Zealand patients can also get information through direct-to-consumer advertising.

i. Patient information leaflets and disease awareness ads

A British survey of 29 patient information leaflets (PILs) for nonsteroidal anti-inflammatory drugs found that only 4 clearly explained that the NSAID only relieves symptoms, none discouraged efforts by the patient to obtain complete relief with the drug, 13 did not mention stopping the medication if stomach symptoms occurred and 10 advised stopping only if serious symptoms occurred (i.e., bleeding or severe stomach pain).¹ Similarly, a Canadian insert produced by Janssen-Ortho for cisapride had major shortcomings.²

A Canadian disease information awareness ad for high cholesterol, drawing on the results of a study in Scotland³, claimed that “one particular medication [pravastatin], with a good diet and lifestyle can reduce the risk of first heart attacks by 31%.” While technically this ad was accurate, to properly reflect the population studied and the outcome what it should have said was “if you’re a male, aged 55 or older and have high cholesterol and have a 50% chance of smoking, and you are willing to take a drug for 5 years you can reduce your chance of a heart attack from 7.9% to 5.5%.” Anecdotal reports from Australia, Sweden and The Netherlands indicate that the Canadian experience with this type of advertising is not unique.

So far there is no evidence that poor quality patient leaflets or disease awareness ads leads to either poor decision making or poor health outcomes in developed countries. In Third World countries promotion to consumers is even more inappropriate than in developed countries. *Promoting Health or Pushing Drugs*, a 1993 publication from Health Action International gives graphic illustrations of irrational promotion to

consumers. In the Philippines, Pfizer advertised the antidiarrhoeal product Rheaban (attapulgite) under the caption “Don’t hold diarrhea in.”⁴ According to a 1990 report from the WHO “attapulgite [has] no place in the management of acute diarrhoea in children and should not be used.”⁵ Janssen’s ad in the Manilla Bulletin for Antiox (mebendazole), a drug used to treat intestinal worms, contained no information about side effects or interactions with other drugs. It did not mention that it should not be used in children under two years of age, and the ad suggested mixing the drug with food or drinks, although Antiox is insoluble in water.⁴

In some developing countries drugs are promoted through children. In Malaysia, students, including those in kindergarten, regularly receive samples of ointments, pimple creams and vitamins.⁶ One Filipino mother received a “letter” from her son’s school in Quezon City. The letter came with a “prescription” and a starter sample for Multi-Sanostol Syrup, a multi-vitamin preparation manufactured by Byk Gulden, a subsidiary of a German company. The letter to parents, although signed by the school physician, was obviously prepared by the drug company.⁷ Although all of these examples are more than a decade older, once again anecdotal reports indicate that this type of promotion is still continuing albeit perhaps not as widespread.

There is also some limited older evidence showing that consumers in developing countries rely heavily on promotion^{8 9} and associating promotion with poor medication choices. British doctors working in Nepal believe that there is a direct connection between the massive advertising carried out in the towns of Nepal by Indian and multinational drug companies and overspending on drugs.¹⁰

As van der Geest points out a great deal of the commerce in drugs in the Third World takes place in the informal market.¹¹ This informal market is elusive and difficult to check and as such does not easily respond to “corrections” such as new information or even the formal withdrawal of a drug. Therefore, beliefs about the effects of certain drugs which have been inculcated in people’s minds by alluring ads remain fixed and may not be altered for a long time. For example, Organon’s Menstrogen (a high dose estrogen-progestin combination) continued to be used in Bangladesh as a pregnancy test long after Organon began to list pregnancy as a contraindication to its use in the literature about Menstrogen.

The heavy advertising of medication can also create a dependence on a “particular form of therapy--modern, brand-name and often prescription medication--and the agents and institutions that make them available in the community . . . In Asuncion [El Salvador], this dependence has altered local health care traditions and the means of coping with illness that were previously common in the community, drained away resources without providing any long-term improvement in living conditions, and actually caused illness.”¹²

ii. Direct-to-consumer advertising

Studies that have been done consistently document significant problems with the quality of DTCA in the United States. From late 1997, when the FDA relaxed its broadcast advertising regulations, until early 1999, 33 products were fully advertised on US radio or TV, i.e. with product name and one or more health claims.¹³ Seventeen of the 33 (52%) were found to violate the Federal Food, Drug and Cosmetic Act. The most common violations were inadequate communication of risks, overstatement of benefits, and a lack of fair balance between presentation of benefit and risk information.¹⁴ An FDA presentation at the Drug Information Association on ‘What’s New in the Regulation of DTC Promotion?’ in June 2000 described the current trend as an increase in submissions of questionable quality occurring across the board, but also in broadcast ads, and asked whether outrageous overstatements of efficacy had become the norm.¹⁵ Violations have continued to be common, with over 90 DTC ad campaigns found to violate FDA regulations to May 2001.¹⁶

The evidence from two systematic evaluations of information in DTC advertisements is that balance is frequently missing and that advertisements often ignore significant safety information. Consumer Reports magazine looked at the accuracy and usefulness of 28 ads that appeared in top U.S. magazines in 1996, asking a panel of 32 medical specialists to assess accuracy, information content and the potential usefulness of the information in the ads to consumers. Two to three doctors specializing in the relevant field reviewed each ad. Overall, two-thirds were judged to be factually accurate and to contain statements backed by scientific evidence in what they said. However, only half conveyed important information on side effects in the main promotional text and only 40% were honest about efficacy and fairly described the benefits and risks in the main section. Eleven ads (39%) were considered ‘more harmful than helpful’ by at least one reviewer.¹⁷

Roth collected 39 distinct print advertisements representing about 90% of all full DTC drug ads (ads mentioning both the drug name and indication) placed into consumer media from January 1993 to mid-1995. Two specially trained pharmacists assessed these ads in terms of the US FDA’s criteria for fair balance of risk and benefit information. Just over one-third did not contain a fair balance of benefit and risk information in the main body of the ad and 15% made no mention of risks in the advertising copy. Only 12% gave information about potential misuse and more than half lacked directions for use.¹⁸

Bell and colleagues (2000a) analyzed print DTCA in 18 U.S. consumer magazines over a 10 year period, 1989-1998 inclusive. The magazines were chosen to represent a broad range of target audiences and be market leaders in their category. The authors identified six key types of information patients need to know about a drug treatment in order to participate in informed decision-making, and five key types of information about the health condition it treats. The authors used a very low bar for educational content: whether not specific types of information were present or absent, not their accuracy, completeness, relevance to the target audience or readability. However, most ads did not contain basic elements of information a person might need to judge the usefulness of a treatment, such as how a drug works (missing in 64%) or the likelihood of treatment success (missing in 91%). Only 29% of advertisements mentioned any treatment

alternatives and very few provided educational content on the treated health condition beyond its name and, in 60% of ads, one or more symptoms. Ninety-one percent of the ads did not discuss any myths or misconceptions about the disease(s) the drug was designed to treat.¹⁹

The evidence that DTCA leads to inappropriate choices and prescribing of medications is at this point only indirect. About 70% of the time, if a patient requests a prescription drug by name, physicians grant that request.^{20 21} In order for the prescription for the requested brand name drug to be the most appropriate response to patients' problems it must be assumed that patients have accurately self-diagnosed and chosen the best of available treatment options, in terms of efficacy, safety, convenience, cost and relevance to their individual situation (including co-morbidities, other treatments, etc.) Since many prescription drugs treat conditions that are difficult to self-diagnose, and advertising provides little information on alternative treatment choice it seems highly unlikely that their treatment choice will be correct 70% of the time, which is how often they receive the requested product.

Mintzes and colleagues used a cross sectional survey to examine the relationship between patients' requests for medications and physicians' prescribing decisions. In order to assess physicians' confidence with their prescribing decisions they asked doctors "If you were treating another similar patient with the same condition, would you prescribe this drug?" An answer of "very likely" indicated confidence in choice and "possibly" or "unlikely" indicated some degree of ambivalence. Physicians were ambivalent about the choice of treatment in about half the cases when patients had requested advertised drugs compared with 12% for drugs not requested by patients. The authors concluded that if physicians prescribe requested drugs despite personal reservations, sales may increase but appropriateness of prescribing may suffer.²¹

2. Doctors

Even a cursory reading of the literature on pharmaceutical promotion shows that marketing by drug companies is heavily biased in both developed and developing countries. Studies in Australia, Finland, France and the United States uniformly show that sales representatives fail to spontaneously bring up safety issues and that benefits are often exaggerated.^{22 23 24} An expert assessment of 109 ads in American medical journals concluded that in 44% of cases the advertisement would lead to improper prescribing if a physician had no other information about the drug other than that contained in the advertisement. Fifty-seven percent of advertisements were judged by two or more reviewers to have little or no educational value. Overall, reviewers would not have recommended publication of 28% of the advertisements and would have required major revisions in 34% before publication.²⁵ In comparison to the American Physicians' Desk Reference the equivalent Brazilian publication showed an absence of important data including contraindications, adverse effects and drug interactions.²⁶ Compared to British and American journal advertisements, those in Indian medical journals contained less safety information.²⁷

Over the past 30 years a series of studies in developed countries have looked at the association between sources of information about medications and the quality of prescribing. With the exception of one paper,²⁸ all of the rest^{29 30 31 32 33 34 35 36 37 38 39 40} have found an association between increased reliance on promotion and less appropriate prescribing (see Table 1). While all of these studies have methodologic limitations, and none of them proves causality, the consistency of the results despite different methods of assessing prescribing (e.g., measures of caution and rationality of drug prescriptions, to cost of prescriptions, to prescriptions of dangerous drugs) is a strong signal that what has been shown is not a chance observation. Furthermore, interactions with industry can lead to poorer prescribing even when doctors are consciously unaware of the effect^{41 42} or when they deny that such interactions can influence them.⁴³ None of these studies looked at the health outcomes of inappropriate prescribing decisions.

There is also literature from developing countries on sources of information and prescribing decisions. While these studies tend to be older than the ones from developed countries and weaker methodologically they come to the same conclusion; an association between inappropriate prescribing and the use of promotional sources of information. In the early 1980s, over 75% of 135 Manila doctors prescribed drugs for diarrhoea while under 25% prescribed rehydration therapy. The three most frequently cited sources of drug information by these doctors were all commercial--Philippines Index of Medical Specialties (84.4%), literature that accompanies drug samples (74.1%) and detailers (63.7%).⁴⁴

A 1989 survey of 129 urban and rural practitioners in the Philippines concluded that drugs were generally prescribed even when they were not indicated; inessential pharmaceutical products were being prescribed commonly; dangerous pharmaceutical products, including those banned in other countries were being prescribed even for trivial complaints; and the treatment of choice for most common illnesses was generally not being prescribed. Based on responses to other questions, the author of this study

concluded that it was “quite logical . . . that the prescribing behaviour of physicians is determined primarily by the drug industry.”⁴⁵

A 1988 survey of Pakistani doctors with a substantial pediatric population in their practices found that 41% were prescribing Lomotil to children with diarrhoea, despite the well-recognized dangers of this drug. Fourteen percent of the doctors prescribed Durabolin, an anabolic steroid, as an appetite stimulant. Ninety-five percent of these doctors cited detailers and promotional materials as their main sources of prescribing information, versus 6% who used discussions with pharmacists and 2% who cited discussions with colleagues.⁴⁶

Seventeen Malaysian general practitioners prescribed reasonably well for the treatment of diarrhoea: 76% recommended oral rehydration solution and only 6% prescribed an antibiotic. But, for symptoms of an upper respiratory tract infection, 89% recommended an expectorant, 30% gave an antibiotic and none of them suggested the need of only supportive measures which is what UNICEF recommends.⁴⁷ When these doctors were asked about their sources of information 83% cited textbooks and journals and 76% the Drug Index of Malaysia and Singapore, a commercial compendium.⁴⁸

Once again, the health outcomes are not explicitly investigated but given the well known dangers of the drugs being prescribed by these developing world practitioners it is not difficult to believe that many of their patients had negative outcomes.

**QUESTION 2:
CAN PATIENTS AND PRESCRIBERS RECEIVE APPROPRIATE
INFORMATION IN THE ABSENCE OF MARKETING?**

1. Patients

Providing patients with appropriate information is a challenge especially in developing countries. Even in developed countries resources are scarce. Two well respected, objective sources are *Worst Pills, Best Pills* from Public Citizen's Health Research Group in the United States and *Treatment Notes* published in the United Kingdom by the Consumers' Association. *Worst Pills, Best Pills* is available in an on-line edition but both publications require a subscription.

Self-help groups or patient organizations are another source of information but material from these groups needs to be closely evaluated as some of these groups are heavily subsidized by the pharmaceutical industry and their publications may be biased.⁴⁹ In a recent report Malcolm and Medawar illustrate the range of patient groups in a single country (see Table 2).⁵⁰

The internet is another potential source of information about medications, but once again caution is advised in using internet based material. The group or organization hosting the web site is not always obvious and biases in the information may not be picked up.⁵¹ The WHO has made recommendations regarding sponsorship of web sites that should help resolve some of these problems: disclosure of website ownership or financial support; statements about who the intended audience is and the purpose of the information; provision of accurate, balanced information, including information on dangers and adverse effects; and careful selection of internet linkages.⁵²

An innovative source of information is DIPEX, a multi-media approach to sharing experiences and information.⁵³ DIPEX is a database of patients' experiences, accessible via the internet or by CD. The aim is to combine a systematic collection and analysis of interviews with people about their experience of illness with evidence of the effects of treatments, information about support groups and other appropriate resource materials. The aim is for each condition, from hypertension to breast cancer to atrial fibrillation, to have its own offshoot site with all such information, but all under the general DIPEX umbrella.

2. Doctors

In order to decide if doctors can get appropriate information about pharmaceuticals from nonpromotional sources two important pieces of information are necessary: the number of important new drugs that are introduced into the marketplace per year and the number of drugs that physicians actually use.

The Canadian Patented Medicine Prices Review Board (PMPRB) puts new patented medications into one of three categories for the purposes of determining whether the introductory price is excessive. Between 1996 and 2000 a total of 415 new patented drug products, mostly prescription-only products, were marketed in Canada for human use. Only 25, or just over 6%, were classified as “breakthrough” medications or substantial improvements over existing therapies, with the rest being line extensions (40%) or moderate, little or no therapeutic improvements (54%).⁵⁴

The French drug bulletin, *Prescrire International*, has recently published summary statistics on almost 2500 new preparations or new indications for existing drugs that it evaluated between 1981 and 2001. In that time period it rated just 76 (3.0%) as major or important therapeutic gains while close to 1600 were assessed as being superfluous because they did not add to the clinical possibilities offered by previously available products.⁵⁵

The U.S. National Institute for Health Care Management (NIHCM) has analyzed 1035 prescription drugs approved by the FDA from 1989 to 2000. The report looked at whether products were accepted by the FDA for “priority” or “standard” review and whether they included new active substances or were improvements on existing active ingredients. Priority drugs that were new active substances were considered the most innovative followed by drugs given a priority rating that were modifications of existing medicines. Out of the 1035 products only 153 fell into the former group and 91 in the latter, leaving 76% of the total in the least innovative categories.⁵⁶

Although each of these evaluation agencies used differing criteria, leading to differences in percentages of drugs found to offer some degree of incremental value, they were consistent in finding that for the large majority of drugs, no evidence could be found of a therapeutic advantage.

Lexchin has previously looked at the number of drugs used by general practitioners in Canada. Although there were over 3500 prescription drugs on the Canadian market at the time of his review, general practitioners/family doctors used between 120-200 different drugs and, on average, 50% of prescriptions were written for under 30 medications.⁵⁷ (The makeup of the 120-200 drugs used will vary depending on the particular needs of the patients seen by any individual doctor.)

The obvious conclusion from this brief review is that not only do general practitioners, who write the bulk of prescriptions, use surprisingly few drugs and also in any given year there are only a handful of new drugs that they need to add to their armamentarium. Knowledge about existing drugs can be gained through a variety of independent publications including the *Australian Medicines Handbook* (Australia), *British National*

Formulary (U.K.), Drugs of Choice (Canada), Therapeutic Guidelines (Australia) and Therapeutic Options (Canada) and the WHO Model Formulary. Many of these sources are available electronically, and the CD version of the WHO Model Formulary is free. In addition, and very importantly, these sources provide comparative information about medications something that is not available through promotional sources.

Information about the small number of new drugs also need not be acquired through the promotional efforts of the pharmaceutical companies. The internet has made thousands of electronic journals available and many of these, including leading general medical journals such as the British Medical Journal and the Canadian Medical Association Journal, are free on-line. There are also scores of independent drug bulletins – the International Society of Drug Bulletins has a membership of 56 drawn from 34 countries on all five continents. Once again, some are free and available on-line, e.g., Australian Prescriber (Australia) and Therapeutics Bulletin (Canada).

CONCLUSION

This brief review documents the poor quality of information that both doctors and patients receive from the pharmaceutical industry and the consequences of that information in terms of poor prescribing by doctors and inappropriate use by patients. Objective sources of information exist for both groups and the internet has made access to high quality material easier than ever. There is no reason for either party to continue to rely on promotion to guide them in prescribing and using drugs.

Table 1: Association between source of information and quality of prescribing

Author	Jurisdiction	Date	Study group	No. in study group	Dependent variable	Independent variable	Conclusion	Comments
Becker et al <29>	USA (middle Atlantic state)	1970	GPs Internists Osteopaths	29 3 5	Appropriate use of chloramphenicol	Use of journal ads to learn about usefulness of new drugs; Detailers as sources of prescribing information for new drugs	Better prescribing: infrequent use of journal ads ($p < .05$); disapproval of detailers as information sources ($p < .01$); poor perception of detailers ($p < .01$)	Prescribing and knowledge assessed by expert panel; participation rate 84% (primary care doctors in county asked to participate)
					Prescribing behaviour for five common illnesses & five common complaints; knowledge of five specified medications	Detailers as sources of prescribing information for new drugs	Better prescribing: disapproval of detailers as information sources ($p < .01$); poor perception of detailers ($p < .01$)	
Linn et al <30>	USA (Los Angeles county)	~1970	GPs Internists	107	Attitudes about when psychoactive drugs should be used	Preference for professional/scientific sources of information vs. commercial sources	Doctors using commercial sources significantly more likely to prescribe this class of drugs in response to problems encountered in everyday social situations ($p < .05$)	Random sample; response rate 55.6%
Mapes <31>	UK	1972	GPs	54	Use of preparations which have the property of frequently displaying unwanted side effects (incautious prescribing)	Dependence on pharmaceutical literature	Incautious prescribing associated with dependence	Database cohort of 900 practitioners who started in 1970 (116 initially selected possibly on random basis), up-to-date details available for 60)
Hemminki	Finland	1971	GPs	47	Quantity of	Main source of	No difference in	Systematic sample

<28>				psychotropic drug prescribing	information on drugs: medical journals, textbooks, information given by drug companies	prescribing found between doctors choosing either medical journals, textbooks or information from drug companies	(alphabetical order); 71% response rate; relationship between quantity and other measures of appropriateness of prescribing not established
Haayer <32>	Netherlands	1979	GPs	Appropriateness of prescribing for 8 constructed case histories	Reliance on and a more positive attitude towards information provided by drug companies	Less rational prescribing associated with greater reliance (p<.05)	Prescribing assessed on: Appropriateness of symptoms/disease presented and for which no better therapy exists; effective for treatment of symptoms/disease; safe (as few side effects as possible); right dose and duration; 148 GPs in region, 17 not considered because of technical and methodological reasons; 2 did not complete case histories
Ferry et al <33>	USA (Pennsylvania)	1979	GPs Family physicians Internists	Knowledge of drug treatment for the elderly	Importance of drug ads as source of information for prescribing to the elderly	Greater importance negatively associated with test score (p=.0067)	Expert panel of 6 devised questionnaire and determined score considered adequate; questionnaire mailed to stratified random sample of 607 of 6154 doctors (corrected sampling number 569)

Blondeel et al <34>	Belgium	Not stated	GPs	358	<p>Proneness and quality of prescribing for 8 constructed case histories</p> <p>Proneness and quality of actual prescribing over 4 weeks</p>	<p>Being against detailers; influence of commercial formularies</p> <p>Number of detailers seen; taking samples; being against detailers; first knowledge of drug from pharmaceutical industry</p>	<p>Doctors who did not see detailers less prone ($p < .01$); more influence that commercial compendia had poorer quality of prescribing ($p < .05$)</p> <p>Doctors were more prone the more detailers seen ($p < .05$) and less prone more often refused to take samples ($p < .05$); more doctors refused to see detailers the better the quality ($p < .05$); more doctors influenced by commercial compendia poorer the quality ($p < .05$); more often doctors first heard about drugs directly from companies poor the quality ($p < .01$)</p>	<p>Proneness = measure wherein doctor starts again and again immediately with a drug treatment in different situations;</p> <p>quality = treatment offered taking into account available scientific information and characteristics of simulated patients; cases constructed and prescribing assessed by expert committee; representative sample of Flemish GPs</p>
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Bower et al <35>	USA	1984	GPs	575	Habit of prescribing generics	Use of detailers as source of information about new drugs	More generic prescribing associated with less reliance on detailers (p<.05)	GPs randomly selected; responses from 317/501 eligible
Cormack et al <36>	UK	Not stated	GPs GP trainees	19 18	Ability to recognize ten common generic names	Reliance on journal ads as source of information on new drugs	Recognition highest among those least reliant on ads (p<.05)	Characterization of high and low prescribing based on data from Prescription Pricing Authority; GP sample drawn from those attending annual refresher course and willing to participate; trainee sample from those attending training event on benzodiazepines and willing to participate
Berings et al <37>	Belgium	Not stated	GPs	128	Mean number of benzodiazepines prescribed (actual prescribing)	Number of detailers received; estimated utility of commercial information	Those with more positive attitudes about utility (p<.10) and seeing more detailers (p<.10) prescribed more benzodiazepines	More recent graduates prescribed fewer benzodiazepines; random sample of 450 GPs from two provinces
Caudill et al <38>	USA (Kentucky)	Not stated	Primary adult medicine practitioners	446	Relative cost of prescribing based on physician responses to treatment choices for three case scenarios in primary care	Frequency of use of information provided by pharmaceutical representatives	In multivariable regression model frequency of use was significant (p=.02) independent positive predictor of cost	Four choices offered for each scenario, choices had equal efficacy but widely varying costs; cases developed by academic internists; survey mailed to all 1603 physicians in Kentucky with primary care specialties

Powers et al <39>	USA	Not stated	Family medicine and general internal medicine faculty and residents	Not stated	Actual prescribing of ACE inhibitors and calcium channel antagonists for hypertension	Frequency of interaction with pharmaceutical representatives	Higher level of interaction correlated with more frequent prescribing	Abstract
Caamaño et al <40>	Spain	1993	Primary care physicians	311 (234 replied)	Units prescribed by physician; expenditure by physician	Utilization of information provided by pharmaceutical representatives	Higher volume and expenditure correlated with higher utilization (p = 0.035, p = 0.048)	Results felt to reflect credibility of information.

Table 2: National self-help groups and support organizations in the U.K.

Principal focus/classification	Number of groups
Disability	69
Cancer	29
Blind/partially sighted	25
Learning difficulties, mental handicap	19
Deafness	14
HIV/AIDS	12
Mental health	12
Heart	10
Phobias	10

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