

Understanding and Responding to Pharmaceutical Promotion

A Practical Guide

First edition

Working Draft for Pilot Field Testing



World Health Organization/Health Action International
Collaborative Project

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This manual is dedicated
to the memory of
Lisa Waller-Hayes

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Preface

Medicines can play a crucial role in the attainment or maintenance of health but it is vital that they are used rationally. If a patient needs treatment, he or she must have access to the right medication, in the right dosage and for the appropriate course of treatment. Health-care professionals, such as doctors and pharmacists, play a key role in ensuring that medicines are used appropriately. As gatekeepers to care, they need to assess different treatment options, including pharmacotherapy, and consider each for potential benefit and harm.

In 1994, the World Health Organization (WHO) published the *Guide to Good Prescribing*. This publication was developed and field tested extensively before its release. After publication, it was translated into multiple languages and was widely used. This guide highlighted the need for students to learn to focus in a very practical way on treatment goals when making prescribing decisions, and to develop their own personal formulary for commonly treated conditions. The report of the evaluation was published in *The Lancet* (1995).

However, in recent years, growing concern has focussed attention on the relationship between health-care professionals and the pharmaceutical industry - particularly the industry's influence on prescribing and dispensing decisions through a range of promotional tools, which can influence treatment choices. This influence can lead to less than optimal medication choices, sometimes to the detriment of patient health.

Despite the fundamental nature of these treatment decisions and the important role of pharmaceutical promotion in shaping them, health-care professionals receive little or no instruction on how to assess pharmaceutical promotion and how to understand its often subtle influence on their behaviour. In 2005 a WHO/Health Action International (HAI) cross-sectional, international survey of educational initiatives on pharmaceutical promotion found that whilst many medical and pharmacy faculties included this topic in their curriculum, most spent less than one day on the subject - with some schools devoting only one to two hours to the issue. The survey also showed that even though educators recognise the need for instruction on pharmaceutical promotion and sometimes do their best to incorporate it into their work, it is mostly limited. There is, therefore, both an identified need and an expressed determination by educators to further develop curricula in this area.

This new publication is modelled on and should be seen as a companion module to the *Guide to Good Prescribing*. It will assist teachers and health-care professionals to teach medical and pharmacy students about pharmaceutical promotion. *Understanding and Responding to Pharma-*

ceutical Promotion – A Practical Guide has been produced as part of a collaborative HAI/WHO project focusing on pharmaceutical promotion and its effect on the rational use of medicines in many countries around the world. It has been made possible thanks to the expertise and knowledge of numerous WHO and HAI staff members and a broad group of educators and activists working with the HAI network on pharmaceutical promotion.

This draft manual is a first step in addressing the need for medical and pharmacy professionals to reconsider their central role as a target for pharmaceutical marketing and to provide some understanding of how this fits into the wider context of promotion. Its nine chapters explore a spectrum of related topics that will help them be better prepared to face the promotional activity to which they will be exposed and to analyse information about medicines in order to make choices that will contribute to the health of patients.

We do not consider this to be the final product. We encourage feedback on the material included in this book so that it can be improved and updated as it is vital that this publication reflects the real needs of students and educators. The manual will be rigorously pilot tested and evaluated at a number of sites during 2009-2010 using English and Spanish versions of the text. Afterwards, it will be revised following close examination of feedback and evaluation data. In addition, classroom experiences using this text and its exercises will be collected in order to revise the material for wider use in the future. We hope that the manual provides material for thought-provoking discussions and we look forward to receiving your comments.

Hans Hogerzeil

Director

ESSENTIAL MEDICINES AND PHARMACEUTICAL POLICIES

WORLD HEALTH ORGANIZATION

Geneva

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Amsterdam

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Abbreviations and Acronyms

ABPI	Association of the British Pharmaceutical Industry
ARR	Absolute Risk Reduction
CLASS	Celecoxib Long-Term Arthritis Study clinical trial
CME	Continuing Medical Education
DDMAC	US Food and Drug Administration's Division of Drug Marketing, Advertising and Communication
DTCA	Direct-to-Consumer Advertising
FDA	US Food and Drug Administration
HAI	Health Action International
IFPMA	International Federation of Pharmaceutical Manufacturers & Associations
INN	International Nonproprietary Name
KOL	Key Opinion Leaders
NNT	Number Needed to Treat
PhRMA	Pharmaceutical Research and Manufacturers of America
ROI	Return on Investment
RRR	Relative Risk Reduction
Rx&D	Canada's Research-based Pharmaceutical Companies
UK	United Kingdom
US	United States of America
VIGOR	Vioxx Gastrointestinal Outcomes Research clinical trial
WHO	World Health Organization

Chapter 1

Promotion of medicines and patient health

Barbara Mintzes

Why discuss pharmaceutical promotion?

Medical and pharmacy students often begin to have contact with pharmaceutical industry representatives early in their training. For example, a survey in Finland found that nearly half of all medical students attended presentations by sales representatives at least twice a month (Vainomaki et al., 2004). In the United States (US), third-year medical students on average received one gift or attended a sponsored activity each week, and over nine out of ten had been asked by faculty members to attend sponsored lunches (Sierles et al., 2005). Most students in both surveys believed that their own prescribing was unlikely to be affected by pharmaceutical promotion and many students accepted gifts although they disapproved of them in principle.

In India, final-year medical and pharmacy students were unaware of incentives offered by pharmaceutical manufacturers to pharmacies to boost medicine sales. However, most had seen prescription-only medicines being dispensed without a prescription (Kumar et al., 2006).

Links between pharmaceutical manufacturers and medicine and pharmacy are omnipresent but students often receive very little education about the effects of these interactions or how to manage them (Mintzes, 2005). This can create a 'hidden curriculum' in which students subconsciously learn that promotional information, sponsored education and acceptance of gifts and free samples are accepted norms of professional practice (Sierles, 2005).

This manual aims to bring this 'hidden curriculum' into the open, to give you an opportunity to think beforehand about how to manage interactions with industry representatives and to develop skills that you can use throughout your professional life. It covers techniques used by the pharmaceutical industry to influence the use of medicines, advertisements, sales representatives, promotions aimed at the public, ethical conflicts, regulation and avoiding bias in information about medicines. Each chapter is accompanied by practical exercises and illustrative examples. We hope that you will find the manual a useful preparatory resource for your professional practice.

Aims of this chapter

This introductory chapter describes the extent and types of pharmaceutical promotion and provides an overview of the research evidence on effects of promotion. By the end of the session based on this chapter you should be able to:

- Document the scale of promotion in terms of industry spending;
- Describe the different types of pharmaceutical marketing;
- Describe evidence showing the effects of pharmaceutical marketing on professional practice.

Tension between health and commercial aims

Medicines are a core part of health-care services and their use has grown enormously during the last century with the advent of effective antibiotics, anaesthetics, painkillers, antiretrovirals and many other medicines. They can cure diseases, relieve symptoms and prevent future ill-health. Appropriate medicine use means providing the right medicine at the right dose, when it is needed, and avoiding medicines that are unnecessary or are unlikely to result in health benefits. It means choosing the treatment with the best effectiveness and safety profile among available alternatives and the least costly of equivalent treatments.

These decisions require knowledge of a person's health condition, life situation and preferences and access to unbiased, comparative information on the benefits and harmful effects of the range of available treatment options.

The international pharmaceutical industry plays an important role in the development, production and distribution of medicines. In many countries, it has also become the major funder of continuing medical education (CME) and research. However, a tension exists between pressures to expand product sales within a competitive market and patient care. The World Health Organization (WHO) described *"an inherent conflict of interest between the legitimate business goals of manufacturers and the social, medical and economic needs of providers and the public to select and use drugs in the most rational way."* (WHO Europe, 1993).

The global medicines market

In 2007, global pharmaceutical sales amounted to US\$712 billion (IMS, 2008). The top product, in terms of sales, was the cholesterol-lowering medicine Lipitor (atorvastatin), which had sales of US\$13.6 billion (Scrip, 2007). This is more than the gross national income of over half of the world's countries (World Bank, 2008). The effects of promotion in fuelling sales of specific brands should not be underestimated. For example, sales of Lipitor (atorvastatin) were much

higher than sales of simvastatin and pravastatin, two medicines in the same class that have similar effectiveness and are less costly (Prescrire, 2006).

Newer medicines are not necessarily better

To get a new medicine to market, a company must provide evidence of effectiveness, safety and manufacturing quality. Effectiveness and safety evidence includes laboratory, animal and clinical studies. The largest are ‘phase III,’ randomised, controlled trials in patients with the disease the medicine aims to treat. Most of these studies compare a new medicine to a placebo. Many people are unaware that manufacturers do not need to show that a new medicine is better than existing treatments. The new medicine must have the claimed beneficial effect to an acceptable extent compared with placebo and be acceptably safe. To test the medicine’s efficacy, the manufacturer carries out the randomised, controlled trials involving patients with the condition to be treated by the new medicine. These are usually relatively short-term studies and may last a few weeks to a few months, even when the treatment is for a chronic disease. For some serious diseases for which placebo treatment would be unethical, a new medicine is compared with existing treatments. However, these studies aim to show that a new medicine is as effective as alternatives, or no less effective; it does not need to be better.

When a new medicine comes to market, it has only been tested on highly selected groups of clinical trial participants. For example, the elderly and those with co-morbid, chronic conditions are usually excluded. Too few people have been exposed to assess rare harmful effects, generally 3,000 to 5,000 people. Because of this inevitably incomplete safety assessment, there is a rationale from a public health perspective and an individual patient care perspective for a slow, cautious approach to the introduction of new medicines.

Table 1 presents an overview of ratings by an independent drug bulletin, *La revue Prescrire*, of new medicines and newly approved indications for medicines in France over a 24-year period. Around 10% were judged to have advantages over existing therapies. As this table further shows, when it comes to medicines, newer is not necessarily better. As already mentioned, a new drug does not need to show any improvements over existing treatments to be approved for marketing. However, companies need to recoup investments in drug development as well as make a profit for shareholders and so new medicines tend to be heavily promoted, whether or not they offer treatment advantages.

Table 1: New medicines and indications in France 1981-2004

Rating	Explanation	Number of new medicines or indications (%)
Bravo!	Major therapeutic advance	7 (0.2)
A real advance	Important therapeutic advance, with certain limitations	77 (3)
Offers an advantage	Some advantages, but not enough to fundamentally affect clinical practice	223 (7)
<i>Subtotal: Advantages over existing treatments</i>		<i>307 (10)</i>
Possibly helpful	Minimal advantages over existing treatments	467 (15)
Nothing new	No additional value	2,109 (68)
<i>Subtotal: Minimal to no advantage</i>		<i>2,576 (83)</i>
Judgment reserved	Inadequately documented safety and/or efficacy	126 (4)
Not acceptable	Real or potential disadvantages over existing therapies	87 (3)
<i>Subtotal: To be avoided - inadequately tested or worse clinical profile</i>		<i>213 (7)</i>
Total		3,096 (100)

(Source: La revue Prescrire, 2005)

Widespread influence

Links between the health professions and the pharmaceutical industry have grown enormously in the late 20th and early 21st centuries, leading to a call from physician educators for strong ‘firewalls’ to protect the independence of academic medical centres (Brennan, 2006). In a large US survey (Campbell, 2007), over 90% of physicians reported some type of relationship with the pharmaceutical industry:

- 8 out of 10 received gifts, usually free food at their workplace;
- 8 out of 10 received free medicine samples;
- 4 out of 10 had their expenses paid to attend meetings and conferences;
- 3 out of 10 were paid consultants, on a company speakers’ bureau or advisory board.

Surveys in wealthy, industrialised countries have found that physicians see an average of one sales representative a week (Wazana, 2000). In Turkey, however, more than half of urban physicians in the third largest city, Izmir, saw at least one sales representative each day and one-third spent more than 30 minutes a day with sales representatives (Guldal, 2000). Although two-thirds of the surveyed physicians believed that sales representatives did not influence their prescribing, most said that they used advertisements and brochures as an information source.

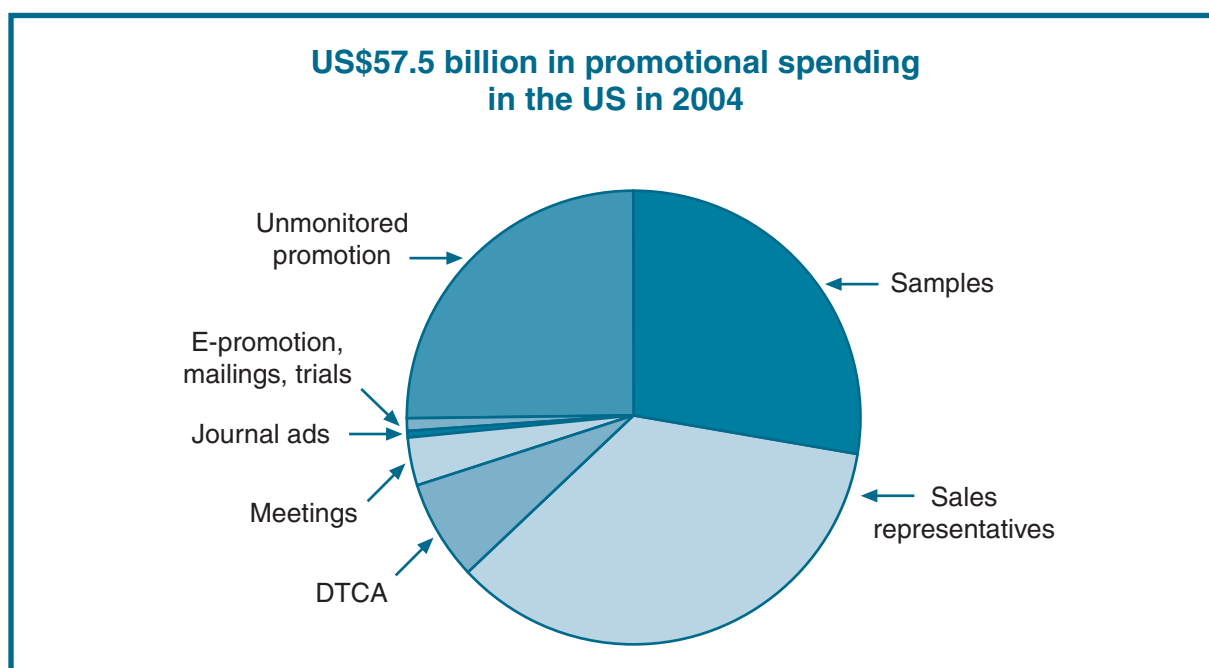
There have been relatively few studies of relationships between pharmacists and the pharmaceutical industry. One national US survey examined attitudes to the pharmaceutical industry and to pharmaceutical promotion (Farthing-Papineau, 2005). Two-thirds of this random sample of 1,640 pharmacists in hospital and community practice reported that sales representatives provide gifts to pharmacists that have no relation to patient care.

Spending on pharmaceutical promotion

Figure 1 provides a breakdown of promotional spending in the US in 2004, where information on spending is publicly available. Advertising in professional journals is a small part of spending – only 2%. In terms of direct company expenses, the largest promotional category is ‘detailing to doctors’. ‘Detailing’ is a North American term for one-to-one sales representatives’ visits. Sales representatives also distribute samples during sales visits so these two types of promotion are strongly linked.

The US is unusual among industrialised countries in allowing direct-to-consumer advertising (DTCA) of prescription medicines on television, magazines and billboards. In 2004, spending on DTCA reached US\$4 billion (Gagnon, Lexchin, 2008).

Figure 1: US promotional spending on prescription medicines, 2004



(Source: Gagnon, Lexchin, 2008)

Figure 1 is an analysis of promotional spending in the US that includes the most accurate estimates from two pharmaceutical market research firms, IMS Health and CAM. The figure is notable for the approximately 30% of spending on ‘unmonitored promotion’. What types of activities are covered? In part, this includes a range of non-traditional promotional activities described in the pharmaceutical marketing literature and in court cases about pharmaceutical promotion (Steinman, 2006).

Box 1: Non-traditional forms of marketing

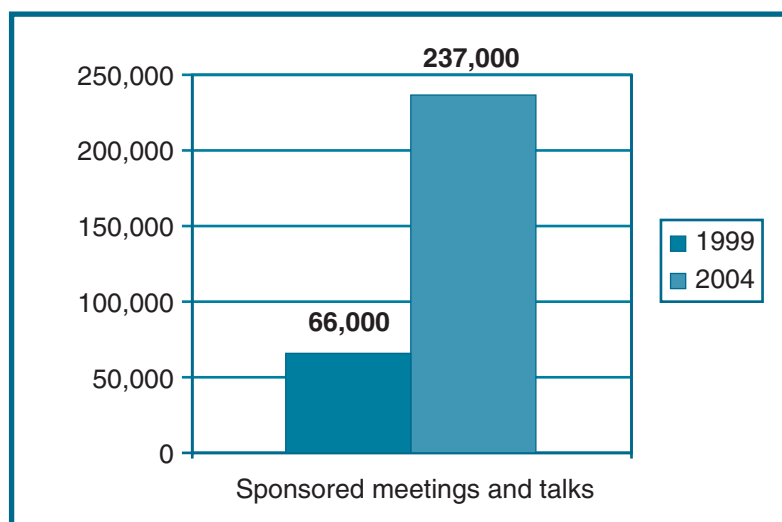
- Industry-sponsored continuing medical and pharmacy education
- Funding of key physician ‘opinion leaders’
- Ghost-writing of journal articles
- Funding of diagnostic and treatment guideline development
- Public relations campaigns including unbranded ‘disease-oriented’ advertising
- Funding of patient groups and medical societies
- Market seeding research (‘Phase IV’ studies without clear scientific objectives)
- Internet advertising
- Journal supplements and free journals
- Pharmacy discounts linked to sales volume*

**A common form of promotion in many developing and middle-income countries, where prescription-only status of medicines is not enforced.*

Key opinion leaders

Figure 2 shows the number of pharmaceutical-industry-sponsored meetings and presentations held in the US in 1999 and five years later, in 2004, showing a quadrupling of the frequency of these sorts of events.

Figure 2: Number of sponsored meetings and talks in the US, 1999 and 2004



(Source: Caplovitz, 2006)

Presentations by a physician who is sponsored by a company may not look like direct advertising to the audience and this may increase their effectiveness. Documents from rofecoxib (Vioxx)'s manufacturer Merck, cited in the *Wall Street Journal*, stated that physicians attending lectures by a sponsored physician wrote, on average, an additional US\$624 worth of prescriptions during the following year compared to doctors who had not attended such presentations (Hensley, 2005). In contrast, meetings with sales representatives generated an increase of US\$166. These internal documents suggest that sponsored talks were an integral part of Merck's marketing strategy (Caplovitz, 2006).

Pharmaceutical marketers refer to paid health professional spokespeople as 'key opinion leaders'. "An awful lot of the doctors in the audience are naive about the fact that these are really sales talks," comments Jerry Avorn of Harvard Medical School, US, (Hensley, 2005). In one US state, Minnesota, over one year more than 20% of physicians received payments from pharmaceutical companies, and over 100 physicians received more than US\$100,000 (Spurgeon, 2007).

Continuing medical education

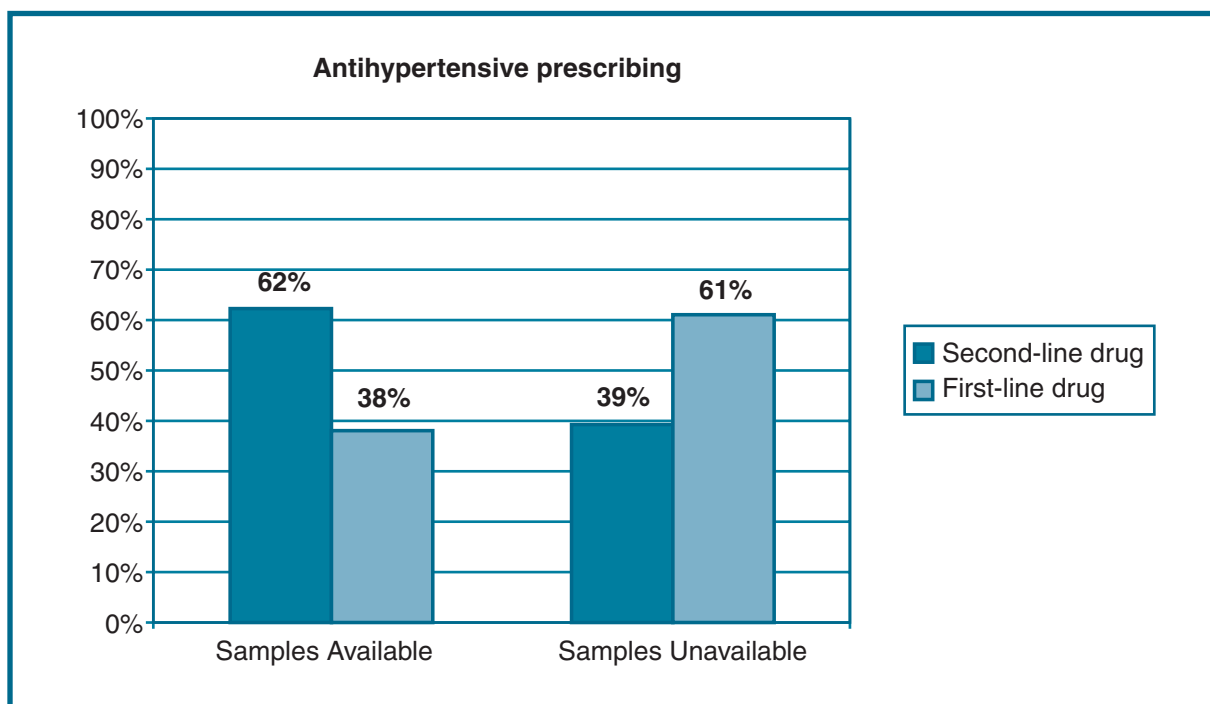
Between 1998 and 2003, financing of CME by pharmaceutical companies nearly tripled in the US, from US\$302 to \$971 million, and most CME is funded by the pharmaceutical industry (Steinbrook, 2005). The standards governing commercial support do not prevent sponsors from discussing content with academic providers and suggesting topics or speakers.

Free samples

Many physicians view free samples positively and stock them to provide to patients who would otherwise have to pay for medicines and cannot afford them. A key reason that many physicians see sales representatives is to obtain free samples.

One study compared prescribing decisions before and after a family practice outpatient clinic brought in a policy prohibiting free samples (Boltri, 2002). Figure 3 compares initial prescriptions of medicines for high blood pressure during the two time periods. Current treatment guidelines had identified diuretics and beta blockers as first-line treatments for uncomplicated hypertension (National Institutes of Health, 1997). These inexpensive, off-patent medicines were not being actively promoted. When samples were available, patients received second-line treatments more often as initial therapy. These should generally be reserved for patients unable to tolerate first-line treatments or for whom first-line medicines are ineffective. The conclusion of this study was that banning samples improved the quality of care provided to patients.

Figure 3: Effect of free samples of medicines on prescribing decisions



(Source: Boltri, 2002)

Sponsored clinical practice guidelines

The sponsorship of authors of treatment guidelines raises concerns that the advice provided may be biased in favour of sponsors' products. A study of over 200 guidelines from a variety of

countries included in a US National Guideline Clearinghouse found that around one-third of authors had financial links to companies producing the treatments they were evaluating, and nearly three-quarters of guideline panels included authors with conflicts of interest (Taylor, 2005). It is not only a problem of a specific product being favoured. Treatment norms can also be affected and a shift in criteria can mean that millions more people can be defined as needing therapy. For example, when European Society of Cardiology guidelines were applied to a county in Norway, three-quarters of the population was defined as being at 'increased risk' and potentially needing treatment (Heath, 2006).

Ghost-writing

Ghost-writing of journal articles refers to a practice in which research publications with academic authors are in fact written by pharmaceutical company employees or medical communication companies working for pharmaceutical companies.

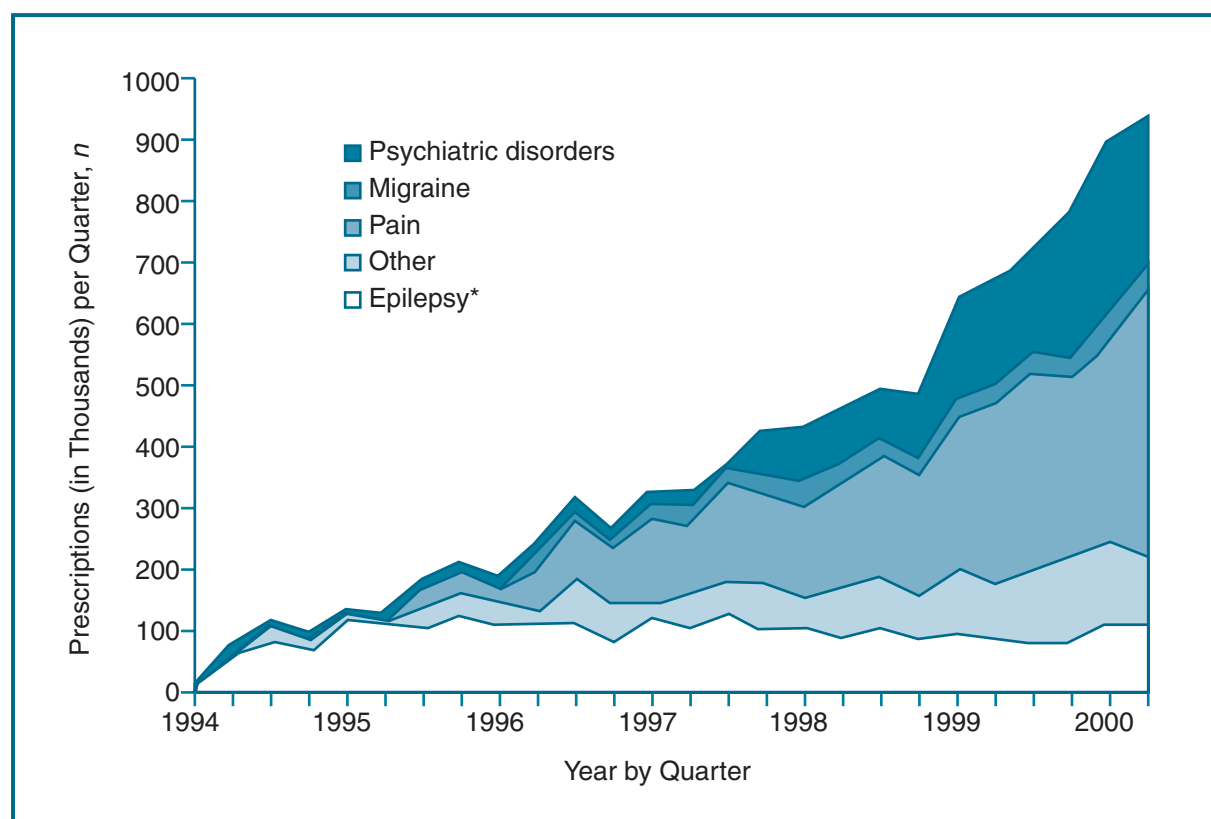
David Healy, a psychiatrist at the University of Wales, describes having been invited to speak at a sponsored medical conference and being presented with a ghost-written paper for inclusion in an associated journal supplement. He refused the paper and wrote his own, only to find the ghost-written paper published with a different academic author's name on it (Healy, 1999). He also describes more systematic use of ghost-writing to market sertraline (Zoloft), which surfaced in a document prepared by the medical information company Current Medical Directions Incorporated (CMD) that became public during a US court case (Healy, 2003). CMD listed draft articles with authors "to be determined" and 55 subsequently published articles were linked to CMD's list. These included the results of 25 clinical trials, all favourable to sertraline. On average each had 6.6 listed authors; some academic authors appeared more than once. A ghost-written paper may also condemn a competitor's products. A US physician described an article she was asked to sign that did not mention the sponsor's medicine, but raised safety concerns about a competing treatment (Fugh-Berman, 2005).

In response to the problem of ghost-writing, major medical journals have tightened up their guidelines for authorship (see: <http://jama.ama-assn.org/cgi/content/full/284/1/89>). However, many journals publish company-sponsored supplements, usually consisting of reports of sponsored symposia and presented papers. The company pays for these extra journal issues and has a large degree of editorial control over contents. Bero and colleagues (1992) analysed over 600 symposia reports appearing in 58 major medical journals over 23 years. Those with a single pharmaceutical company sponsor were more likely to have misleading titles and use brand names rather than generic names or the International Nonproprietary Names (INN) and were less likely to be peer-reviewed than articles in regular issues of the journal.

Activities aimed at increasing sales

Several recent US court cases have led to the release of internal documents that highlight the variety of activities used to increase sales of medicines. Gabapentin (Neurontin) was approved in the US as a secondary treatment for epilepsy. As Figure 4 shows, soon most prescriptions were for unapproved or ‘off-label’ use. Promotion of unapproved uses of a medicine is illegal both in the US, where this court case occurred, and elsewhere. The problem with promotion of medicines for unapproved uses is that the company has not provided systematic evidence of efficacy or safety to the national regulatory agency for these uses. In many cases, the medicine has not been adequately tested and potential benefits may not outweigh potential harm. This was the case for many of the uses for which gabapentin was promoted (Steinman, 2006). Details about promotional activities that encouraged off-label use surfaced in this court case: “*Gabapentin [Neurontin] was promoted by using education and research, activities not typically recognized as promotional, ‘independent’ continuing medical education, ‘peer-to-peer’ selling by physician speakers, and publications...*” (Steinman, 2006).

Figure 4: Gabapentin (Neurontin) use for unapproved indications



* The only use for which gabapentin was approved over this period.

(Source: Steinman, MA et al., 2006)

From promotion to medicine use

The prescribing pattern for gabapentin (Neurontin) illustrated in Figure 4 is consistent with the promotional activities described during the Neurontin court case (Steinman, 2006). However, in surveys, physicians typically report that promotion has little effect on their prescribing decisions. For example, a study of internal medicine residents found that only 1% believed that promotion had a strong effect on their prescribing decisions and most felt it had no effect (Steinman, 2001).

Evidence shows promotion affects health-care provision

If promotion of medicines did not affect treatment decisions, would pharmaceutical companies pour billions of dollars into marketing targeting professionals each year? Given companies' need to show a healthy profit to their shareholders, this seems unlikely. Market research companies calculated the average return, in increased sales, per dollar invested in pharmaceutical promotion in 2004 at US\$8.34 (Arnold, 2005). Fortune 500 ratings also consistently rank the pharmaceutical industry as having among the highest returns on investment of any industry: in 2006 it ranked second, after the oil industry, with a 19.6% rate of profits as a percentage of total revenues (Fortune, 2007). The research evidence confirms the fact that promotion does affect professional practice.

Inaccurate beliefs about promotion's influence

Despite this profitability and the numerous examples of industry influence on health care, many health professionals underestimate the effects of pharmaceutical promotion on their beliefs and professional practice. The first study to examine the contrast between beliefs about influence, and a measure of that influence, surveyed a sample of Boston area physicians about their beliefs in two 'commercial myths' that were not supported by scientific evidence (Avorn, 1982). These were beliefs that: (a) propoxyphene, an analgesic with a poor safety profile, was more effective than aspirin; and (b) poor blood flow was a major cause of senile dementia. The latter supported the use of vasodilators to treat dementia, although they had not been shown to be effective. Although most of the surveyed physicians stated that they relied on scientific information sources, they also believed these non-scientific 'commercial myths'. More recent studies of effects of free samples and sponsored symposia on prescribing behaviour have similarly found an effect on prescribing despite health professionals' beliefs that they were unaffected (Adair, 2005; Orłowski, 1992).

Negative effects on prescribing

In 2005, Norris et al. conducted an extensive review of 2,700 journal articles in the WHO and Health Action International (HAI) database on pharmaceutical promotion (www.drugpromo.info). They found that physicians frequently use promotion as a source of information about new drugs and, agreed with Avorn et al.'s findings, that promotion influences attitudes more than physicians realize (Norris et al., 2005). Much less research was available on effects on pharmacists' or other health professionals' attitudes.

Physicians who report that they rely to a greater extent on promotion prescribe less appropriately, have higher prescribing volumes and adopt new medicines more quickly (Norris et al., 2005). Industry sponsorship can affect the content of CME and industry-funded research and is more likely to show results that are favourable to the sponsor. Additionally, patients with exposure to DTCA of prescription medicines are also more likely to request advertised medicines. Norris et al. highlighted the need for more research on the public health impacts of pharmaceutical promotion.

A systematic review published in the *Journal of the American Medical Association* identified 29 studies published from 1994-1999 that examined the effects of interactions between physicians and the pharmaceutical industry and effects on knowledge, attitudes and behaviour (Wazana, 2000). These were comparative studies pre- and post-exposure to promotion, comparative cohort studies, case-control studies and cross-sectional surveys. Here are the key findings:

- Most surveyed physicians denied that gifts could influence their practice;
- The more gifts physicians received, the less likely they were to believe their prescribing would be affected;
- The more frequent the contact with sales representatives, the greater the likelihood that physicians would request addition of sponsors' products to hospital formularies;
- Payment for conference travel, industry-sponsored meals, research funding and honoraria also increased the likelihood of requests for formulary additions versus other physicians who had not received such payments;
- More exposure to talks by sales representatives was associated with less ability to recognise inaccurate claims about medicines;
- CME funding increased the likelihood of prescribing sponsors' products;
- More frequent contact with sales representatives was associated with higher prescribing costs, more rapid prescriptions of new medicines and less prescribing of generics.

Little regulation

As described, promotion affects prescribing and medicine use, with likely negative effects on both costs and quality of care. Many countries have laws governing pharmaceutical promotion. Manufacturers are generally prohibited from providing deceptive or misleading information or promoting medicines for unapproved uses. These laws reflect a recognition that medicines can lead to harm as well as benefit; and therefore need to be provided and used with care. Additionally, an international set of standards exist for regulation of promotion, the WHO *Ethical Criteria for Medicinal Drug Promotion*, with the aim to “support and encourage the improvement of health care through the rational use of medicinal drugs.” (WHO, 1988).

In conclusion: far from a trivial issue

In parallel to the lack of priority given to regulation, pharmaceutical promotion has received relatively little attention in medical and pharmacy education (Mintzes, 2005). This lack of attention stands in stark contrast to the billions of dollars spent each year on pharmaceutical promotion. Health professionals often incorrectly believe that they are not being influenced by promotion and may have little training on how to distinguish ethical from unethical promotional practices.

Unethical promotion can affect patient care negatively. Shahram Ahari, ex-sales representative for Eli Lilly’s antipsychotic medicine olanzapine (Zyprexa), imagines the management decisions that led to the instructions he received to downplay risk information: “*Decisions like these are simply a cost-benefit analysis somewhere up there. This diabetes, this weight gain, sure it exists, but if we start talking about it now we’ll lose billions of dollars.*” (Ahari, 2007).

Interactions between health professionals and the pharmaceutical industry often begin early in training. Discussing these interactions can help to distinguish ethical from unethical relationships and biased from accurate information. Training in therapeutics is an important part of professional education. It is also important to understand the context in which these therapeutic decisions about medicine use are made. The aims of this manual are to raise awareness among pharmacy and medical students of this broader context surrounding medicine use; to provide background information about the types and extent of promotion and the research evidence on its effects; and to assist in the development of practical skills to guide interactions with the pharmaceutical industry in professional practice. The goal, ultimately, is improved patient care.

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Chapter 2

Techniques that influence the use of medicines

Peter R Mansfield

The pharmaceutical industry's marketing activities are successful in achieving sales because they are able to influence the decision-making process of health professionals and patients, and therefore the prescribing and dispensing of medicines. Health professionals often have a limited awareness of the influence of promotion, and promotion is more effective than many realize. It is common for health professionals to believe that "promotion doesn't affect me". As one family physician put it, "*Just because I have a pen with the name of a drug on it, doesn't mean I'm going to prescribe it.*" (Prosser et al., 2003). Often, however, professionals have less confidence in the abilities of their colleagues to resist misleading persuasion (Zipkin and Steinman, 2005).

Aim of this chapter

The aim of this chapter is to help you understand the techniques that pharmaceutical companies use to promote the use of medicines. It is important that you are aware of the impact these techniques have and your own vulnerability to them in order to best care for your patients. By the end of the session based on this chapter you should be able to:

- Explain why health professionals are vulnerable to influence techniques;
- Describe some of the common techniques used to influence the decision-making of health professionals;
- Discuss strategies for responding to pharmaceutical promotion.

Vulnerability to marketing influences

Anyone can be influenced by sophisticated marketing techniques, and all too often we are

unaware of this influence. Health professionals are no different from other human beings in this respect. However, a major difference between promotion aimed at health professionals and many other forms of marketing is that the aim is to affect recommendations made for patients, not purchases made by professionals themselves.

Box 1: A selling success

Promotion versus scientific evidence

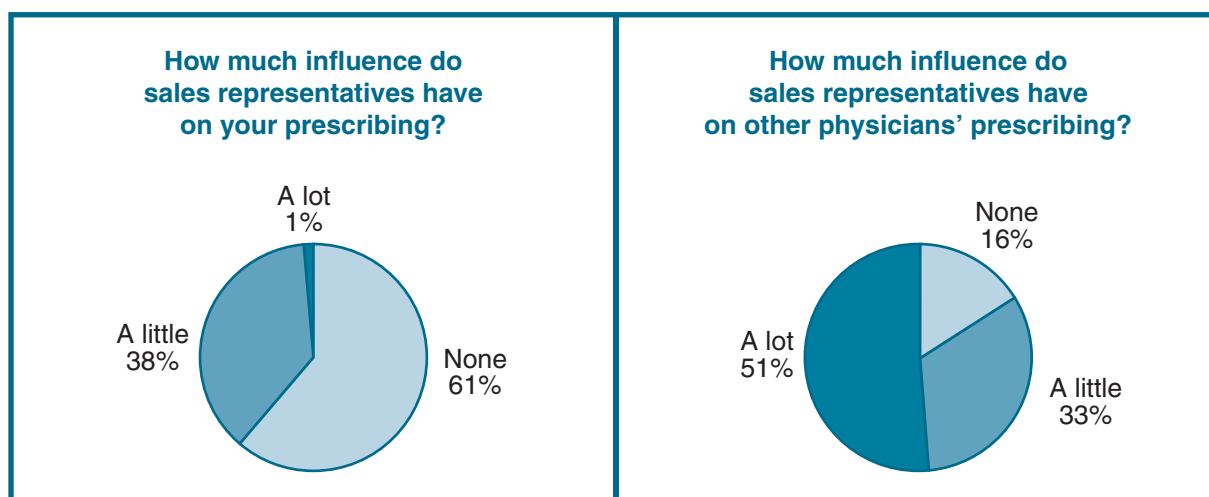
The US\$3.8 billion in sales for esomeprazole (Nexium) in 2003 (a medicine used to treat heartburn and other stomach acid problems) is an example of the ongoing importance of commercial influences on prescribing (Anon, 2003). Without a strong 'commercial myth' of superior effectiveness informing prescribing decisions, this sales volume would be highly unlikely, as the same treatment effect can be achieved much less expensively with esomeprazole's parent medicine, generic omeprazole, when used at equipotent (equivalent) doses (Therapeutics Initiative, 2002).

Health professionals know they have a fiduciary responsibility to put patients' interests and care first, before their own personal gain. Thus pharmaceutical marketers must ensure that their activities appear to contribute to patient care, whether the medicine they are promoting is the best available treatment for a professional's patients or not. A number of marketing techniques assist in this process, as described throughout this manual. Two key factors also contribute to health professionals' vulnerability to marketing influences: belief in their own invulnerability and the use of 'decision-making shortcuts'.

Belief in invulnerability

Many health professionals believe that they are not personally influenced by pharmaceutical promotion, but that their colleagues are affected (Zipkin and Steinman, 2005). For example, a survey of internal medicine residents asked them how much influence pharmaceutical sales representatives had on their prescribing. As Figure 1 shows, there was a large difference in their beliefs about influences on their own prescribing and that of colleagues (Steinman et al., 2001).

Figure 1: Survey of hospital doctors about sales representatives' influence



(Source: Steinman, 2001)

Psychologists have found that it is normal for people to believe that only *other* people are vulnerable to being misled by promotional techniques. This is called **the illusion of unique invulnerability** (Sagarin et al., 2002).

That such beliefs are illusory is reinforced by the research evidence: *“Increased promotion is associated with increased medicine sales, promotion influences prescribing more than doctors realise and doctors rarely acknowledge that promotion has influenced their prescribing. Doctors who report relying more on promotion prescribe less appropriately, prescribe more often and adopt new drugs more quickly.”* (Norris et al., 2005).

Decision-making shortcuts

Health professionals are continually faced with decisions about whether a treatment is needed and which of a range of available treatments to recommend. Because of the need to constantly make pragmatic decisions to try to resolve patients' health problems quickly and efficiently, health professionals often rely on decision-making shortcuts. These can include, for example, trust in experts' recommendations, use of a medicine because many colleagues are prescribing it, or choice of the first treatment that comes to mind or is available as a sample, rather than researching all available alternatives for treating a particular condition.

These shortcuts create additional vulnerabilities where promotion may influence physicians. Experienced health professionals often use shortcuts with little awareness of doing so, similarly to the way experienced drivers change gears with little conscious effort (Robinson, 2000). Decision-making shortcuts and the techniques that influence them have been studied by logicians,

psychologists, advertising agencies and others – some were even described by Aristotle around 350 BC. (For more on this, see Fischer, 1970; Chaiken, 1999 and Zaltman, 2003.)

The aim of promotional activities

In a crowded marketplace with many available treatments, pharmaceutical companies have a commercial imperative to persuade professionals that their product is the best choice in order to maximise profits. This is done through a variety of influence techniques that form the core of successful marketing. The aim is to persuade professionals who are initially unaware of a medicine's existence to move through the following series of stages:

Unawareness → Awareness → Interest → Evaluation → Trial → Use → Repeat use

(Lidstone and Collier, 1987; Prochaska and DiClemente, 1983)

Pharmaceutical companies use a mix of delivery methods including advertisements, pharmaceutical sales representatives, sponsorship and public relations. Messages delivered with these different methods reinforce each other. Promotional techniques can influence prescribers at different stages of this process. Companies often use advertising as a cost-effective way to create awareness of a product. Pharmaceutical sales representatives can build from this and focus on moving through subsequent stages. Use of expert or peer key opinion leaders to discuss a new product can also be effective in shifting health professionals from unawareness to awareness and ideally (for the marketer) interest in a product.

Evaluation of a new medicine is based on an impartial examination of the scientific evidence. However, even when evidence is available, few busy clinicians have the time required to perform systematic reviews or to critically appraise research reports. Additionally, the available evidence may be flawed due to poor research design, incomplete reporting, its funding source and publication bias or it may not be relevant to patient care decisions a clinician is facing. Sometimes an independent research group will have carried out a systematic evaluation of treatment options, but these evaluations may not be readily available or familiar to professionals. (See Chapter 8 for information sources.) Sponsored consensus statements and guidelines provide professionals with an existing evaluation that can be positively biased in favour of using the sponsor's product. For example, treatment guidelines for patients with kidney disease that were sponsored by Amgen, the manufacturer of epoetin alfa (EpoGen), recommended high-target haemoglobin levels (Coyne, 2007). This recommendation was likely to have led to more widespread prescribing of epoetin alfa in patients with kidney disease (Coyne, 2007).

Both marketing trials and provision of free samples are means of moving physicians past this evaluation stage to the stages of ‘trial’ and ‘use’, in other words, to get them to try out a product on their patients, with the aim of stimulating broader use and repeat use. These are forms of ‘market seeding’. Marketing trials are studies that have a commercial rather than a real scientific objective, in which doctors are generally asked to prescribe a medicine to a certain number of patients and record outcomes. Usually there is no comparison group or any precise research hypothesis being tested. Prescribers are usually paid to be part of these marketing trials.

Misleading information

In this chapter, we refer to a variety of techniques that aim to influence the use of medicines as ‘influence techniques’. Influence techniques can lead to good or harm. These are techniques that pharmaceutical companies employ in promotional activities. They are harmful when linked to misleading information. Systematic evaluations of advertisements and other promotional information sources have found a consistent trend towards exaggeration of benefits and down-playing of harmful effects (Norris, 2005). This is similar to what happens in marketing of other products, such as the ‘whiter than white’ claims for laundry soap. However, exaggerating a medicine’s benefits can lead to negative effects on patient health. There are three main ways that information can be misleading:

- Inclusion of flawed information (e.g. inaccurate, exaggerated, ambiguous or oversimplified);
- Omission of relevant information;
- Distraction with irrelevant information.

Omissions and distractions can as effectively misrepresent the existing evidence as inaccuracies, but are often harder to spot. For example, systematic analyses of pharmaceutical advertisements consistently find that inadequate information is provided about the known harmful effects of the promoted medicine (see Chapter 3).

Sales representatives

Table 1 describes some examples of common influence techniques used by sales representatives, as recorded in a qualitative study of sales representatives’ presentations in Australia (Roughead, 1998).

Table 1: Common influence techniques used by sales representatives

Unconscious influences on a person's judgement	Use of this unconscious influence for marketing purposes
Experts know best	"Professor Z recommends medicine B."
Peers know best	"Medicine B is the most frequently prescribed medicine for indication X."
People we like can be trusted	Use of attractive, friendly representatives.
We should help others who have helped us	Use of gifts, including free samples of expensive new medicines.
People should be consistent with their past statements	<p>Sales representative: "Do you treat many people with indication X?" Doctor: "Yes." Sales representative: "So you need to know about the treatments for indication X?" Doctor: "Yes." Sales representative: "Would you like me to tell you about our medicine B for indication X?" Doctor: "Yes."</p> <p>Note: this is an example of the commitment consistency technique - getting the physician to agree to successive statements that are consistent with one another, ending up at the conclusion the marketer wants, although if the final question had been asked first, the physician would probably not have agreed. Often the final statement is, "So doctor, will you try medicine B for your patients with indication X?"</p>

(Adapted from Cialdini, 2000; Roughead, 1998)

Box 2: A sales representative describes how to boost sales

Michael Oldani worked for nine years as a sales representative for a multinational pharmaceutical company. He describes a number of influence techniques he and his colleagues learned to use. For example, when physicians objected to a promotional claim, he would reply empathetically about how pleased he was they had brought up this point before countering the objection, then 'close the loop' using a commitment consistency technique (see Table 1). He also discusses the importance of a 'socially intimate relationship between doctors and drug reps' in shaping each other's practice. In other words, friendly relationships work well to boost sales (Oldani, 2004).

Expert and peer endorsement

The influence technique of triggering trust in experts is often called the ‘appeal to authority fallacy’ by logicians. However philosopher John Locke (1690) used the more insightful term ‘appeal to modesty’. He described this influence technique as a way to gain agreement or silence opposition by taking advantage of the tendency for people to think it immodest to challenge statements from an expert.

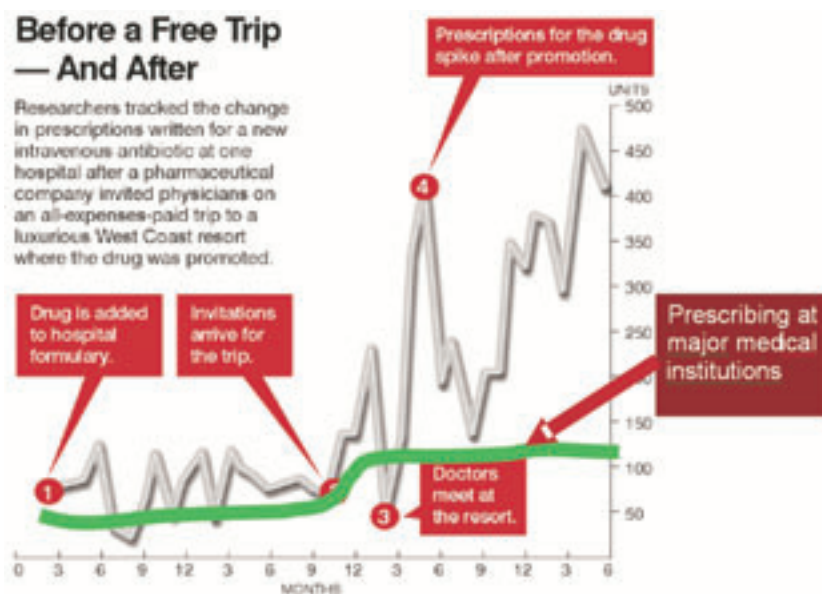
Reference to expert and peer endorsement are among the five most common ways influence techniques are used by sales representatives in promotion (see Table 1), (Cialdini, 2000; Roughead, 1998). Trust in an expert rests on the assumption that the expert is competent and unbiased. When this is justified, it will provide a quick and easy shortcut to obtaining a good answer. Unfortunately when it is not justified, it can mislead us into incorrect beliefs. Further complicating this, when people are misled they do not know that their beliefs are unjustified. Documents released during a US court case on promotion of the epilepsy medicine gabapentin (Neurontin) describe the recruitment of influential physicians in ‘peer-to-peer selling’ programmes and the funding of academic physicians identified as ‘thought leaders’ as part of this promotional campaign (Steinman, 2006). These thought leaders in some cases oversold the medicine’s potential benefits for a range of unapproved uses. A presentation by a medical specialist to professional colleagues does not look like promotion in the same way as a presentation by a company employee. The success of this influence technique may be due in part to the audience’s lack of awareness that it is part of a product-specific promotional campaign.

As mentioned in Chapter 1, in the US, the number of physician presentations sponsored by pharmaceutical companies increased from 66,000 in 1999 to 237,000 in 2004, a nearly four-fold increase over only five years (Caplovitz, 2006). This type of rapid increase in spending on a specific marketing technique is a good indication that the technique is effective. An internal Merck analysis made public by the *Wall Street Journal* suggests that talks by expert physicians are much more effective in stimulating sales than more traditional marketing techniques such as sales visits (Hensley, 2005).

A physician who is funded by a company to speak at continuing medical education (CME) sessions, hospital grand rounds or other educational events may have considerable leeway in presenting information on the treatment of a specific condition. However, there is usually a range of opinions amongst experts. A company is more likely to choose an expert who will recommend its own medicines, particularly profitable new ones. Consequently, whilst some expert recommendations are justified there is an overall bias towards funding support for experts who promote more profitable medicines. In most countries, companies are not required to report the funding they provide to opinion leaders. Five US states have laws requiring such disclosure and one, Minnesota, publicly discloses physician-specific payments. Physician speakers received on average US\$6,600 in 2003-2004 and the highest payment was US\$922,239 (Ross, 2007).

Figure 2 describes the shift in the prescribing of a new intravenous antibiotic that occurred after physicians at a university hospital attended an all-expenses-paid symposium at a luxury resort, where the medicine was promoted (Orlowski, 1992). The authors compared prescribing rates in their hospital before and after the symposium, and also looked at how their hospital compared with rates at other major hospitals. The physicians who had attended the symposium were asked whether they believed that attending all-expenses-paid events at luxury resorts would affect their prescribing; most believed that they would not be influenced.

Figure 2: Effects of "cme" on volume of prescribing



(Source: Orlowski, 1992; see slide from www.nofreelunch.org)

Building relationships

Pharmaceutical companies often select people to become sales representatives who have proven or potential sales skills and who are attractive. They often receive more ongoing job training than health professionals. Their training may include advice on how to dress and behave in order to be more likeable, including video role plays so that they can fine-tune their body language, what they say, and how they say it. Sales representatives often record detailed information about health professionals’ personal preferences and interests. These detailed profiles enable them, and their colleagues in the same company, to tailor the next encounter around the physician’s profile. They often build up relationships with professionals over many years so that they become

trusted as friends. However, they are not normal friends because they are paid to build up that relationship. Having spent a long time gaining a professional's trust, a sales representative may be able to persuade him or her to favour a new medicine in just a few minutes. This is an example of an influence technique that takes a long time to deliver but triggers a shortcut – trusting the advice of people we like – that can lead to a decision very quickly.

The use of gifts

The pharmaceutical industry provides many types of gifts to health professionals, from pens and meals to sponsored CME, research funding, consultancy fees, speakers' honoraria and travel to exotic locations. In some cases, national regulations and industry self-regulatory codes limit the types of gifts that may be provided (see Chapter 7 on regulation) but generally gifts of limited value and educational or research funding are allowed.

What explains the power of even small gifts to shape or manipulate behaviour? Self-interest is not always the only or even the main factor involved. What the pharmaceutical companies understand, but health-care professionals often overlook, is that much of social life is based on **reciprocity**. The need to return benefit for benefit, kindness for kindness, and favour for favour is a basic motivator in virtually every human society (Schafer 2004, Sahlins, 1972). As one researcher wrote, *“Each of us has been taught to live up to the rule [of reciprocity], and each of us knows the social sanctions and derision applied to anyone who violates it.... Every time we accept a gift we become beholden to the person who has given it to us.”* (Cialdini, 2000).

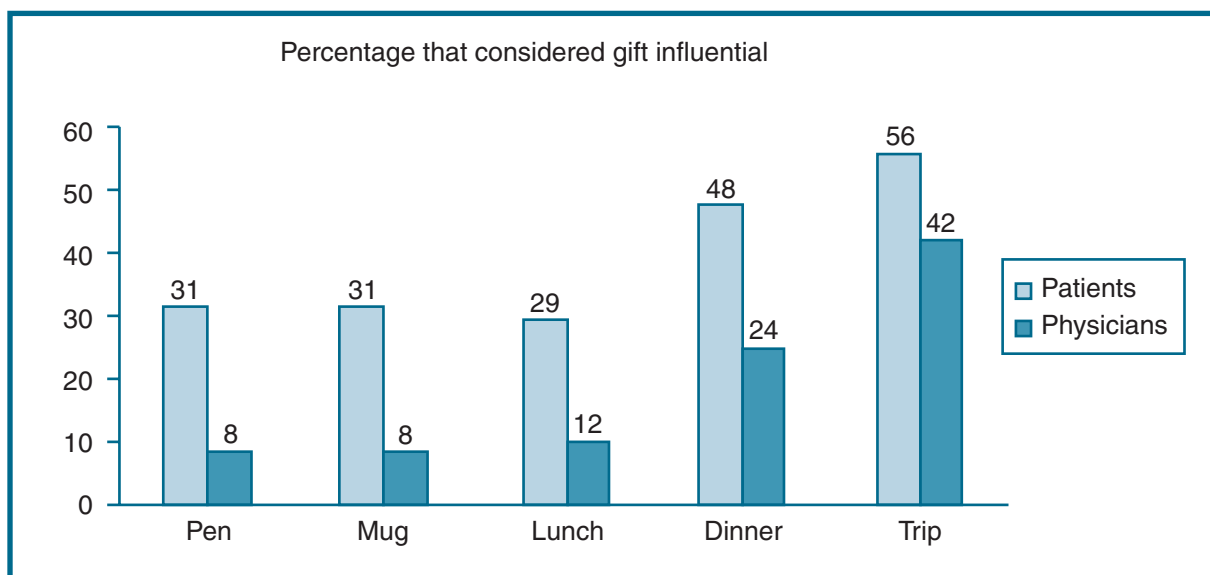
Even token gifts such as coffee mugs can have a surprisingly large effect (Steinman, 2001). Importantly, trinkets and baubles – small gifts of all kinds – buy ‘face time’ and help to establish a friendly and powerful relationship between the pharmaceutical companies and the health-care professionals to whom they are attempting to market their products effectively. As Katz (2003) observes, *“Those who do not acknowledge the power of small gifts are the ones most likely to be influenced, because their defenses are down.”* Contrary to what people expect, small gifts can be as or more effective in changing attitudes than larger incentives (O’Keefe, 2002). Health professionals who receive valuable and expensive incentives from pharmaceutical manufacturers may be more aware that the aim is to influence them than if they receive small token gifts of little value. However, in both cases, health professionals may be influenced through feelings of reciprocal obligation.

To put this point in another way, whether intended or not, every grant and gift from a pharmaceutical company to doctors, pharmacists or students comes with strings attached - strings which are often difficult to recognise but which are nevertheless psychologically influential. Gift-giving leads to many health professionals feeling an obligation to accept visits from sales representatives and to be open to what they have to say. Gift pens with a medicine's brand name on them are

particularly effective because they constantly remind prescribers of the medicine's name so that it will be more likely to be the first to come to mind when making a decision.

In one US survey, patients were asked the same questions as physicians about the influence of a variety of gifts (see Figure 3). They were much more likely to see even small gifts such as a pen or mug as influencing physician prescribing (Gibbons et al., 1998). (For additional information on gifts from an ethical perspective, see Chapter 6).

Figure 3: Patient and prescriber views on the influence of gifts in a US survey



(Source: Gibbons et al., 1998)

Common beliefs about promotion

Despite evidence that promotion is effective, many surveys have shown that health professionals prefer to think they are not influenced by promotion, as illustrated in Figures 1 and 3. A few commonly used rationalisations tend not to stand up to closer scrutiny:

- **“I’m too clever to be influenced.”**

Health professionals often believe that they are not vulnerable to being misled because they are intelligent and well educated. Intelligence and education do not protect people from being misled or influenced. Promotion aimed at health professionals takes the skills and education level of the target audience into account. Intelligence can help a person to see through some promotional techniques but a person rarely has the time and skills required to see through all of them.

- **“I’m just helping out my patients.”**

Many health professionals appreciate receiving free samples of new, expensive medicines that they can in turn provide as a ‘gift’ to patients. This is seen as especially important in settings where many patients must pay for their medicines themselves and where patients may be unable to afford their medicines. Prescribers sometimes say that the only reason they see sales representatives is to receive free samples for their patients. What this ignores is the role of free samples as a form of ‘market seeding’ to generate sales, and the evidence that free samples can shift prescribing choices, in some cases towards less appropriate therapy (Boltri, 2002). Patients do not pay for their first sample packs, but may end up taking unnecessarily expensive medicines in the long run.

- **“I don’t take any notice.”**

Some health professionals believe that they are not adversely influenced by pharmaceutical promotion because they pay it little attention. However, influence techniques can be more effective if they are not subjected to careful critical attention. Subtle messages that might be rejected if they were carefully considered instead ‘sneak in under the radar’ to link the brand or indication with desires, fears or other emotional responses. This was reflected in a marketing company’s boast to pharmaceutical companies that its advertisements “go straight to the hippocampus” (Wolfe, 1996). Even simple repetition has an effect: hearing the same brand name many times helps it be the first to come to mind when prescribing or dispensing (Mansfield, 2003).

- **“I see them all so I’m not influenced by any.”**

Another common belief is that exposure to promotion from several companies balances out competing biases. However this strategy ignores certain biases shared by all competing companies. For example, pharmaceutical companies promote their most profitable products. Consequently, expensive new medicines are promoted rather than older generic products regardless of which is best. Additionally, pharmaceutical companies only have an incentive to promote medicines. Non-drug treatments and the option not to treat are unlikely to receive equal attention, even when they are the best option for a specific patient.

From awareness to action

Promotional influences on prescribing and medicine use are a problem because they can lead to inappropriate treatment choices. This can occur if a medicine is used when it is not needed;

if it is used incorrectly (i.e. for an untested use, at the wrong dose or by the wrong patient); if it is a poor treatment choice because of its (often unknown) safety and effectiveness profile; or if it is more expensive than equivalent alternatives. Promotional influences are also a problem for the profession if they affect public perceptions and result in a loss of trust.

It may be possible to reduce the risk of being misled by learning to recognise influence techniques and become more wary of promotional activities that use misleading techniques (Shaughnessy et al., 1994). However, there is evidence from psychological studies that the key to becoming less vulnerable is initial recognition of one's personal vulnerability (Sagarin et al., 2002).

There are three main strategies for reducing the risk of pharmaceutical promotion leading to inappropriate prescribing:

- Trying to minimise exposure to promotion;
- Trying to avoid or reduce harm from exposure to promotion;
- Consistent use of techniques that are likely to lead to best practice, including reliance on more reliable sources of information.

While they are commonsense, none of these strategies has been tested and health professionals must decide themselves how to respond to the challenge of promotion. Some of the strategies used to minimise exposure include choosing not to see sales representatives, avoidance of sponsored CME, and refusing gifts and use of medication samples. Other strategies include learning to recognise use of specific influence techniques. It is also important to be aware of the 'red flags' that highlight potential conflicts of interest or bias, for example, recognising that speakers at an educational event are using slides created by the sponsoring pharmaceutical company.

Having a personal plan and identifying and following robust policies concerning potential ethical conflicts of interest will make it easier to identify and deal proactively with such situations. The American Medical Student Association's PharmFree pledge is an example of a clear set of criteria to avoid undue influence (see Box 3). (For a more detailed discussion on conflicts of interest, see Chapter 6.)

Box 3: American Medical Student Association's PharmFree Pledge

As part of a broader campaign to make US medical students more aware of pharmaceutical promotion, the AMSA developed a simple pledge for physicians to endorse:

"I am committed to the practice of medicine in the best interests of patients and to the pursuit of an education that is based on the best available evidence, rather than on advertising or promotion.

I, therefore, pledge to accept no money, gifts, or hospitality from the pharmaceutical industry; to seek unbiased sources of information and not rely on information disseminated by drug companies; and to avoid conflicts of interest in my medical education and practice."
(AMSA, 2001).

The foundations for good clinical practice include development of skills in rational prescribing and dispensing, including the use of practical, evidence-based, decision-making techniques that are aligned with such skills. Examples of these might be the development of a personal formulary and patient-oriented treatment goals. The WHO manual *Guide to Good Prescribing* provides a practical framework for the development of prescribing skills (available at: http://whqlibdoc.who.int/hq/1994/WHO_DAP_94.11.pdf). There are also other good resources available on improving prescribing appropriateness. (Chapter 8 gives further information on how to critically appraise research evidence and find sources of independent information.)

Conclusion

One of the greatest ethical challenges facing health professionals is the influence of pharmaceutical promotion on professional practice. Interactions between the pharmaceutical industry and health professionals are complex. Strategies involving a combined approach are therefore likely to be needed to be aware of one's own vulnerability to influences, avoidance of conflicts of interest and unnecessary exposure, awareness and transparency when exposure and conflicts of interest are unavoidable and development of positive strategies to improve prescribing and dispensing. Whatever the strategy, the key goal is to ensure that good patient care comes first.

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Chapter 3

Analysing pharmaceutical advertisements in medical journals

Joel Lexchin

Although the pervasive presence of pharmaceutical advertisements in medical journals may suggest otherwise, companies only spend a small fraction of each promotional dollar on advertisements. US figures from 2005 show that medical journal advertising cost companies US\$499 million out of a total promotional budget of US\$27.7 billion (IMS, 2005). Journal advertising is used with visits from sales representatives and detailing aids (material left behind by sales representatives) to deliver and reinforce a message about a medicine. According to an executive from the research organisation that has undertaken the most extensive media research on the prescription medicine industry: “*Advertising magnifies the detailing effort at a fraction of detailing expense. In effect, detailing provides the power in the marketing effort and advertising provides the efficiencies.*” (Liebman, 2000). For every dollar spent on medical journal advertisements during the first four years that a medicine is on the market, the return on investment (ROI) is US\$2.43; after this time, ROI increases to over US\$4.00 (Liebman, 2000).

Not only are journal advertisements successful in increasing sales, and therefore prescriptions, but there is also some evidence that physicians who use journal advertisements as an information source prescribe less appropriately (Bower, 1987; Ferry, 1985).

Journal advertisements attract attention because they are visually appealing. Professionals may also see them as a way of keeping up-to-date. Since advertisements can affect prescribing, it is important to be able to critically evaluate their contents and to compare the information provided with that obtained from unbiased information sources.

Aims of this chapter

By the end of the session based on this chapter, you should:

- Know what kinds of information the WHO *Ethical Criteria for Medicinal Drug Promotion* recommend for inclusion in journal advertisements;
- Be familiar with the different components of journal advertisements;
- Understand the ways in which each of the components can be used to convey messages;
- Be able to evaluate each of the different components according to the criteria set out in this chapter.

What information should be in a journal advertisement?

The *Ethical Criteria for Medicinal Drug Promotion* developed by the World Health Organization (WHO) suggest the types of information that, as a minimum, should be contained in a journal advertisement (WHO, 1988), (see Box 1). The aim is to ensure that basic information needed for prescribing decisions is present. The medicine's international nonproprietary name (INN), usually the generic name, is a key piece of information that should always be included. Generic names help doctors and pharmacists identify which class a medicine belongs to and can prevent doctors from unknowingly prescribing two medicines from the same class to a patient.

Box 1: Recommended information in journal advertisements

The World Health Organization's Ethical Criteria recommend that the following information be included in pharmaceutical advertisements appearing in medical journals.

- Name(s) of the active ingredient(s) using either international nonproprietary name (INN) or the approved generic name of the medicine;
- Brand name;
- Content of active ingredient(s) per dosage form or regimen;
- Name of other ingredients known to cause problems;
- Approved therapeutic uses;
- Dosage form or regimen;
- Side effects and major adverse medicine reactions;
- Precautions, contraindications and warnings;
- Major interactions;
- Name and address of manufacturer or distributor;
- Reference to scientific literature as appropriate.

(WHO, 1988)

While advertisements from developed countries typically contain nearly all of the information listed in the box, this is not always the case in developing countries. Table 1 from a 1993 study presents the results of a survey comparing advertisements in developed and developing countries. It is obvious from examining this table that safety information is systematically ignored in advertisements from developing countries. More recent work analysing advertisements in India (Lal, 1997; Lal, 1998), Brazil (Mastroianni, 2005) and the Russian Federation (Vlassov, 2001) shows that they continue to leave out essential information recommended by WHO.

Table 1: Information in advertisements in developed and developing countries

Type of information	Percentage of advertisements containing information	
	Developed countries*	Developing countries**
Indications	89	87
Contraindications	61	28
Warnings	55	29
Side effects	64	29

(Herxheimer, 1993)

* Denmark, Finland, France, Ireland, Italy, Norway, Spain, Sweden, Switzerland and United Kingdom

** Brazil, Indonesia, Nepal, Pakistan, Sri Lanka, Turkey, United Republic of Tanzania and Zimbabwe

Just because each of the categories of information is present in an advertisement does not necessarily mean that the advertisement will give a complete picture of the medicine's safety and effectiveness and how to prescribe the medicine appropriately. Although advertisements in Australian journals improved during the 1980s and early 1990s, by 1992, 4% still contained unacceptable graphics, 7% had unacceptable claims and 15% had unacceptable references (Carandang, 1994). In 1992, the *Annals of Internal Medicine* published an article that critically examined the scientific accuracy of over 100 pharmaceutical advertisements in 10 leading medical journals (Wilkes, 1992). Overall, physician and pharmacist reviewers judged that 34% should have had major revisions before being published and 28% should not have been published at all. In 1995, most Irish doctors expressed strong reservations about the quality of advertisements in Irish medical journals, with 90% believing that the advertisements were of poor educational value (Hemeryck, 1995).

Figure 1: What information should a medicine advertisement contain?



(Advertisement from the *Indian Journal of Dermatology, Venereology, Leprology*. Vol 71, Issue 6, Nov-Dec 2005.)

The main components of advertisements

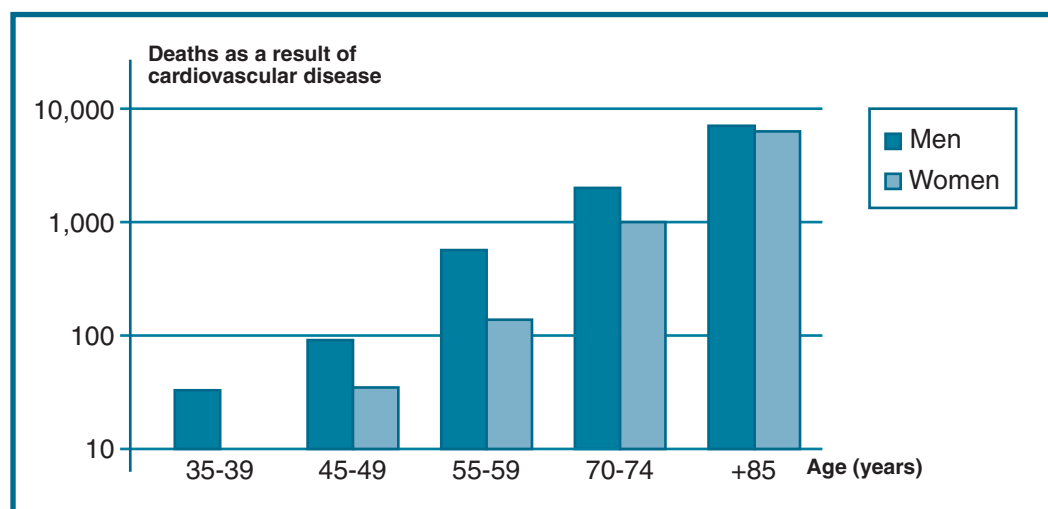
This chapter will consider four main elements of journal advertisements: graphs and data; text; references; and pictures and images.

Graphs and data

Graphs and data are often used in advertisements to provide a scientific justification for the claims that are being made about a medicine. A graph can provide a clear, visually striking summary of study results. However, an analysis of 74 graphs that appeared in 64 advertisements in leading US medical journals found that 8% had errors, 5% were visually confusing and 12% used non-standard graphing techniques. Only 36% of graphs were self-explanatory and there were many more visual distractions and numeric distortions than in graphs found in medical journal articles (Cooper, 2001).

Figure 2 presents an example of a graph on a promotional website with one type of numeric distortion (for details, see caption below figure). There are many other types of examples, including not starting a scale at zero, making a very small difference in outcomes look large, highlighting one small part of a study's results and so on.

Figure 2: What is numeric distortion? An example



(Source: Bayer, Schering Pharma, 2009)

This graph appeared on a website on menopause by Schering, which markets post-menopausal hormone treatments: <http://www.menopause-infoline.com/scripts/en/consumer/index>. and http://www.menopause-infoline.com/scripts/en/consumer/01/c_01_04_02.php. The graph accompanies text that stresses the increase in heart disease risk faced by women as they age.

The y-axis, on the left, is a logarithmic scale, an unusual scale to use on such a graph. Readers glancing at the graph might assume the scale was arithmetical, with equal numbers between the horizontal lines. For example, if one glances at the bars for ages 70-74, it looks like nearly as many women as men are represented. In fact, the bar represents 1,000 deaths among women versus 2,000 among men.

Data on medicine benefits and harmful effects

Closely related to the issue of the quality of graphs is whether advertisements convey information as a relative risk reduction (RRR), absolute risk reduction (ARR) or number needed to treat (NNT).

A **relative risk reduction** is the percentage reduction in the risk of targeted complications between two groups. A drop in mortality from 2% to 1% would be a RRR of 50%, because 1%, or 1 in 100 people, is half as many as 2%, or 2 in 100 people. An **absolute risk reduction** is the absolute percentage difference in the risk of targeted complications between two groups. A drop in mortality from 2% to 1% would be an ARR of 1%. The **number needed to treat** is the number of patients who have to be treated in order to provide the desired effect from the medicine in one person. A drop in mortality from 2% to 1% would be a NNT of 100 (ARR=1; NNT=100/ARR). In other words, for every death prevented, 100 people would need to be treated. There is evidence that physicians' enthusiasm for a treatment varies depending on how the results are presented. Specifically, the inclination to use a particular medicine therapy is greatest when

results are given as a RRR and lowest when they are given as a NNT (Cranney, 1996; Naylor, 1992). A 50% relative reduction looks much more impressive than a 1% absolute reduction. Often the word ‘relative’ is not stated, adding to the confusion. (Chapter 8 describes these outcome measures in greater detail.)

Figure 3: Misleading use of relative risk reductions



(Advertisement brochure from Alonso, 2007.)

This advertisement for raloxifene (Evista) is an illustration of a brochure distributed by sales representatives to family physicians in Spain. Raloxifene is approved in Spain to prevent fragility fractures in women with osteoporosis. The advertisement was judged by regional medicine authorities in Madrid to be illegal because it promotes an unapproved use. The lower box with the large “75%” is promoting use in women without a diagnosis of osteoporosis (“75% reduction in vertebral fractures in women with osteopaenia”) (Alonso, 2007).

Impressive risk reductions, but what do they really mean?

47% relative risk reduction in radiological vertebral fractures

- A radiological vertebral fracture is not a broken bone in the traditional sense as the woman has no symptoms. It is a loss in vertebral height seen on x-ray. The cut-off for the amount of loss in height considered to be a fracture is arbitrary, and is 15% in some studies, 20% in others, including this study.
- What is the absolute risk reduction? Over 3 years, 6% of women on raloxifene had radiological vertebral fractures versus 10% on placebo, a 4% difference.
- Numbers needed to treat: 25 women must be treated for 3 years to prevent one radiological vertebral fracture. However, only a difference on x-ray would be prevented, not pain or disability.

75% relative risk reduction in symptomatic vertebral fractures

- These x-ray changes led to back pain and were therefore clinically meaningful.
- In total, less than 1% of women had clinical vertebral fractures in 3 years. No breakdown is provided of numbers on raloxifene versus numbers on placebo.
- The published report does not allow ARR to be calculated – a guess from the relative risk reduction figures and total number of women is around 0.7%.
- In the same cited study, 1% of women on raloxifene developed venous thromboembolism (deep vein thrombosis or pulmonary embolism) compared to 0.03% on placebo; absolute risk increase = 0.7% (Ettinger, 1999).

A Canadian study that looked at 22 journal advertisements found that half of the time, in 11 of these advertisements, results were reported only as a RRR. The other 11 provided enough information to calculate ARR and NNT, however, they did not state these values directly (Lexchin, 1999). Australian advertisements that made claims explicitly reporting quantitative outcomes also did not report data as either the ARR or NNT (Loke, 2002).

Advertising copy cannot contain all the methodological and statistical detail found in the original reports but it should allow readers to know if the research being cited meets the basic criteria for validity, significance of results and applicability to the reader's practice (Rothermich, 1996). Gutknecht analysed 43 data presentations in 33 advertisements that contained quantitative research results. References to randomisation and blinding were found in less than one-half of the 43 data presentations. *P* values (the probability that a specific result occurred by chance) were frequently provided, but confidence intervals and references to power and NNT were not

provided in any of the advertisements (Gutknecht, 2001). Similarly, a study of Finnish advertisements found that these adverts failed to mention confidence intervals or NNT (Lankinen, 2004).

Box 2: How to evaluate data and graphs presented in pharmaceutical advertisements

- Is information presented as either absolute risk reductions (ARR) or number needed to treat (NNT)?
- Does the advert indicate if a study was randomised and blinded?
- When statistical significance is given are confidence intervals and power calculations included?
- Are graphs simple to read and do they have appropriately labelled axes?
- Are graphs obscured by other visual material?
- Are the titles of graphs clear and do they explicitly say what the graph is about?
- If the graph comes from an article or another source is it reproduced exactly as it appeared in the original source?
- Are data in graphs presented in such a way as to make it easy to determine whether or not any differences are clinically meaningful?

Advertising text

• Claims made in advertisements

One of the essential features of a journal advertisement is the product claims. These claims can take many forms. They may be about effectiveness, safety, enhancement of quality of life, or sometimes costs or convenience. Sometimes a precise claim is made about a measurable treatment outcome; other times claims are much more vague.

The claims made in a sample of 245 advertisements from four major Finnish medical journals published in 2002 were examined (Lankinen, 2004). These claims were classified into four groups: unambiguous clinical outcome, vague clinical outcome, emotive or immeasurable outcome and non-clinical outcome. Out of 883 claims only 337 (38%) were referenced. Nine percent of the claims implied unambiguous clinical outcomes, 68% included vague or emotive statements. Twenty-one percent of the references were irrelevant to the claim. There was a fair amount of non-scientific and scientific support for the 73 unambiguous claims, but not a single

claim was supported by strong scientific evidence (meta-analysis or multiple high-quality studies). Vague, emotive and non-clinical claims were significantly more often supported by irrelevant references than unambiguous claims.

Advertisements from medical journals in other countries are little different from those in Finland with respect to whether or not they contain supporting information. Only 45% of 855 claims in Australian advertisements were supported by compelling evidence (randomised, controlled trials or better) (Loke, 2002). A review of Spanish advertisements found that 44% of claims for which a reference was cited were not supported by the referenced studies. Usually this was because the advertisement recommended the product for a patient group that was not included in the study (Villanueva, 2003).

• **Quality of life claims**

Quality of life claims may reflect one or more of three dimensions: physiologic, functional (physical, social and psychological functioning) and overall well-being. Advertisements most often claim that the product improves quality of life in either the physiological or physical functioning dimensions. In a US review of these claims (Rothermich, 1996), 11 out of 26 advertisements (42%) making claims about quality of life were non-compliant with US Food and Drug Administration regulations, mainly because of biased information presentation, with too much prominence given to medicine benefits as compared to harmful effects.

• **Claims about costs and economic benefits**

Doctors often do not know the relative costs of the medicines they prescribe, but they may try to prescribe lower-cost medications to low-income patients and those without medicine insurance (Ryan, 1990; Safavi, 1992). Therefore, it is not surprising that economic messages in advertisements typically claim that a medicine is “less expensive” than alternatives. One study of such advertisements found that simple cost differences were usually supported by evidence, but most claims of cost-effectiveness or of positive effects of the treatment on patients’ productivity were not supported by evidence (Neumann, 2002). Inaccurate or deceptive information about economic benefits could lead to doctors prescribing more expensive medicines that do not offer any clinical advantages.

• **Efficacy and safety claims**

Claims about clinical outcomes are important since this is the key aim of pharmacotherapy. Table 2 summarises the types of claims in Australian and Finnish advertisements and shows that in both countries only a minority of the claims are about unambiguous clinical outcomes (Loke,

2002; Lankinen, 2004). A significant proportion is emotive, for example, “one of a kind” or “a source of healing power”, and almost a quarter are for non-clinical outcomes which are usually about surrogate markers, such as changes in laboratory measures or physiological measurements, rather than meaningful clinical changes in morbidity events or mortality. Surrogate end points may or may not correlate with outcomes that are important to patients.

Whatever the nature of a claim, it should be presented clearly, should be based on methodologically strong research and should accurately reflect cited references. Ideally, claims should also reflect treatment outcomes of importance to patients’ health and lives.

Table 2: Types of claims in pharmaceutical advertisements

	Unambiguous clinical outcome		Vague clinical outcome		Emotive or immeasurable outcome		Non-clinical outcome		Total number of claims
	No.	%	No.	%	No.	%	No.	%	
Australia	418	28	437	29	301	20	346	23	1,504
Finland	81	9	326	37	270	31	206	23	883

(Source: Loke, 2002; Lankinen, 2004)

References in advertisements

Advertisements should include references whenever a claim is made that reflect scientific evidence. The claim must be consistent with cited research and the research should be designed with adequate methodology. For example, effectiveness claims should generally be based on evidence from double-blind, randomised, controlled trials. It is also important for health professionals to be able to retrieve cited references, so that they can independently evaluate them. Otherwise, any limitations or inconsistencies between the evidence and the claims will remain hidden.

These are a few common problems with referencing in advertisements:

- No references are provided for claimed treatment effects;
- Reference is to company “data on file”, which is not publicly available and has not been independently reviewed;
- A poster presentation is cited; generally inadequate information is provided on methods in poster presentations to judge reported results;

- Review articles that selectively present results are cited, not original research;
- The referenced article is in a journal supplement sponsored by the manufacturer;
- Study results in the cited reference are inconsistent with the advertising claim;
- The study is of poor methodological quality, raising questions about the validity of the results.

For example, Lexchin and Holbrook requested all references for a set of published advertisements, 87 in total, from the manufacturers (Lexchin, 1994). Ten of these references were to unpublished “data on file”. They eventually received 90% of the requested references; 4 of the 10 “data on file” were not sent. Although 76% of the references supported cited claims, the overall methodological quality of the references was judged to be unacceptably low (Lexchin, 1994).

In a similar study, Villanueva and colleagues (2003) retrieved 82% (102 out of 125) of references cited in advertisements. However, almost half of the references that were not found were to “data on file”. Over three-quarters of the references came from journals with a high impact factor (a measure of how often articles in a journal are cited) and 82% of the 102 were from randomised clinical trials.

In another analysis of references in advertisements, Cooper and Schriger (2005) only received 37 replies to 88 requests for cited “data on file”, 19 of which were refusals; only 18 (20%) were provided. Out of 294 references citing original research, 58% were sponsored by or had authors affiliated with the product’s manufacturer. When pharmaceutical companies sponsor research on their products, the results are four to five times more likely to be favourable to the product than when financing is from other sources (Als-Nielsen, 2003; Lexchin, 2003). Finally, in developing countries it may not be possible to retrieve references because the information in citations is incomplete. This was the case 90% of the time in one study in India (Lal, 1996).

Box 3: How to evaluate references in pharmaceutical advertisements

- Do citations contain all of the information necessary to identify references?
- Are all references cited retrievable including those to “data on file”?
- Are references of high methodological quality?
- Do journal references come from peer-reviewed medical or pharmacy journals?
- Did the company finance the research reported in the reference?

• **Claims in antibiotic advertisements**

Advertisements for antibiotics raise specific concerns, as overuse of antibiotics can lead to resistance and diminish the usefulness of these medicines. Many advertisements for antibiotics do not mention resistance (Gilad, 2005). In some cases, as in the advertisement shown in Figure 4, advertisements fail to state that a common infection usually resolves without antibiotics or that it is often wiser to reserve newer broad-spectrum antibiotics for second-line use, when older narrower-spectrum products fail, in order to avoid unnecessary development of resistance.

Figure 4: Antibiotic advertising



(Advertisement from the *Canadian Medical Association Journal*, 13 September 2005.)

This advertisement for clarithromycin (Biaxin) suggests putting the medicine “at the top of your list” to treat children. Many common childhood infections do not require antibiotics.

Box 4: How to evaluate the text in pharmaceutical advertisements

- Are generic names used as frequently as brand names and is the type the same size as that used for the brand name?
- Are claims in advertisements restricted to unambiguous clinical outcomes or meaningful economic claims?
- If there are claims about surrogate endpoints is there also information that directly links changes in these end points to meaningful clinical outcomes?
- Are all claims for safety, effectiveness and cost-effectiveness in advertisements backed up by high-quality evidence (evidence from meta-analyses or randomised, controlled trials)?
- If there are claims for use of a medicine in a particular population are they based on high-quality evidence that comes from medicine use in that population?
- Is information about safety given the same prominence and placement as information about effectiveness?
- Do economic claims give actual prices of different alternatives? Are there vague claims about costs, such as “costs less”?
- Do advertisements for antibiotics recommend use that is consistent with guidelines to prevent unnecessary development of resistance?

Pictures and images in advertisements

Pictures and images in journal advertisements can help shape the way that doctors view patients. Some common portrayals are: as helpless victims of disease, as partners in developing therapeutic options, as people who are demanding, as being intelligent or emotional. The images in advertising can also sway how physicians and pharmacists view themselves, for example, as caring professionals able to solve a patient’s problem.

These pictures can either reinforce or challenge generally held societal prejudices about different groups of people. Pictures and images can also serve as metaphors as advertisers seek to identify their products with a particular image, e.g., a maker of an antidepressant may hope to identify its medicine with images of brightness as a symbol of recovery. The use of metaphors tends to reduce illness to a single dimension and treatment to a single modality (medicines) thereby taking illness out of its social context and simultaneously denying a role for any other form of therapy.

• Reinforcement of social stereotypes

Much of the analysis of the way different groups are portrayed in advertising has focused on women. A random sample of US general and specialty medical journals found that men were usually depicted as doctors and women as patients taking medicines. In general, men were more often portrayed as workers and when women were shown working, it was usually in stereotypically feminine jobs such as secretaries and waitresses (Hawkins, 1993).

An analysis of advertisements for antidepressants in Scandinavian and US journals in 1995 showed that the Scandinavian advertisements tended to construct antidepressants as female gendered and depression as detached from any social context. Both US and Swedish advertisements used images of couples and showed the medicine as being key to maintaining the relationship, and the woman as the person needing the medicine (Lovdahl, 1999).

Figure 5: Images of women in antidepressant advertising



(Advertisement from the American Journal of Psychiatry 2006;163(9)).

The image in this advertisement suggests a number of things about depression, women and pharmaceutical treatments.

Although depression is diagnosed about twice as often in women than in men the ratio of females to males in advertisements in the *American Journal of Psychiatry* was 5:1 and in *American Family Physician* it was 10:0. The authors of this study speculated that the overrepresentation

of women may reinforce cultural stereotypes and result in diagnosis and treatment of women in gender-biased ways (Hansen, 1995). Another analysis noted that women were under-represented in advertisements for cardiovascular medications and that this could contribute to under-diagnosis of cardiovascular disease in women, together with factors such as differences in symptoms and expression of disease (Ahmed, 2004; Leppard, 1993).

There are also biases in the way that the elderly are presented in journal advertisements. In a sample of advertisements from Canadian medical journals, Lexchin (1990) found that the special needs of the elderly often did not appear to be taken into account and this could contribute to misprescribing to the elderly. Finally, in multicultural societies, advertisements have a preponderance of whites both as health-care providers and as patients (Hawkins, 1993; Munce, 2004).

• Appeals to myth

The use of images to construct mythical and potentially misleading associations between disease and medicine was evaluated in 26 advertisements appearing in issues of the *British Medical Journal* between 1999-2001 (Scott, 2004). This analysis suggests *“that myth is often deployed in drug advertising to depict exaggerated therapeutic efficacy: armed with such drugs, the clinician can liberate patients from the oppression of disease and restore them to normality. With medicine as their alibi advertisers exploit the nude.... Mythology transports the clinician into a wider sociocultural context than that of medicine alone. Viewing exotic or erotic scenes derived from ‘old masters,’ the reader is relocated from office to gallery, obtaining visual relief from the clinical grind.... Associations between diseases and drugs are made to seem natural, unmotivated by commercial interest.”*

Ferner and Scott (1994) note that symbols in advertisements have complex and multiple meanings and are able to evoke strong feelings. Doctors may be unaware of the hidden messages in images or may be reluctant to acknowledge them and this reluctance may leave them vulnerable to misprescribing.

Psychotropic medicine advertisements are particularly prone to using symbols or metaphors to convey hidden meanings. Kleinman and Cohen (1991) showed how images in advertisements distort debate over treatment options and legitimise existing social relations and attitudes. The majority of advertisements in the *British Journal of Psychiatry* and its Irish counterpart used metaphors as their main marketing strategy instead of providing adequate information necessary for appropriate prescribing (Quinn, 1997). Finally, an analysis of eight advertisements for antidepressants appearing in issues of the *Canadian Journal of Psychiatry* between 1989 and 2002 showed *“how existing paradigms of social worth can be used by the drug industry to create perceptions of their products, with the intention of promoting sales.”* (Peppin, 2003).

Box 5: How to evaluate pictures and images in pharmaceutical advertisements

- Do the people portrayed in the advertisements reflect the racial and ethnic composition of people in your country?
- Are both men and women portrayed in advertisements as both patients and health-care providers in equal numbers?
- Are the ways that men and women are portrayed (as workers, facial expressions, body language, etc.) similar?
- How are the elderly portrayed in advertisements?
- Are symbols or metaphors used in advertisements?
- What kinds of associations do these symbols and metaphors convey?
- Are illnesses portrayed as individual events or are they put into a social context?

Conclusion

As a minimum, advertisements for prescription medicines should contain the key information listed in the WHO Ethical Criteria concerning the medicine name and manufacturer, who it is indicated for, key beneficial and harmful effects and reference to scientific evidence to back treatment claims. This provides basic knowledge of a medicine's characteristics required for prescribing decisions. However, the presence of this information does not ensure that the advertisement promotes appropriate use. To critically appraise advertisements, it is important to systematically look at all of the advertisement's elements: data and graphs, text, references and images. Often social as well as medical dimensions come in, such as the portrayal of the relationship between doctors and patients, or the way women or the elderly are portrayed. Additionally, myth and emotive imagery may be used to create an impression of a brand that has little to do with evidence of the product's effects and characteristics. Underlying any critical appraisal of advertising, the key question is what the messages and images in the advertisement mean for patient health.

Student exercises

1. Advertising analysis

- Look at the advertisement shown in Figure 1 in this chapter. Compare the information provided to the types of information that should be present, according to the WHO Ethical Criteria (Box 1). What information is missing? Next to each type of missing information, explain whether you think it is needed and why or why not.
- Pick three or four advertisements from current issues of the major medical or pharmacy journal(s) in your country and examine and compare them to reliable and unbiased sources of information about the medicine to determine if they contain the information recommended in the WHO Ethical Criteria. (See Chapter 8 for more details on sources of reliable and unbiased information.)
- Find a local advertisement that includes at least one graph. Use the criteria given in Box 2 in this chapter to evaluate the content.
- Collect the advertisements in the latest issue of your national medical or pharmacy journal. How many advertisements include references? How many are to “data on file”, to poster presentations, or to review articles? How many citations are incomplete? How often did companies sponsor the studies? Try to retrieve all of the references from one advertisement. Did you succeed? Why or why not? Using the section in Chapter 8 on critical appraisal, comment on the strength of methodology and relevance to claims for which they were cited.
- Analyse the different components of the advertisements (graphs and data presentation, text, references and pictures/images) according to the criteria outlined in this chapter.
- See the list of independent information sources in Chapter 8. Try to find a reference covering at least one of the medicines for which you have an advertisement. How does this information compare with the messages in the advertisement?
- Choose a convenience sample of health-care professionals, such as your professors, friends or colleagues. Show the current advertisements to them and ask them their opinions of the advertisements. Do their opinions match your analysis? What differences are there and how do you think those differences would affect prescribing?

2. Create your own spoof advertisement

- Choose a medicine that is currently being heavily advertised and for which you also have a source of independent information (see Chapter 8 for references).

- Pick a recent advertisement for the medicine.
- Go through the advertisement and pick out any implied or stated messages in images, text or graphs and data that are inconsistent with the independent information.
- Look as well for any social messages or use of myths in the advertisement.
- Create your own spoof advertisement for this medicine using similar messages. This can be in any form: a journal advertisement, a poster, a promotional patient brochure, a song to play on radio, a short play, a video and so on.

3. Debate the role of advertising in medical journals

- Some critics of pharmaceutical advertising say that health professional journals should not accept any advertisements from pharmaceutical or medical device companies. (See: Fugh-Berman A, Alladin K, Chow J (2006). *PLoS Medicine* 3 (6):e130. (See: <http://medicine.plosjournals.org/perlserv/?request=get-document&doi=10.1371/journal.pmed.0030130>).
- Others cite freedom of expression and say that pharmaceutical companies should be able to advertise as long as the advertisements are not deceptive.
- Divide into teams and debate the pros and cons of health professional journal policies banning pharmaceutical advertising entirely versus continuing to run the advertisements but regulating them more strictly.

4. Types of advertising claims

- Collect 6 advertisements from a medical or pharmacy journal.
- Make a list of all the claims in the text and headlines for each of the advertisements.
- How many of them fit into each category listed in Table 2?

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Chapter 4

Pharmaceutical sales representatives

Andy Gray, Jerome Hoffman and Peter R Mansfield

The presence of pharmaceutical industry sales representatives almost seems a fact of life at many modern medical centres and universities around the world. Many medical and pharmacy students come into contact with pharmaceutical industry sales representatives during their training. Later on in the careers of many health professionals, encounters with sales representatives can occur on a daily basis, taking up a substantial portion of a busy health professional's time. However, health professionals have a choice in the matter - they may choose not to see pharmaceutical sales representatives at all or they may attempt to manage such interactions.

This chapter aims to provide information to help you make up your own mind on this issue. This choice has important consequences for health professionals' practice and patients, so requires careful consideration.

Aims of this chapter

By the end of the session based on this chapter, you should be able to answer a series of questions on your interactions with sales representatives:

- In what ways, if any, might I hope to benefit from meeting with sales representatives?
- How are sales representatives selected, trained, supported and managed?
- What information do sales representatives provide?
- How might contact with sales representatives influence me in a positive or negative way?
- Should I have contact with sales representatives at all?
- Is it possible, if I choose to have contact with sales representatives, to minimise the potential harm and maximise the potential benefit for my professional development and practice?

This chapter presents evidence that we believe can be helpful in addressing these questions, and ends with a series of activities that will allow students to work on the issue in more depth.

The current situation

Many medical and pharmacy students come into contact with pharmaceutical sales representatives during their training. Sales representatives may be invited to address students in a formal setting or may exhibit their products at various functions. They may provide food and drink or sponsorship for educational sessions.

In general, most of sales representatives' time is directed at one-to-one contact with practising health professionals. Spending on this form of promotion – also called 'detailing' – represents a large proportion of the pharmaceutical industry's marketing budget. In 2004, in the US, it was estimated that there were 90,000 sales representatives and that pharmaceutical manufacturers spent more than US\$10 billion on this form of marketing (Lam, 2004). This may represent more than a quarter of their total marketing expenditure and represent at least US\$8,000 to US\$13,000 spent on such activities per year, for each physician in the US. Sales representatives are also involved in the provision of medicine samples. The pharmaceutical industry ranks as among the most profitable, and much of its success can be traced to effective marketing of its products, to both health professionals and consumers. The industry would not continue to spend as much as it does on sales representatives (and samples, where allowed to do so) if this form of promotion was not effective. There is also research evidence that one-to-one 'detailing' visits are one of the most effective techniques for changing prescribing behaviours (Oxman, 1995). This is partly because sales representatives can adapt their messages and influence techniques immediately depending on how health professionals respond.

Box 1: Why physicians should refuse to see pharmaceutical representatives

Whether physicians ought to interact with pharmaceutical sales representatives (reps) is a question worthy of careful ethical analysis. The issue presents a challenge to both professional integrity and time management. Empirical data suggest that interactions with pharmaceutical reps increase the chances that the physician will act contrary to duties owed to the patient. Ideally, a physician might both interact with reps and also do the research necessary to counteract the commercial bias in their messages. But a physician who actually did that research would, in turn, be devoting a good deal of time that might better be spent in other activities. The counterargument, that one is obligated to see representatives to obtain free samples to best serve one's patients, can be shown in most practice settings not to be compelling. Physicians ought to refuse to visit with representatives as a matter of both professional integrity and sensible time management (Brody, 2005).

Sales representatives are employed primarily to market their company's products, whilst health professionals aim first and foremost to provide health-care services to patients. It is unclear whether contact with pharmaceutical sales representatives can effectively be *managed*, and critics of this approach have instead made very strong arguments for 'divestment'. The abstract of one such paper, by Howard Brody, is shown in Box 1.

Could you benefit from meeting with sales reps?

Before addressing other aspects of this issue, it is important to ask why health professionals might wish to establish such relationships in the first place and examine the evidence supporting these beliefs. There would seem to be only three possible areas of 'benefit' that arise from this activity:

- Sales representatives might be able to provide information that is useful to health professionals;
- These industry representatives provide items (including medicine samples) that can be given to patients who might not otherwise be able to afford them;
- They provide personal blandishments (gifts).

Any such 'benefits' would of course have to be balanced against the risk that the information is biased and other 'harms' (ethical, financial, or otherwise) that might be inherent to this relationship.

The quality of the information provided is addressed later in this chapter, in relation to the training given to sales representatives and the ways they are managed. It is worth noting that substantial time and effort would be required if individual health professionals chose to listen to such presentations, and insisted upon verifying the accuracy of the information provided. This issue is addressed in detail by Brody (2005). Contrary arguments have been made, for example, by those who see promotion as raising awareness of untreated medical conditions and thus providing a societal good (Dubois, 2003).

Industry does contribute large numbers of medicine samples to physicians' offices and clinics. This practice is fundamentally a promotional tool used to influence prescribers and dispensers and to increase the sales of new (and often expensive) medicines. However, health professionals should question whether this practice is an efficient and equitable way to provide access to medicines for poor patients. Even without considering the fact that samples are *not* routinely used in this fashion, physicians who provide samples to poor patients may find that they have chosen sub-optimal medicines simply because they were available as samples. After such samples run out, these patients – who almost invariably are continued on the expensive brand-name products – end up paying much more for their medicines than if they had been given a therapeutically equivalent, or even more preferable, generic medication, all along.

Provision of gifts

Many recipients of industry ‘gifts’ vehemently deny that these items (particularly when they are of relatively little monetary value) influence their practice, despite strong evidence to the contrary (Wazana, 2000; Steinman et al., 2001; Dana and Loewenstein, 2003; Katz et al., 2003). They also believe that revealing the existence of such gifts to their patients will resolve the ethical problems that may exist. Brennan and colleagues (2006) have written about what they call the ‘myth of small gifts and full disclosures’. They have also summarised the evidence for the social science finding that it is the creation of a *relationship* that leads to influence on behaviours, rather than the size of the ‘gift’. Anyone who receives a gift will feel the need to reciprocate, to give something in return. There is a fundamental conflict of interest for health professionals who accept ‘gifts’ from the health industry (including the pharmaceutical industry) and are then asked to decide whether and how to spend *someone else’s money* for products the giver of such gifts is selling. This is very different from taking a ‘gift’ from a salesman who is asking you to spend your own money on one of his products. Even in this case, accepting a gift can lead to what would otherwise be an unwanted purchase (Cialdini, 2000).

Some of the items provided by sales representatives could be passed on to patients. In many instances, patients would not choose to buy these items if they had to pay for them directly. It is important to remember that, in general, patients do, in fact, pay for these items (even when they are not passed on) through higher drug prices. If patients were given a choice of lower prices without the gift item, many would choose the lower price.

Selection and training of sales representatives

Although some sales representatives have a background in the health sciences, this is by no means a requirement. In fact, sales representatives are typically chosen for their ability to build relationships with prescribers and dispensers. Commenting on the recent, pronounced trend of companies hiring sports cheerleaders for these positions, Lamberto Andreotti, President of Worldwide Pharmaceuticals for Bristol-Myers Squibb, said "*Obviously, people hired for the work have to be extroverts, a good conversationalist, a pleasant person to talk to; but that has nothing to do with looks, it's the personality.*" (Saul, 2005). Notably, there was no mention of the scientific training necessary to provide what is sometimes claimed by pharmaceutical companies to be primarily an educational and scientific task.

Although details of representative training are not typically made public, some information about this is available, from the companies themselves, individuals who previously held such positions, and (in a few instances) in sworn testimony at legal proceedings. It seems clear that there is intensive training on selected aspects of the products they promote, the conditions for which such products can be used, and the sales techniques most likely to increase their use. This

includes training on how to criticise competitors' products and on how to handle objections or difficult questions that their customers may pose. However, in at least some cases, they are coached to change the subject when the questions are uncomfortable or to point out evidence contrary to the claims being made (Merck, 2001). These techniques are practised in role plays and covered again in refresher training. In many countries, sales representatives are videotaped practising their techniques with colleagues role-playing a wide range of doctor 'types', so that the sales representative gets feedback about even the tiniest details of his or her performance. Sales representatives are often required to pass a test on their product knowledge before being allowed into the field. In some cases, training will cover the code of conduct written by the pharmaceutical manufacturers' association or the regulatory authorities in that area.

Sales representatives are rewarded for increasing sales figures. They are often paid a bonus in addition to their salary, based on sales achieved. Sometimes the bonuses are a large percentage of their total remuneration.

"I wonder today, more than ever before, how am I to continuously keep finding that tiny little spot in my customer's mind to absorb and accept my product message, so that I can get the prescriptions that any pharma marketer so earnestly works for."

– Percy Asundaria, a pharmaceutical sales representative
(Asundaria, 2009)

What information do representatives provide?

Sales representatives are hired to sell particular products and rewarded for doing so successfully. This is true regardless of whether the products they are detailing are as good as or better than those of competitors. It is not possible that every medicine is the best one available, and indeed there are many instances where it can be argued that taking *no* medicine is preferable to those that are being promoted. There is good evidence that the information provided by pharmaceutical sales representatives is frequently incomplete, and biased towards the products being marketed (Ziegler, 1995; Lexchin, 1997; Roughead et al., 1998; Roughead et al., 1998a; Maestri et al., 2000). There is often a lack of balance in the information provided, with greater emphasis on purported benefits of the company's product and less information about the potential risks associated with that medicine. Pharmaceutical sales representatives may fail to mention side effects, contraindications and interactions. Over time, they may also extend or change the indications that are presented, promoting use of the medicine in conditions for which it is not registered. A recent example was the promotion of gabapentin for indications other than epilepsy (Sweet, 2003).

Even though they may be aware of these potential biases, many prescribers and dispensers continue to rely heavily on sales representatives for information about medicines. They may even list sales representatives and their promotional literature as their most important source of pharmaceutical information (Norris et al., 2005). Health professionals generally want information about the indications and benefits of a medicine, its safety, and how it compares with other new medicines used for the same problem. They prefer to have this information presented in as simple and unambiguous a form as possible. They may, however, recognise that available evidence is sometimes not that clear cut.

Brody (2005) has argued that busy health professionals do not have the time to access and evaluate the primary literature to verify the information received from sales representatives. It is also true that most health professionals are not trained in critical appraisal of the literature. Seeing sales representatives, in addition to accessing and evaluating the primary literature (if one did have the time and training to do so), would take even *more* time and effort. Sources of information about medicines that are independent of the pharmaceutical industry exist and present an important resource for health professionals. (See Chapter 8 for a list of independent information sources.) Brody concludes that the time spent seeing sales representatives could be more effectively used reading up-to-date, evidence-based information.

“Unfortunately, most new drugs that appear on the ... market offer little or no advantage over existing therapies. A company may feel obliged to try to sell them, but does a doctor necessarily need to feel obliged to see a sales representative to learn about them?”

– Joel Lexchin, emergency physician, professor
(Lexchin, 2001)

Could contact with sales representatives influence you?

Influence on prescribing

There is evidence that exposure to pharmaceutical promotion – including contact with sales representatives – has an adverse impact on prescribing habits. The decision to start using a ‘new’ medicine is often the result of contact with a pharmaceutical sales representative (Peay and Peay, 1988; Prosser et al., 2003). Many observational studies have found an association between prescriber reliance on sales representatives and more frequent or lower quality prescribing. (See the following references for more on this topic: De Bakker et al., 2007; Muijers et al., 2005; Steinman et al., 2007; Stafford et al., 2004 and Prosser and Walley, 2003). The more a prescriber has contact with the pharmaceutical industry, the more likely he or she is to recommend that a

medicine be added to the hospital formulary or essential medicines list – even when such new medicines represent little or no therapeutic advantage over those already available and cost substantially more (Chren et al., 1994). The authors of this chapter are not aware of any studies that have found an improvement in the quality of prescribing associated with exposure to sales representatives.

Influence techniques

Tape recordings of sales representatives visiting doctors in Australia show that they frequently use five of the main types of influence techniques that have been identified by social psychologists (Roughead et al., 1998a). The five techniques are: trust experts, trust peers, trust people we like, commitment consistency and gifts. The techniques used to influence health professionals have been discussed in Chapter 2, but the main points relating to sales representatives are reinforced here. The techniques used by sales representatives include appeals to authority figures ('opinion leaders' – such as experts or academics), well-known hospitals or specialist groups, as well as social validation (such as references to peer group behaviour). Influential providers who participate in 'educational' activities on behalf of industry can receive substantial payment for such work, far in excess of the relatively smaller amounts given to individual prescribers. It is unclear to what extent such large financial payments influence the beliefs (and thus pronouncements) of these opinion leaders, above and beyond that accomplished simply by the 'gift relationship'.

A sense of entitlement

The relationship that develops between a sales representative and a prescriber or dispenser is often based on reciprocation. This is, in turn, based on the creation of a positive relationship between individuals (Oldani, 2004). The sales representative provides 'gifts', in the form of samples, printed material, pens or other practice-related items, or invitations to social or educational events. It is natural for this to create a positive response. Humans are flattered by such attention and generosity – particularly when they feel it is deserved, given how hard they work, often with what may seem like inadequate recognition.

Creating feelings of obligation

It is normal for gifts to automatically lead to a desire to reciprocate, by providing something in return. The health professional may, for example, agree to prescribe or sell the medicine being promoted or just agree to give the representative a good hearing. Because reciprocal obligation can work without conscious awareness, health professionals may not be aware that they would

not have agreed to the representative's request if they had not received a gift. Large gifts are more effective than small gifts at changing the immediate behaviours of larger numbers of people. Small gifts, however, may be more effective at changing attitudes than large gifts. This is because human beings tend to construct beliefs and attitudes that are concordant with our own behaviour, and it is more comfortable to believe that we have done something because it was 'correct' than to admit that it was based simply on a small gift received. Thus, because of their impact on attitudes and beliefs, small gifts may actually be more effective, in the long term, at changing behaviour (O'Keefe, 2002).

Effects of samples or starter packs on patient care

A common feature in some countries is that sales representatives offer prescribers and dispensers samples of the medicines they are promoting. The assumption is that these samples will be given to patients, particularly ones who are unable to afford them, thus saving them or the health system money. There is evidence, however, that samples are actually most often used by physicians and staff themselves, and/or given to patients who can easily afford them (Westfall et al., 1997; Adair et al., 2005). Samples of expensive new medications are often provided, which may lead providers to prescribe these same agents to other patients. It can be difficult to change patients who receive such samples to other, less expensive alternatives once the samples are no longer available. This may result in the faster and more extensive adoption of expensive new medicines. Some countries, such as South Africa, have banned the use of sampling altogether (Republic of South Africa, 1965). Individual institutions have also done so, as reported by MacKinnon (2004).

"The evidence available today, therefore, seems conclusive on 2 points — first, that we are indeed heavily influenced by reps [pharmaceutical sales representatives]; and second, that we ourselves are very poor judges of the extent of that influence."

"Reps [pharmaceutical sales representatives] are not evil, but they are time-consuming and serve interests that often are at odds with those of our patients."

- Howard Brody, family physician, professor
(Brody, 2005)

Can you engage critically with sales representatives?

As noted earlier, some commentators suggest that providers can meet with sales representatives, but that for this to be productive and ethical, it must involve some form of critical engagement

(Day, 2000). In France, the independent medicines information bulletin *La revue Prescrire* has developed a checklist for use in an ongoing survey of the content of pharmaceutical sales representatives' visits. It suggests that the questions posed can be used as the basis of a more critical engagement with sales representatives (see Box 2) (Bardelay and Bécél, 1995). It suggests asking for the data sheet or package insert approved by the medicines regulatory authority and comparing what it says with what the representative says. It also suggests that the areas that should be questioned critically are:

- Efficacy – especially compared to the medicine or non-pharmaceutical option you currently use for that indication.
- Safety – especially in the patient population you may be treating (for example, the elderly).
- Utility – characteristics of the new medicine that will make it easier to use, cheaper or more convenient.
- Evidence for the claims made and the opinions on the medicine expressed by respected authorities (such as the national treatment guidelines).

The information provided by sales representatives rarely addresses these questions (Bardelay and Bécél, 1995).

Box 2: La revue *Prescrire* survey about sales representatives

1. Do the indications match those on the data sheet?
2. Does the dose regimen match that on the data sheet?
3. Did the representative spontaneously mention side effects?
4. Did the representative spontaneously mention contraindications?
5. Did the representative spontaneously mention drug interactions?
6. Given the type of drug, do you think the representative should have mentioned information on side effects, contraindications and drug interactions?
7. Was the representative willing to answer your questions?
8. Did you find the representative convincing?
9. Were there strong inducements to prescribe the drug?

(Bardelay D, Bécél D, 1995)

In order to engage critically, one must evaluate evidence in a systematic way. This is, of course, far less simple than a series of check boxes, and there is an entire discipline of clinical epidemiology (now popularly thought of as ‘evidence-based medicine’), in which individuals can spend several years of training to develop true expertise. (Some additional material about evidence-based medicine is provided in Chapter 8.)

Institutional policies on sales representatives

Instead of leaving the choice to individual health professionals, many institutions have tried to develop policies to govern the interaction between their staff (and students) and sales representatives and their employers. (An example of one such policy document is provided in Box 3 at the end of this chapter in the student activity section. This box includes the key points in a policy on pharmaceutical sales representatives’ on-site activities, developed by the University of Pennsylvania Hospital, US.)

A general format for such a policy would include the following elements:

- Reference to any self-regulatory or government-enforced regulations regarding pharmaceutical promotion;
- A clear process that either prevents or restricts access to the health facility or teaching institution by sales representatives (for example, by requiring that they first make arrangements with a central office, such as the hospital pharmacy or a drug and therapeutics committee’s secretariat);
- Restrictions on access by sales representatives to patient care areas;
- Rules about how promotional material may be displayed and distributed;
- Rules about the provision of medicines for use in clinical trials, particularly phase IV post-marketing trials;
- Rules about the provision of samples to staff and patients.

Should you continue contact with sales representatives?

Brody has written that “*our medical culture stresses a sense of entitlement to reps’ [sales representatives] goodies and that we have an apparently endless ability to rationalize why we see reps [sales representatives] and accept their gifts while imagining we are little influenced as a result*” (Brody, 2005). In reality, however, physicians and pharmacists face a choice (Doran et al., 2006):

- Avoidance of sales representatives;

- Critical engagement; or
- Uncritical engagement.

The avoidance approach is based on the view that health professionals and the pharmaceutical industry serve interests that sometimes overlap, but may also conflict. Since there is no proven way to ensure that contact with pharmaceutical sales representatives does not influence a health professional's behaviour, avoiding contact would seem to be the most prudent choice. Any attempt to 'filter' the potentially biased information received will be time-consuming. Is it not better to use the time instead accessing independent, unbiased sources of information? A similar argument has been made in relation to continuing medical education (Relman, 2001).

The other option that has been discussed is to continue to see sales representatives but to try to engage critically in the process, to pose questions and assess the information provided. Rules of engagement might include some or all of the following:

- Limiting interactions with sales representatives to group rather than one-to-one presentations in a clinic, hospital or pharmacy;
- Limiting the frequency of representatives' visits;
- Developing a set of ethical guidelines concerning food, gifts, invitations, etc.;
- Writing a guide for sales representatives on information to cover in a presentation, similar to the list in Box 3, as well as materials to leave behind, such as the drug data sheet;
- Designating one member of staff to evaluate presentations and provide feedback to the sales representative, for example, on information to include or omit next time. If improvements occur, contacts could be maintained, if not, they could be curtailed.

Contacts during professional education

Institutions offering undergraduate and postgraduate education to health professionals (such as residency or specialist training programmes) have expressed concern about the potential impact of unregulated contact between their staff and students and the pharmaceutical industry (Sandberg et al., 1997; Rogers et al., 2004; Zipkin and Steinman, 2005). Some have suggested that the best way to prevent such unregulated contact is to initiate it, under some type of supervision, during a doctor or pharmacist's training – although there is no evidence that this can be done in a way that mitigates the problems discussed earlier. In contrast, there is evidence that prohibiting contact with representatives leads to more skeptical attitudes (McCormick et al., 2001).

Conclusion

Medical practitioners and the pharmaceutical industry have been described as serving “*interests that sometimes overlap and sometimes conflict*” (Komesaroff and Kerridge, 2002). The same can be said of pharmacists. Although there are programmes at some institutions to educate students about pharmaceutical promotion, they are still few in number (Mintzes, 2005). One of these has shown that students become more uncertain about the accuracy and ethics of sales representatives’ activities after completing the programme (Wilkes and Hoffman, 2001). The authors concluded that their duty, as educators, was “*to raise questions and concerns in the minds of students*”, “*to teach them to think critically ... including about aspects of the ‘medical culture’ into which they have been so forcefully introduced*”. This chapter hopes to have achieved the same aim – to have unsettled long-held views and to have provoked critical thought and debate.

Student exercises

1. Watch sales representatives

View and discuss a video clip of a pharmaceutical sales representative's presentation, if you have access to one. Use the *Prescribe* checklist to analyse contents. Make a list as well of the types of persuasive techniques the sales representative used.

2. Start a debate

Using the following references, organise a debate between two groups of students. One group will argue that it is better not to have any contact with pharmaceutical sales representatives at all. The other group will argue that it is possible to engage critically and to the advantage of the health professional and his/her patients.

- a. Day R (2000). How to make the most of a visit from a pharmaceutical company representative. *Australian Prescriber* 23:97-99.
- b. Wofford JL, Ohl CA (2005). Teaching appropriate interactions with pharmaceutical company representatives: the impact of an innovative workshop on student attitudes. *BMC Medical Education* 5:5.
- c. Brody H (2005). The company we keep: why physicians should refuse to see pharmaceutical representatives. *Annals of Family Medicine* 3: 82-86.
- d. Wazana A (2000). Physicians and the pharmaceutical industry. Is a gift ever just a gift? *Journal of the American Medical Association* 283:373-380.

For additional material, the following reference can be used: Norris P, Herxheimer A, Lexchin J, et al. (2005) Drug promotion. What we know, what we have yet to learn. Geneva, World Health Organization and Health Action International.

3. Find evidence

Outline the evidence that exists for the impact of pharmaceutical representatives on professional practice (e.g. prescribing). To do this, students should break into small groups, each working with two or three of the references listed below. All of the groups should present their findings to the rest of the class.

- a. Roughhead EE, Harvey KJ, Gilbert AL (1998). Commercial detailing techniques used by pharmaceutical representatives to influence prescribing. *Australia New Zealand Journal of Medicine* 28:306-310.
- b. MacKinnon NJ (2004). Use of drug samples as a threat to seamless healthcare. *American Journal of Health-System Pharmacy* 61:1497-1500.
- c. Lexchin J (1997). What information do physicians receive from pharmaceutical representatives? *Canadian Family Physician* 43:941-945 (<http://www.pubmedcentral.nih.gov/picrender.fcgi?artid=2255515&blobtype=pdf>, accessed 10 March 2009).
- d. Watkins RS, Kimberly J (2004). What residents don't know about physician-pharmaceutical industry interactions. *Academic Medicine* 79:432-437 (http://journals.lww.com/academicmedicine/Fulltext/2004/05000/What_Residents_Don_t_Know_about.12.aspx, accessed 10 March 2009).
- e. Steinman MA, Shlipak MG, McPhee SJ (2001). Of principles and pens: attitudes and practices of medicine housestaff towards pharmaceutical industry promotions. *American Journal of Medicine* 110:551-557 (http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6TDC-42YF53S-6&_user=2822922&_rdoc=1&_fmt=&_orig=search&_sort=d&view=c&_acct=C000058881&_version=1&_urlVersion=0&_userid=2822922&md5=f11583a13168d1f6ebed19f67d704c5c, accessed 10 March 2009).
- f. de Bakker DH, Coffie DS, Heerdink ER et al. (2007). Determinants of the range of drugs prescribed in general practice: a cross-sectional analysis. *BMC Health Serv Res.* Aug 22,7:132 (<http://www.biomedcentral.com/1472-6963/7/132>, accessed 11 March 2009).
- g. Muijers PE, Grol RP, Sijbrandij J et al. (2005). Differences in prescribing between GPs: impact of the cooperation with pharmacists and impact of visits from pharmaceutical industry representatives. *Family Practice* 22(6):624-30 (<http://www.fampra.oxfordjournals.org/cgi/content/full/22/6/624>, accessed 11 March 2009).
- h. Steinman MA, Harper GM, Chren MM et al. (2007). Characteristics and impact of drug detailing for gabapentin. *PLoS Med.* Apr;4(4):e134 (<http://www.medicine.plosjournals.org/perlserv/?request=get-document&doi=10.1371/journal.pmed.0040134&ct=1>, accessed 10 March 2009).

- i. Stafford RS, Furberg CD, Finkelstein SN et al. (2004). Impact of clinical trial results on national trends in alpha-blocker prescribing, 1996-2002. *Journal of the American Medical Association* 291(1):54-62 (<http://www.jama.ama-assn.org/cgi/content/full/291/1/54>, accessed 11 March 2009).
- j. Prosser H and Walley T (2003). New drug uptake: qualitative comparison of high and low prescribing GPs' attitudes and approach. *Family Practice* 20(5):583-91 (<http://www.fampra.oxfordjournals.org/cgi/content/full/20/5/583>, accessed 11 March 2009).

4. Write a policy

Based on the example of the university hospital policy provided (see Box 3), develop an appropriate policy for a community health clinic or an educational institution on dealing with pharmaceutical sales representatives. The following reading materials may also be consulted:

- a. Rogers WA, Mansfield PR, Braunack-Mayer AJ et al. (2004). The ethics of pharmaceutical industry relationships with medical students. *Medical Journal of Australia* 180:411-414 (http://www.mja.com.au/public/issues/180_08_190404/rog10715_fm.html, accessed 10 March 2009).
- b. Barfett J, Lanting B, Lee J et al. (2004). Pharmaceutical marketing to medical students: the student perspective. *McGill Journal of Medicine* 8:21-27 (http://www.medicine.mcgill.ca/MJM/issues/v08n01/orig_articles/barfett.pdf, accessed 11 March 2009).
- c. Moynihan R (2003). Who pays for the pizza? Redefining the relationships between doctors and drug companies. 2: Disentanglement. *British Medical Journal* 326:1193-1196 (<http://www.bmj.com/cgi/content/full/326/7400/1189?view=long&pmid=12775621> or <http://www.pubmedcentral.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=12775621>, accessed 17 April 2009).

Box 3: Key points in a university hospital policy

PHARMACEUTICAL COMPANY REPRESENTATIVE ACTIVITY

Extracted and adapted from the University of Pennsylvania Hospital Policy Manual – September 2006. See:

<http://www.med.upenn.edu/fapd/documents/pharmaceuticalreppolicy.pdf>

Procedures

- All sales representatives must register with Pharmacy Services and sign a copy of the policy on their first visit to the hospital.
- Sales representatives must have scheduled appointments.
- The hospital can set limits on numbers of representatives/company.

Authorised and unauthorised areas

- No sales representatives allowed in patient care units, including operative areas and the emergency department.
- Sales representatives may not see patients, review charts or medical records, go to rounds or attend surgery.

Non-formulary drugs

- If a drug has been evaluated by the Pharmacy & Therapeutics Committee and been denied formulary status, it may not be promoted on hospital premises.
- If a sales representative promotes a drug to hospital staff, they must first provide the Pharmacy Drug Information Service with formulary packets and information on the medication.

Sample medications and promotional items

- No samples allowed on premises.
- Vouchers for medication samples are prohibited in inpatient areas.
- Promotional items such as pens, notepads and 'reminder' items are prohibited.

Education

- Continuing Medical Education (CME) content is to be controlled by course directors and not the company providing the educational grant.
- Pharmaceutical company representatives are expected to communicate warnings and contraindications with the same fervor with which they promote indications and endorsements by medical experts.
- All in-services, lectures or other presentations to staff must be registered at least one month beforehand and pre-approved by the director of the relevant department.
- All non-CME programmes must be limited to discussion of formulary drugs.

Meals and gifts

- Gifts to professional staff are prohibited.
- Food is not to be provided directly by sales representatives.
- Hospital personnel or resources such as e-mail may not be used to distribute information on promotional events.
- No compensation allowed for time listening to promotional presentations.

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- de Bakker DH, Coffie DS, Heerdink ER et al. (2007). Determinants of the range of drugs prescribed in general practice: a cross-sectional analysis. *BMC Health Serv Res*. Aug 22,7:132 (<http://www.biomedcentral.com/1472-6963/7/132>, accessed 17 April 2009).
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- Brennan TA, Rothman DJ, Blank J et al. (2006). Health industry practices that create conflicts of interest. A policy proposal for academic medical centers. *Journal of the American Medical Association*, 295(4): 429-433.
- Brody H (2005). The company we keep: Why physicians should refuse to see pharmaceutical representatives. *Annals of Family Medicine*, 3: 82-86.
- Chren MM, Landefeld CS (1994). Physicians' behavior and their interactions with drug companies. A controlled study of physicians who requested additions to a hospital drug formulary. *Journal of the American Medical Association*, 271(9):684-689.
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Chapter 5

Promotion to consumers: Responding to patient requests for advertised medicines

Barbara Mintzes, Les Toop and Dee Mangin

Since the 1990s, pharmaceutical manufacturers have increasingly begun to promote their medicines directly to the public. This marketing has been shown to lead to more prescriptions and therefore more sales of medicines (Gilbody, 2005). It also has profound implications for the public perception of medicines and the relationship between patients and health professionals.

Direct-to-consumer advertising (DTCA) of prescription medicines through television, radio, magazines, newspapers and billboards is legal in only two countries, New Zealand and the US. In countries that do not allow advertising of prescription medicines, however, other forms of direct and indirect promotion to the public often occur. These include industry-sponsored disease awareness campaigns, patient compliance and disease management programmes, promotional material on the Internet and sponsored television ‘infomercials’. Some countries allow unbranded advertising campaigns that prompt consumers to “ask your doctor” for a new treatment. Disguised promotion, in the form of promotional press and video news releases and resultant news coverage, is also common. Advertising campaigns targeting the public have thus become a reality in many countries despite their sometimes questionable legal status.

In countries with well-enforced laws governing prescription-only status, people who view advertisements for a prescription-only medicine cannot buy the product directly; they must first ask a physician for a prescription. In lower-income countries, prescription-only status is often poorly enforced, and a person can generally buy any medicine directly without first seeing a doctor. In these countries, it is pharmacists who are likely to be most affected by patient requests for advertised medicines.

All health professionals face the dilemma of how to respond to patient requests for advertised medicines. Patient requests are sometimes based on inaccurate beliefs about a medicine's effects or appropriateness for their own situation. Patients can also be forceful. This can create a tension between evidence-based decision-making and patient-centred care. Misunderstandings on both sides may interfere with appropriate care. It is important for health professionals to understand the mechanisms behind promotion-influenced patient requests and develop appropriate responses.

The aim of this chapter is to introduce you to the research evidence on consumer-directed advertising of medicines and the way that promotion targeting the general public affects prescribing decisions. The chapter also provides some guidance on ways to respond to patient requests for advertised medicines.

Aims of this chapter

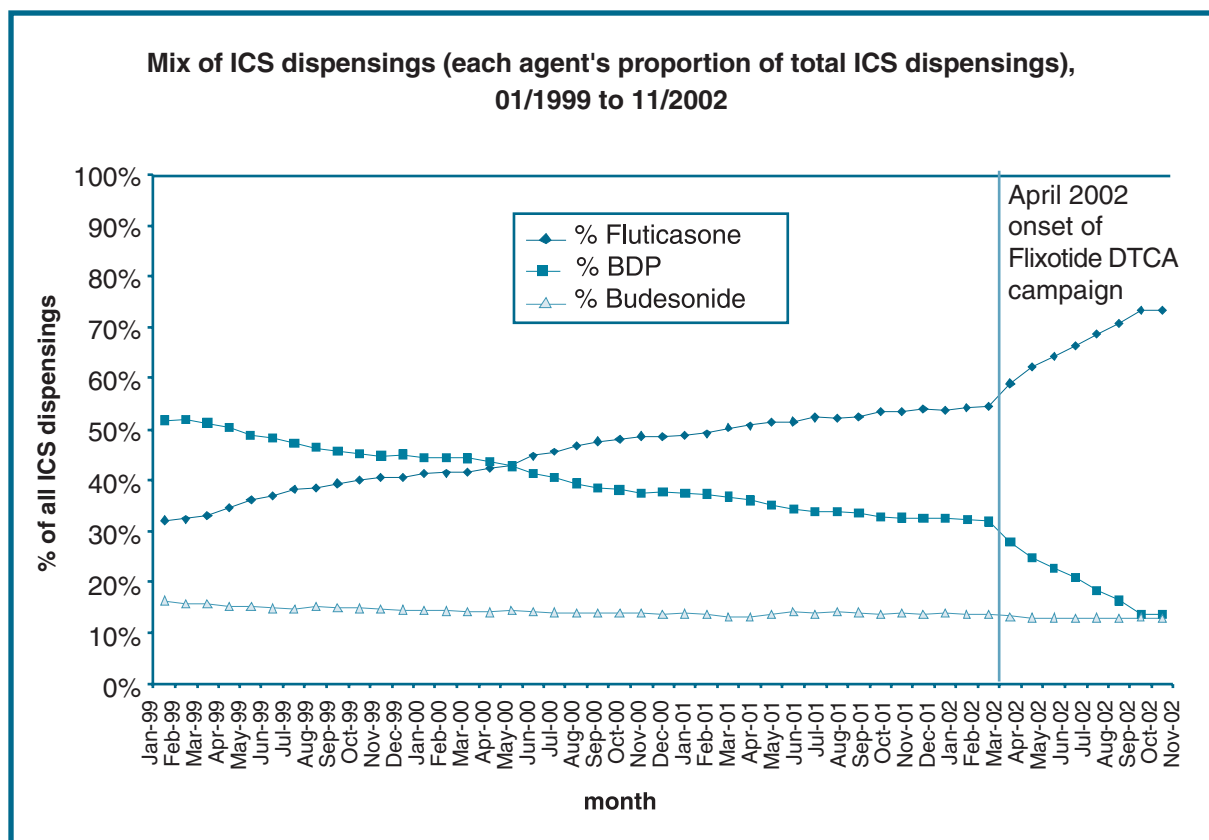
At the end of the session based on this chapter, you should be able to:

- Discuss, with examples, how promotion of medicines to the public has been shown to affect patient care;
- Describe the range of techniques used to promote medicines to consumers;
- Discuss strategies you can employ when responding to requests from patients driven by promotional messages.

Promotion's effects on behaviour

Do patients request advertised medicines from their doctors and do doctors prescribe requested medicines? Research from both New Zealand and the US suggests that advertising of medicines does affect prescribing and use. Figure 1 shows the rates of prescribing for two types of asthma inhalers before and after a DTCA campaign for one of the inhalers, Flixotide (fluticasone). The graph shows that many patients who had been prescribed beclomethasone switched to fluticasone. These are two different types of corticosteroids used to prevent asthma attacks. At the time of this campaign, Flixotide (fluticasone) was more expensive than beclomethasone. It is no more effective at equivalent doses, but is more potent per microgramme, which can be a problem when switching, especially with treatment of children. This switch in medication resulted in expenditure of nearly US\$3 million more than if the less expensive inhaler had been used.

Figure 1: DTCA leads to substitution of a more expensive steroid inhaler: dispensing data from New Zealand's public drug plan (PHARMAC)



ICS = inhaled corticosteroids, BDP = beclomethasone dipropionate

(Source: PHARMAC; In Toop, 2003)

There is also evidence from the US that advertising affects the choice of medicine that is used. For example, a US analysis of a large administrative database of prescriptions found that more patients began use of an advertised brand of proton pump inhibitor (a medicine for gastric reflux and ulcers) than a similarly effective non-advertised brand when advertising levels were high and when their insurance plan covered most of the cost of their medicines (Hansen, 2005). This study suggests that when consumers are not paying directly for their medicines they are especially likely to be influenced by advertising.

The research arm of the US Congress, the US General Accounting Office, estimated in 2002 that eight million Americans requested and received medicines in response to DTCA each year, based on consumer surveys (Heinrich, 2002). New Zealand consumer surveys show proportionally similar results (Toop, 2003). In other words, advertising of medicines does lead directly to patient requests that result in increased prescription rates and rates of use.

How does advertising to the public affect prescribing?

If a prescription medicine is advertised on television in New Zealand or the US, the viewer cannot simply go to the store and buy it, as they might buy an advertised pair of shoes or a soft drink. Viewers must ask their doctors for a prescription. However, prescriptions are medical treatments with inherent dangers, not consumer products, and doctors are legally responsible for the prescriptions they provide. So does advertising really affect prescribing decisions?

Two prospective studies in doctors' offices have compared consultations in which patients requested advertised medicines with consultations in which they did not. One was a comparison between patients of family doctors in Sacramento, US where DTCA is legal, and Vancouver, Canada, where DTCA is illegal but there is some cross-border exposure from the US (Mintzes, 2003). The other was an experimental study that compared consultations in which actresses pretending to be patients ('standardised patients') did and did not request an advertised medicine (Kravitz, 2005).

In the first study, patients filled in a questionnaire in the waiting room, which was matched with a physician questionnaire following the consultation. The physicians reported on all new prescriptions they had provided and any that the patient had requested. US patients and those with more self-reported exposure to DTCA were more likely to request an advertised medicine. Physicians prescribed three-quarters of requested DTCA medicines. However, they were often ambivalent about these decisions; they judged half of new prescriptions for requested advertised medicines to be only "possible" or "unlikely" choices for other similar patients. In contrast, physicians judged only one out of eight prescriptions for medicines not requested by patients to be "possible" or "unlikely" choices for other similar patients.

In the second study, the 'standardised patients' made nearly 300 unannounced visits to family doctors in three cities (Kravitz, 2005). The visits were randomly allocated to several scenarios. The 'patients' either described symptoms of clinical depression or of an 'adjustment disorder' - a normal response to a stressful life problem, moving to a new city and being unemployed. For each condition, the 'patient' either asked for a prescription for the antidepressant Paxil (paroxetine), which was advertised on television, for an antidepressant in general, or did not request a medicine.

The doctors prescribed antidepressants in just over half of the visits in which Paxil was requested for both clinical depression and adjustment disorder. In other words, if a patient requested this antidepressant, physicians were equally likely to provide an antidepressant prescription whether or not the patient had depression, the condition the medicine has been tested for and is approved to treat. 'Patients' with adjustment disorder who requested Paxil were 13 times as likely to receive an antidepressant prescription as those who did not request a medicine. The 'adjustment disorder' scenario was a normal response to a stressful life event; it should not have been treated with a medicine. Although these were actors, the study raises strong concerns about the negative effects of DTCA on prescribing quality.

In this study, those with a depression diagnosis were also more likely to receive standard follow-up care (i.e. care that was consistent with treatment guidelines for depression) if they either requested Paxil or asked generally for an antidepressant. A brand-specific request did not increase the rate at which they received this care. They were less likely to receive this level of care, which involved repeat visits and either pharmacotherapy or psychotherapy, if they did not ask for a medicine. However, after controlling for whether or not they received a prescription, there was no difference in whether ‘patients’ with adjustment disorder or depression received follow-up care (Epstein, 2007).

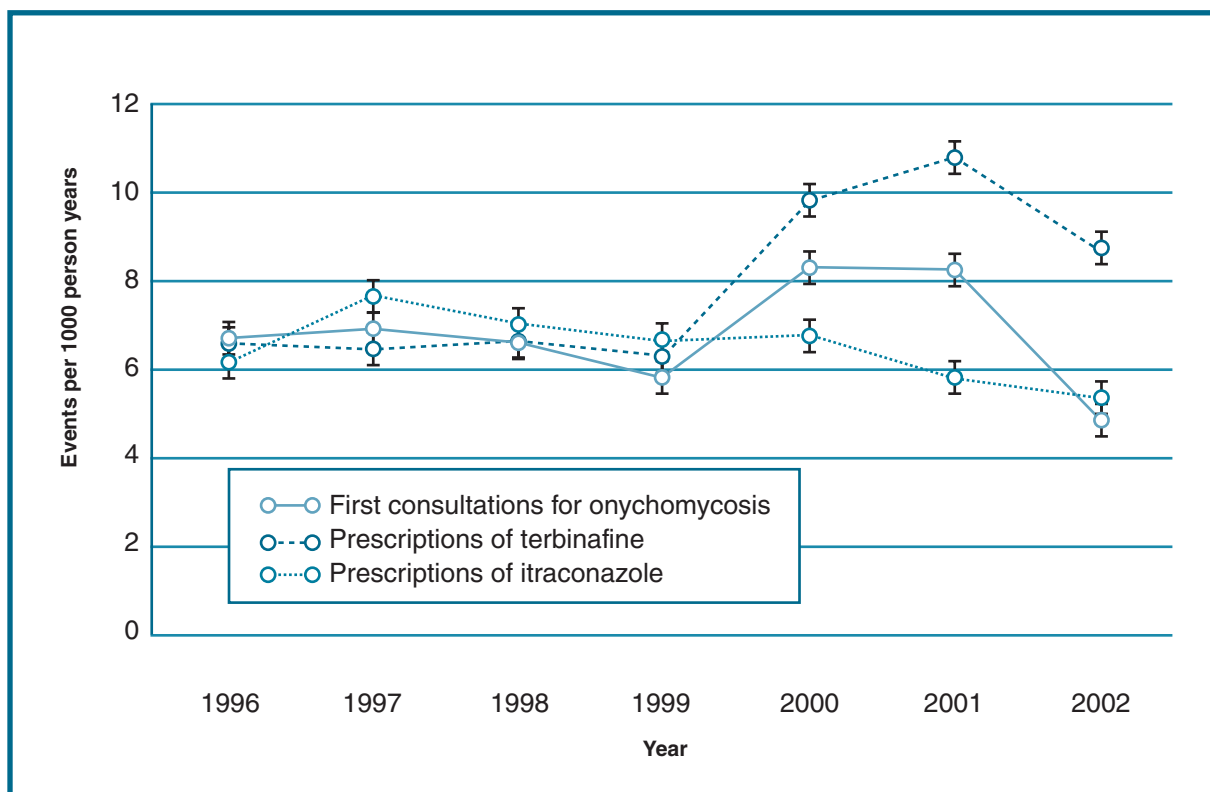
These studies suggest that advertising affects prescribing, both because doctors sometimes prescribe and pharmacists provide medicines they might not prescribe otherwise, and because if a patient asks for a medicine, the doctor is likely to prescribe it. This is consistent with other research showing that even in the absence of advertising, doctors are more likely to prescribe a medicine if they believe the patient wants one (Britten, 1997; Cockburn, 1997).

Do other types of promotion affect medicine use?

In many countries, including both those where DTCA is and is not allowed, companies sometimes run unbranded disease awareness or ‘help-seeking’ promotional campaigns. These discuss symptoms of a condition and suggest that viewers or readers “ask your doctor” about a new treatment.

In the Netherlands, Novartis, manufacturer of the antifungal medicine Lamisil (terbinafine) ran a televised advertising campaign about toenail fungus in 2000 and 2001. The brand name was not mentioned, but the commercials strongly suggested asking your doctor for treatment for toenail fungus. An analysis of effects on consultations and prescribing was carried out in a Dutch primary care research database covering 150 physicians’ practices and more than 470,000 patients (‘t Jong, 2004). As shown in the graph, the prescribing rate for this medicine doubled after the campaign started. Rates of first consultations also went up during the campaign, falling again afterwards.

Figure 2: An analysis of effects on consultations and prescribing of a disease awareness promotional campaign in the Netherlands



(Source: 't Jong, GW et al., 2004)

The authors of this study raised concerns about the effects of these advertisements on the workload of family doctors. They felt that the time spent with patients with this minor and mainly cosmetic condition took time away from patients with more serious health problems. There are two other concerns. This is an expensive treatment of limited long-term effectiveness. In a large randomised, controlled trial, only 25% of patients were completely cured at 18 months (Warsaw, 2005). Additionally, there is a rare but serious risk of liver toxicity ('t Jong, 2004).

In an earlier US study, Basara (1996) also found that an unbranded advertising campaign for Imitrex (sumatriptan), a migraine medicine, led to more prescriptions. These analyses show that even when a brand name is not mentioned, companies can successfully promote sales of a prescription medicine through advertising that tells the public to go to their doctor to seek treatment.

Since 2005, Australian disease awareness advertisements can legally direct viewers to branded Internet advertising. This provision was introduced within a bilateral trade agreement with the US (Australian Govt., DFAT, 2006). As of mid-2007, the effect of this change on attitudes to medicines, medicine use, health or costs has not been studied.

Figure 3: Canadian ‘toe-tag’ advertisement, funded by the manufacturer of a leading cholesterol-lowering medicine

Fear of death used to sell a medicine – even with no brand name mentioned

World Health Organization staff raised concerns in a letter to the UK journal *The Lancet* about a *disease awareness* advertising campaign in France promoting cholesterol testing, by the manufacturer of a leading brand, Lipitor (atorvastatin) (Quick, 2003). Print advertisements showed the tagged toe of a corpse. The image below is from a similar Canadian campaign by the same company. The authors of *The Lancet* letter believed that the advertisements could cause undue anxiety, failed to convey the importance of other risk factors for heart disease, such as smoking, obesity or a sedentary lifestyle, and “*contained misleading statements and omissions likely to induce medically unjustifiable drug use or to give rise to undue risks.*”

Which would you rather have, a **cholesterol test or a final exam?**

For many, the first sign of heart disease is a heart attack. Did you know that one out of two adult Canadians is at risk of developing heart disease because they have high cholesterol? And that cardiovascular disease is the leading cause of death in Canada? High cholesterol is a major risk factor for heart disease but managing your cholesterol can be quite simple.

If any of these apply to you, cut this screening test out and ask your doctor about getting your cholesterol tested:

- Woman 50 years or older
- Man 40 years or older
- Heart disease (angina, heart attack, coronary bypass, stroke, angioplasty)
- Diabetes
- Family history (mother, father, sister, brother or grandparent) of heart disease or high cholesterol
- Two or more of the following:
 - Overweight
 - Physically inactive
 - Smoker
 - High blood pressure

Call toll-free at 1-877-4-LDM-LDL (1-877-436-9333) or visit www.makingtheconnection.ca and you will receive this free booklet describing the connection between cholesterol and heart disease.

OFFICE OF THE MEDICAL EXAMINER

Case No. 5891-10
 Name
 Date of Birth 1/1/1975
 Sex
 Age
 Sex

Canadian Heart Health Alliance

Making a Connection

(Advertisement from: http://www.health-heart.org/final_exam.jpg)

How well does advertising inform the public about available medicines?

Advertised medicines are mainly new, expensive treatments for regular or intermittent long-term use among large population groups. Cheaper, generic, off-patent medicines are rarely, if ever, advertised to the public.

One of the main claims made for medicines' advertising is that it informs the public about the newest available medicines. This is true. What is debatable is whether promoting widespread use of these newest medicines is beneficial. When it comes to medicines, newer is not necessarily better. Companies spent more than US\$800 million advertising just five medicines to the US public in 2004 (see Table 1). None were 'breakthrough' medicines meeting important previously unmet health needs. For example, Nexium (esomeprazole) – the medicine with the top advertising budget in 2004 – is simply one of the two enantiomers or isomers of the racemic mixture which makes up omeprazole, a medicine for which less costly generic equivalents are available. (An enantiomer or isomer of a chemical compound has the same molecular formula but a different structural configuration in space.) Refining the isomer allowed separate patenting, but unsurprisingly Nexium (esomeprazole) is no more effective than omeprazole at equivalent doses (Therapeutics Initiative, 2002).

Table 1: Five top medicines by US DTCA spending January - November 2004

Medicine	Indication	Spending (US\$ millions)
Nexium (esomeprazole)	Ulcer/reflux	\$226.0
Crestor (rosuvastatin)	Lipid lowering	\$193.2
Cialis (tadalafil)	Impotence	\$152.6
Levitra (vardenafil)	Impotence	\$142.0
Zelnorm (tegaserod)	Irritable bowel syndrome	\$122.0
Total – top 5		\$835.8

(Source: Arnold, 2005)

Of the four other medicines in Table 1, three have been subject to safety advisories, and one, Zelnorm (tegaserod) was withdrawn from the US market in March 2007 due to increased risks of heart attack, angina and stroke (US FDA, 2007). There is evidence of greater risks of rhabdomyolysis, a muscle-wasting disorder, with Crestor (rosuvastatin) than other medicines in the class (Public Citizen, 2003). Cialis (tadalafil) and Levitra (vardenafil) are similar to Viagra (sildenafil) and all can cause visual abnormalities (US FDA, 2005).

The choice to intensively advertise a specific brand is a marketing decision, based on the likely return on investment (Arnold, 2005). It is not a public health decision. In these examples, prescriptions stimulated by intensive advertising may not be the best answer for individual patients, either because a more cost-effective or safer alternative exists or because a non-drug solution might be a better option, especially for mild problems.

There is some evidence that people who are exposed to more advertising for medicines for conditions that are affected by lifestyle are less likely to pursue healthy activities. Iizuka and Zhe Jin (2005) compared results of a national US health survey with advertising spending for medicines for diabetes, high cholesterol, obesity and hypertension. They found that when there was more advertising for medicines for these conditions, people were less likely to report that they had regular, moderate exercise. This is consistent with a content analysis of US television advertising, which found that none of the advertisements portrayed lifestyle change as an alternative to taking the product and 18% conveyed the message that lifestyle change was insufficient (Frosch, 2007).

Box 1: Advertising of the arthritis medicine Vioxx (rofecoxib)

Between 1999 and 2004, one of the most heavily advertised medicines was Vioxx (rofecoxib), an arthritis treatment. The medicine's manufacturer, Merck, spent more than US\$550 million advertising this product to the US public (Topol, 2004). In 2000, more was spent on advertisements for Vioxx (rofecoxib) than on Pepsi-Cola advertisements (Findlay, 2001). Over 80 million people took the medicine worldwide. It was withdrawn from the market in 2004 when it was found to increase the risk of heart attacks and strokes.

On the basis of clinical trial findings and population patterns of use, senior US Food and Drug Administration (FDA) official David Graham estimated that between 88,000 and 140,000 extra heart attacks in the US were due to the use of Vioxx (rofecoxib) (Graham, 2005). Merck's intensive advertising of this medicine is controversial not only because of the evidence of serious harm, but because the first major study to show an increased risk of heart attacks, the VIGOR trial, was published in late 2000, four years before advertising stopped (Bombardier, 2000).

Although Vioxx (rofecoxib) is the highest profile medicine to feature in DTCA and later be withdrawn for safety reasons, it was not the first or the last. Other examples include the cholesterol-lowering medicine Baycol (cerivastatin), the diabetes medicine Rezulin (troglitazone) and the irritable bowel syndrome medicine for women Zelnorm (tegaserod).

Figure 4. Advertisement for Vioxx



Dorothy Hamill

VIOXX[®]
(rofecoxib)

**Ask your doctor
or other healthcare professional.**

Available only by prescription.

**For more information on VIOXX
from Merck, call 1-888-VIOXX-11.
vioxx.com**

VIOXX is a registered trademark of Merck & Co., Inc.

MERCK

© 2002 Merck & Co., Inc. All rights reserved. 2620472711-VIO-CON

(Advertisement from: www.todaysseniorsnetwork.com)

This is a 2002 US magazine advertisement for rofecoxib (Vioxx) The woman featured in the photo is Dorothy Hamill, who won an Olympic gold medal in 1976.

Making 'newer' seem 'better'

Advertising campaigns are usually most intensive in the first few years of a medicine's marketing life. This is also when less is known about a medicine's rare or longer-term effects. An analysis of all medicines approved in the US between 1975 and 1999 found that half of medicine safety withdrawals occurred within the first two years a medicine was marketed (Lasser, 2002). In total, one in five new medicines received 'black box' safety warnings or was withdrawn because of serious risks.

There is good reason to be cautious in prescribing or using a new medicine when an acceptable treatment is already available. The implied message in advertising is very different, however. Frosch and colleagues' (2007) content analysis of television advertising in the US found that more than half – 58% – presented the medicine as a breakthrough.

Education or marketing?

How well does advertising inform the public about medicines' benefits, risks and contribution to therapy? In 2000, US researchers published an analysis of more than 300 magazine advertisements published over ten years for the presence or absence of key information needed for informed treatment choice (Bell, 2000). They found that the name and indication (approved use) of the medicine were almost always stated but other necessary information was often missing:

- 90% failed to state the likelihood of treatment success;
- 80% made no mention of other helpful activities, like diet or exercise;
- 70% did not mention causes or risk factors for the treated condition;
- 70% failed to mention any other possible treatments;
- 60% omitted any information as to how the medicine works.

The authors did not examine the accuracy, completeness or relevance of information that was provided, only whether it was present or absent.

Figure 5. Advertisement for a sleeping pill

Ambien CR is the only 2-layer sleep aid with a controlled-release formula:

The first layer dissolves quickly to help you get to sleep fast.
The second layer dissolves slowly to help you stay asleep.**

For a limited time only, get 7 days of AMBIEN CR FREE.
Visit www.AmbienCR.com or call 1-800-797-6138.

Important Safety Information

AMBIEN is indicated for the short-term treatment of insomnia.

When you first start taking AMBIEN, use caution in the morning when engaging in activities requiring complete alertness until you know how you will react to this medication. In most instances, memory problems can be avoided if you take AMBIEN only when you are able to get a full night's sleep (7 to 8 hours) before you need to be active again. As with any sleep medication, do not use alcohol while you are taking AMBIEN.

Prescription sleep aids are often taken for 7 to 10 days — or longer as advised by your healthcare provider. Like most sleep medicines, it has some risk of dependency.

There is a low occurrence of side effects associated with the short-term use of AMBIEN. The most commonly observed side effects in controlled clinical trials were drowsiness (2%), dizziness (1%), and diarrhea (1%).

AMBIEN CR is indicated for treating insomnia.

It is a treatment option you and your healthcare provider can consider along with lifestyle changes and can be taken for as long as your healthcare provider recommends. Until you know how AMBIEN CR will affect you, you shouldn't drive or operate machinery. Be sure you're able to devote 7 to 8 hours to sleep before being active again. Side effects may include next day drowsiness, dizziness and headache. It's not narcotic; however, like most sleep medicines, it has some risk of dependency. Don't take it with alcohol.

sanofi aventis

*Not actual pill size. Please see important patient information on adjoining page. ©2006-2007 sanofi-aventis U.S. LLC. All rights reserved. US-ACR-06.12.00P December 2006. Printed in USA.

(Advertisement from *Good Housekeeping* magazine, April, 2007.)

This is an advertisement for the sleeping pill Ambien CR (zolpidem), offering a free trial of the medicine, which is, in fact, a drug of dependency. When considering the educational merits of this advertisement, one should ask what it says about the likelihood of treatment success (proportion of people helped and/or how much more sleep they get); other helpful activities; causes or risk factors for insomnia; any other possible treatments; or how the medicine works.

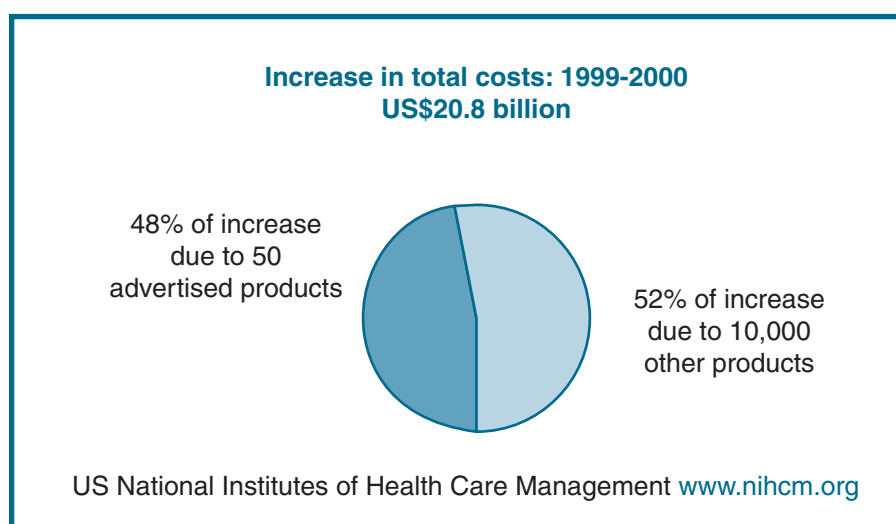
Financial incentives to use a specific medicine

Another study of US magazine advertisements appearing in ten consumer magazines over a one-year period found that nearly 9 out of 10 “*described the benefits of a medication in vague, qualitative terms*” and failed to provide any evidence to support claims (Woloshin, 2001). Nearly one-quarter offered financial incentives to use the medicine, such as free trial offers. In a survey of 263 older Americans in the state of Kansas, many of whom were low-income, nearly half said that they would phone a number listed in an advertisement if a discount coupon or free sample was offered (Marinac, 2004). In contrast, without the mention of a discount, only 1 in 9 believed they would make the phone call. The WHO *Ethical Criteria for Medicinal Drug Promotion* recommend against the use of financial incentives to influence prescribing decisions (WHO, 1988).

Effects on health-care costs

In 2000, over 95% of spending on advertising was on 50 medicines. Nearly one-third of total US retail prescription medicine costs went toward these 50 brands, or US\$41 billion. These same medicines were responsible for more than half of the increase in retail spending between 1999 and 2000 (Findlay, 2001).

Figure 6: Effects on costs of medicines sold in US pharmacies



(Source: Findlay, 2001)

Unrealistic public understanding of safeguards

In two national US FDA surveys of public attitudes and responses to advertising, more than a quarter of consumers thought that only the safest medicines could be advertised to the public (Aikin, 2004). In a California survey, 4 out of 10 people thought only completely safe medicines could be advertised on television (Bell, 1999). Neither statement was true: any licensed medicine may be advertised to the public. These survey findings suggest that a considerable minority of people mistakenly believe that they are better protected by regulation than is the case.

What is left out is as important as what is said

Whether it occurs in an environment where advertising of prescription medicines is legal or in the form of unbranded promotional messages where advertising is illegal, certain messages – and certain omissions – can be expected from pharmaceutical advertising. The main messages are that a person's problem is likely to be serious and that a new medicine exists that can help. The images of treatment success usually suggest that the medicine works 100% of the time. Efficacy is thus oversold. In contrast, known and unknown risks and harms are generally omitted or minimised.

Where people see pharmaceutical advertisements on television each day, they hear the message repeatedly to “ask your doctor” for a new medicine that may help you. They also get the message, again and again, that a medicine may be a solution to their problems. Even if a person does not consciously think that there is ‘a pill for every ill’, seeing the message every day can lead to a shift in their understanding of medicines.

Does DTCA affect the doctor-patient relationship?

The messages in advertising are sometimes inconsistent with a doctor's recommendations for treatment. As one New Zealand doctor explains, this can create disharmony: *"I find that it [advertising] can be a nuisance as it creates doubts in patients' minds about the efficacy of the medication they may already be on."* (Toop, 2003).

Another New Zealand physician, responding to the same survey, believes that sometimes advertising can lead to frustrations and other times it can result in a useful discussion:

“Although I always resist DTCA generated requests to initiate or change medications, these patients simply go to another practitioner (in the same practice!), who gives them anything they ask for. I spend a great deal of time explaining the evidence-based option, the non-drug-based options and the options that will lead to better outcomes at lower doses. I don't know why I waste my breath! ...Very rarely DTC-generated consultations to switch from brown to pink to

red inhalers have alerted me to existing poor compliance/poor inhaler technique and even more rarely, the patient has taken on board the messages about improving technique and compliance.” (Anon., in Toop, 2003).

In a California survey, patients were asked how they would react if their physician refused to prescribe a DTCA medicine they requested (Bell, 1999). Nearly half said they would feel disappointed, one-quarter would try to change the physician’s mind and one-quarter would go to another doctor for a prescription.

How should health professionals respond to patient requests for advertised medicines?

If a patient is convinced that an advertised medicine may help him or her, especially with a problem that has been difficult to treat, it can be tempting to simply ‘give it a try’. This is the path of least resistance: the patient has what he or she wants, the health professional has listened and has appeared to be helpful.

It is important to remember that some medicines are classified as prescription-only because they have greater potential for harm than other medicines. Writing a prescription is one of the most potentially dangerous things physicians do. The patient’s request may be based on incomplete and misleading information and a misunderstanding of the likely effectiveness and safety of the medicine or how it compares to alternatives. If you prescribe a medicine, you are legally responsible for the prescribing decision.

A New Zealand physician comments: *“Patients feel their drug is inferior to the one on TV. Patients with asthma now all want Symbicort® even though a long acting β -agonist (is) not indicated for them.”* (Toop, 2003). Not long afterwards, a systematic review of studies of long-acting β -agonist showed an increase in asthma mortality (Salpeter, 2006). In some cases, doing what patients want may mean providing them with inferior care – an unnecessarily risky treatment. You may not always have the information on hand that allows you to know whether a medicine would or would not be useful for a specific patient. You can take the time to look up additional information before coming to a decision.

When advertisements blur the line between normal life and a medical problem needing treatment this is called medicalisation or *disease mongering* (Moynihan, 2002). Some patients may request an advertised medicine when they do not have a health problem requiring treatment.

Shifting the conversation back to the patient and the problem he or she is experiencing is a good technique for dealing with patient requests for advertised medicines. It is important to discuss the range of treatments available and how this advertised medicine compares to others as well as the outcome with no treatment.

Another strategy is to point out the pharmaceutical company motivation in advertising. A person who asks for an advertised medicine may be much more skeptical of other forms of consumer advertising. In some cases, they may have been convinced by indirect or disguised advertising. Where it is available, direct patients to reliable information sources (see Chapter 8 for additional information).

Box 2: Responding to patients' requests for advertised medicines

Suggestions on how to respond to requests:

- Shift the discussion away from the medicine to the patient and his or her symptoms;
- Determine the diagnosis, if there is one and whether a medicine is needed;
- Explain the range of drug and non-drug treatments, including the likely outcome with no treatment;
- If treatment is needed, explain your recommendation for treatment; if it is not needed, explain why not;
- Explore the beliefs that have led to the request;
- Discuss the role of pharmaceutical advertisers;
- Refer to reliable information sources.

Conclusion

Advertising of medicines directly to consumers strikes at the heart of interactions between patients and health professionals. At its worst, it turns the patient-doctor or patient-pharmacist relationship into a 'health consumer-provider' interaction, the means to obtain a desired brand. This can distract both patients and professionals and lead to unnecessary friction. In many countries, there is strong pressure from the pharmaceutical and advertising industries and media to introduce DTCA of prescription medicines. The motivation for this is clear: advertising is very effective at stimulating sales and increasing profits by driving the consultation in a particular direction. From a public health perspective, however, there is little rationale for emotive advertising, with its promise of an easy, magical solution in the form of a glittery brand.

A person who is facing a health problem or is anxious about a family member needs to know what the available treatment options are, the pros and cons of each, including when treatment is not needed. This type of information cannot be provided by industry advertising, which primarily aims to sell a product.

In Europe, a struggle for legalisation for advertising of prescription medicines to the public ended in a resounding defeat for industry in 2002. This has now been followed by a second-wave attempt at introduction in 2006 and 2007 (Brown, 2007). This time, the ‘A’ word, ‘advertising’, goes unmentioned, and instead the discussion is of ‘medicines information’ provided by pharmaceutical companies about their products, including within public-private-partnerships. The problem with this scenario is essentially one of disguised product promotion. More independent, comparative, consumer health information is clearly needed. The pharmaceutical industry is equally clearly unable to provide this whilst fulfilling its primary duty to its shareholders.

Health professionals may find themselves affected by medicines advertising not only at a professional level in their interactions with patients, but also as citizens. DTCA of prescription medicines is highly profitable, and commercial versus public health struggles over its introduction are likely to continue. Increasingly, even where this advertising is illegal, forms of product promotion that skirt the boundaries of the law – and beyond – are also becoming more and more common. This includes commercial messages that may exaggerate disease risks (Moynihan, 2002). It can be a challenge to maintain a shared understanding of when treatment is and is not needed, and which of a range of available treatments is most appropriate. Both frank discussions with patients and public access to independent appraisals of the scientific evidence on the effectiveness and safety of medicines are part of the solution. The other part of the solution is likely to be political and regulatory.

Student exercises

1. Role play of a patient-physician interaction in which a patient requests a medicine

This is a consultation in which a woman in her mid-twenties presents and requests (forcefully) that you prescribe a new weight loss pill for her. She has read about this amazing breakthrough product in a magazine and also watched it discussed on television. Apparently it has only been available in this country for a few months and some of her friends say it is great. The patient has a body mass index (BMI) of 28 and is very keen to reduce her weight for an upcoming social function (she is getting married in six weeks and wishes to go down two dress sizes to fit into her mother's wedding dress). She takes an oral contraceptive and smokes ten cigarettes per day. Her blood pressure is 135/85 and there is a family history of hypertension.

The medicine requested, like many slimming pills, is known to raise blood pressure and pulse in some people, and has been associated with strokes and one or two unexplained deaths and unusual psychiatric symptoms. Despite having been on the market for less than three years, it has been prescribed to many hundreds of thousands of patients worldwide and the manufacturers steadfastly claim it is safe. Short-term studies of efficacy in obese patients show a modest improvement of a few kilos over diet and exercise alone after several months of treatment. There are no published long-term safety studies.

Debrief as a group on the issues such a consultation poses. What strategies can the group collectively suggest to manage these issues?

2. Critical appraisal of an advertisement and comparison with independent information

Look at the image, headlines and text in Figure 7.

- List the main messages in the advertisement.
- What is implied about beneficial and harmful effects? About seeking care? About the role of medicinal treatment in Alzheimer's disease?
- List positive and negative aspects of the message in the advertisement.
- How do you think the doctor-patient relationship might be affected?

Figure 7. A US advertisement for the medicine Aricept (donepezil) for Alzheimer's disease.

Fighting Back with Aricept®

*I love my life way too much
to just hand it over to Alzheimer's.*

*When my memory started failing,
I knew I had to see my doctor. He put
me on ARICEPT®. Now I'm doing better.**

If a person forgets names, places or facts – and has trouble with everyday things like reading or shopping – it may not be normal aging. It could be Alzheimer's disease. So it's important to see a doctor as soon as you can.

There is no cure for Alzheimer's. But a prescription drug called ARICEPT® has been used by millions of people to help their symptoms.

In studies, ARICEPT® has been proven to work for mild to moderate Alzheimer's. It has helped people improve their memory over time. It has also helped them to keep doing everyday things on their own, longer.

Ask your doctor if ARICEPT® is right for you or your loved one. It is the #1 prescribed drug for Alzheimer's in the world. The sooner you know it's Alzheimer's, the sooner ARICEPT® can help.

ONCE-A-DAY
ARICEPT®
(donepezil HCl)
5 MG AND 10-MG TABLETS

Strength in the face of Alzheimer's™

To learn more and to receive a memory checklist,
call 800-760-6029 ext.92
or visit www.aricept.com

Memory Checklist

ARICEPT® is well tolerated but may not be for everyone. Some people may experience nausea, diarrhea, not sleeping well, vomiting, muscle cramps, feeling very tired, or not wanting to eat. In studies, these side effects were usually mild and went away over time. Some people taking ARICEPT® may experience fainting. People at risk for ulcers should tell their doctors because their condition may get worse.

Please see additional important product information on accompanying page.

*Individual responses to ARICEPT® can be different – people may get better, stay the same or not get better.

(Advertisement from *Woman's Day* magazine, 17 June 2003.)

Compare the information in this advertisement to an independent assessment of donepezil and of medicines for Alzheimer's disease. How does the message in the advertisement compare with this evaluation of the clinical trial evidence on its effects?

Go back to your list of positive and negative aspects of the advertising message:

- Having seen an evaluation of the scientific evidence on the medicine's effects, do you have any additional comments?
- How accurately does this advertisement convey that evidence?
- What is present?
- What is missing?

3. Analysis of advertising messages about a health condition and pharmaceutical treatment

- What is its main message about depression? (see Figure 8.)
- Is self-diagnosis encouraged? Explain the basis for your answer.
- Does the advertisement allow the reader to distinguish from distress in reaction to life problems and a diagnosis of depression?
- What is implied about the rate of treatment success?
- Why is the reader told he or she should try this rather than another treatment?
- Does it suggest any alternatives to pharmacotherapy?

Figure 8. An advertisement for Zoloft (sertraline) for depression

Zoloft
has helped millions
with depression.
This is Denise's story.

Denise P. PhD © THOMSON BI

Story: "I Found an Great Zoloft"

I FELT LIKE I WAS AN OCTAVE LOWER BEFORE ZOLOFT. I WAS DEPRESSED. I HAD TO DO SOMETHING.

...FOUND OUT THAT ZOLOFT WAS THE NUMBER ONE PRESCRIBED BRAND FOR DEPRESSION AND ANXIETY.

SO I ASKED MY DOCTOR ABOUT ZOLOFT. HE TOLD ME IT'S HELPED MILLIONS LIKE ME.

BEFORE LONG, I REALIZED THAT ZOLOFT WAS HELPING ME AT WORK AND AT HOME.

LIFE ISN'T A DRESS REHEARSAL. YOU GET ONE PERFORMANCE. WHY DO IT WITH DEPRESSION?

Denise took comfort in the fact that ZOLOFT has helped many people for so many years. ZOLOFT is safe and effective. It has treated more people with more types of depression and anxiety than any brand of its kind. So she asked her doctor about ZOLOFT. ZOLOFT. #1 for millions of reasons.

zoloft
(sertraline HCl)
www.zoloft.com

(Source: <http://www.futureofthebook.org/itinplace/wp-content/archives/zoloft.jpg>)

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3. Practical regulatory issues

The US FDA's warning and 'untitled' letters on promotional violations are accessible from the following page: <http://www.fda.gov/cder/warn/>, and are organised by year.

Two letters on television adverts found to violate regulations are listed below, as examples of the types of practical issues faced in DTCA regulation:

- a. Letter on Viagra (sildenafil) advert: Television advert: <http://www.fda.gov/cder/warn/2004/12726ad.pdf>
- b. Letter on Seasonale (levonorgestrel/ethinylestradiol) <http://www.fda.gov/cder/warn/2004/12748.pdf>

Chapter 6

Learning how not to do the pharmaceutical industry tango: Raising student awareness of ethical conflicts of interest

Arthur Schafer and Nancy Olivieri

In order to respond in a thoughtful manner to an ethically challenging situation, one must first perceive that the situation has a troubling dimension. This point seems almost too obvious to be worth making. Unfortunately, however, in the real world of doctors, pharmacists and pharmaceutical company representatives, many ethically fraught situations go largely unrecognised as such, or have become accepted as normal. This problem – failure to recognise even the existence of an ethical red flag – arises for medical and pharmacy trainees long before they become qualified practitioners.

The purpose of this chapter is to raise a warning flag around the issue of pharmaceutical industry gifts to students and health professionals. Empirical data are provided which illuminate the function of the gift relationship between giver and recipient. Two related issues are also discussed: (a) the payment of fees to health professional ‘opinion leaders’ whose positive assessment of a product can help to stimulate prescribing and sales, and (b) the underlying question of conflict of interest between a professional’s obligation to his or her patients and relations with pharmaceutical companies.

Aims of this chapter

By the end of the session based on this chapter you should be able to:

- Identify key ethical challenges in the relationship between health professionals and the pharmaceutical industry;
- Define a conflict of interest situation and describe why such situations are especially troubling in medical practice.

The impact of gifts – large and small

Bellin and her colleagues (2004) found that medical students have extensive exposures to pharmaceutical industry marketing during their training and that these exposures increase dramatically when the students progress from the preclinical to the clinical setting. Approximately 72% of students in their clinical years recalled over 20 exposures compared to 33% of preclinical students.

What is meant by the term ‘exposures’? Mostly, we are talking about sponsored events, gifts, free meals and samples of medicines. In short, most medical (and some pharmacy) students benefit in a number of ways from industry generosity. Pizza, and the beer that helps to wash down the pizza at medical school or pharmacy parties, are often supplied by kindly pharmaceutical sales representatives. Gifts of expensive textbooks and pocket texts are not uncommon (Bellin et al., 2004). Overall, gifts to US health sciences students ranged in value from a nominal value, for example, for monogrammed pens, to a value of up to US\$800 for travel subsidies, with a median estimated value of US\$20 (Hodges, 1995). However, frequently even small gifts are highly prized by the students.

A recent report (Sierles et al., 2005) showed that US medical students receive a gift or attend a company-sponsored activity surprisingly often: on average once a week. When asked whether such gifts would influence their prescribing patterns, approximately 70% replied “no”. In a similar vein, Hodges (1995) found, paradoxically, that the more gifts that students, interns and residents in Toronto psychiatric hospitals accepted, the less they felt that their judgement would be influenced. (For more on the use of gifts in pharmaceutical promotion, see Chapter 2.)

Existing evidence strongly indicates that exposure to pharmaceutical industry marketing has a significant influence on physicians’ practice and prescribing patterns (Lexchin, 1993). Bluntly put, gifts *do* influence behaviours, despite the widespread belief by health care trainees and professionals that they are personally invulnerable to such blandishments (Madhavan et al., 1997; Banks et al., 1992).

Although there is a degree of variability because some countries and some institutions restrict the gifts that companies may offer, the practice of providing gifts to health professionals is widespread. Most important to keep in mind is that the shower of coffee mugs and free lunches, pen lights, knapsacks, stethoscopes and pocket textbooks teaches young doctors and pharmacists that accepting gifts from the pharmaceutical industry is a normal part of professional life. Medical or pharmacy school is where gift-giving begins, but scarcely where it ends. The ‘gift economy’, whether in the setting of the hospital or the doctor’s office, on the golf course or in a restaurant, wins the sales representative ‘face time’ with health professionals and establishes a bond between the representative and the professional.

Doctors often cite free samples as the main reason they see sales representatives. This is a special type of gift as it allows the physicians in turn to give to their patients. As is discussed in Chapter 4, free samples are a form of market seeding, generally for new, expensive medicines that are usually no better than less costly older treatments. Thus, free samples lead inexorably to higher costs for patients and insurers in the long term.

The culture of gift-giving by the companies and gift-taking by physicians and pharmacists, hospitals and universities is viewed by most health-care professionals as benign and perfectly legitimate. As one noted physician and journal editor has aptly commented: "*I don't criticise the marketers for behaving like marketers. What they do is make people feel entitled - so it's not a bribe; it's their due. And you end up with a situation where doctors won't walk fifty yards at a big medical meeting without being transported in a drug company bus.*" (Rennie, 2003).

The not-so-free lunch

Health sciences students are often asked or required by their teachers or clinical preceptors to attend sponsored lunches or rounds. Pharmaceutical companies spend vast sums of money on gifts for practising physicians, but they also spend millions more sponsoring and providing free meals for 'educational events' aimed at trainee physicians and pharmacists (Bellin et al., 2004).

Working lunches on the ward and quite often lavish restaurant dinners are regularly paid for by the sales representative. Senior physicians with a national or international reputation benefit financially in even more substantial ways: for example, first class winter travel to the Caribbean or to some luxurious ski resort (Angell, 2004). Consultancy and speaking fees, together with paid positions on advisory boards, often add significantly to the doctor's income (IMS Health, 2005). Industry codes vary from country to country and what is prohibited in one may be permitted in another. In practice, when industry codes prohibit certain kinds of gifts, for example, expensive meals, the prohibition is undermined by such expedients as 'unrestricted grants' from the companies to medical education providers, who then use the money to sponsor lavish meals (Angell, 2004).

The free food has two main functions at these 'educational' events: to attract an audience, of course, but also to create an atmosphere of goodwill, which the sponsoring company expects will extend to the sponsor and the promoted medicine – if only subconsciously.

"I can't be bought for"...

In justifying (or excusing) their acceptance of pharmaceutical company gifts and meals, students often argue that it is permissible to accept these benefits because, as medical or pharmacy

students, they are burdened with sizeable debt but blessed with only minimal income. Since a medical or pharmacy education is expensive and stressful, the availability of such benefits seems to most students to be a good thing. Who but a killjoy could object?

“I can’t be bought for” ... (you fill in the blank: free pizza, a laptop computer, a consultancy fee, free tickets to a concert or sporting event, travel to an exotic destination). Employing these or similar words, physicians, residents, medical students, pharmacists, pharmacy students, pharmaceutical researchers, all indignantly affirm that there is no harm done – and certainly no harm to their own integrity – by the acceptance of pharmaceutical company gifts and sponsorships.

Only a deeply corrupt doctor or pharmacist would consciously and deliberately prescribe a medicine to patients when that medicine is known to be sub-optimal. Virtually all health-care professionals (and trainee professionals) feel confident that they are not corrupt in this way. Unfortunately, however, there is a good deal of evidence provided by social science research that demonstrates that *“even when individuals try to be objective, their judgements are subject to an unconscious and unintentional self-serving bias.”* (Dana and Lowenstein, 2003).

Companies spend a significant part of their marketing budgets on lunches, gifts and recreation for health professionals because they know that such spending brings in extra sales. As Rawlins (1984) pointed out more than two decades ago:

“...few doctors accept that they themselves have been corrupted. Most doctors believe that they are quite untouched by the seductive ways of industry marketing men [and women]; that they are uninfluenced by the promotional propaganda they receive; that they can enjoy a company’s ‘generosity’ in the form of gifts and hospitality without prescribing its products. The degree to which the profession, mainly composed of honourable and decent people, can practice such self-deceit is quite extraordinary. No drug company gives away its shareholders’ money in an act of disinterested generosity.”

Independent education or ‘peer-to-peer’ marketing?

Department chairs and star researchers are sometimes referred to by the pharmaceutical industry as key opinion leaders and are courted assiduously. In an article in *Pharmaceutical Executive*, Dorfman and Maynor (2006) describe why this marketing technique is used:

“Doctors don’t respond well to the traditional sales and marketing push. But, they do respond well to each other. In fact, there are doctors who wield tremendous power of persuasion over their peers. These doctors have earned the respect and attention of other prescribers and have been recognized for their expertise and knowledge of innovative, emerging therapies. But more

important, they are likely to try, adopt, and advocate for new products....From a marketing standpoint, these doctors represent the top tier of the physician hierarchy—the ultimate key opinion leaders.”

Internal company documents that surfaced in a US court case, concerning illegal promotion of gabapentin (Neurontin) for unapproved uses, confirm the importance of physician-to-physician marketing as a promotional strategy. Parke-Davis identified 40 potential ‘thought leaders’ in one US region, more than half of whom were current or future university departmental chairs, vice-chairs or directors of academic clinical programmes. Thirty-five of these 40 ‘thought leaders’ participated in Parke-Davis-sponsored activities, and 14 of them received honoraria, research grants or educational grants from the company (US\$10,000 to \$158,250 per ‘thought leader’) (Steinman et al., 2006). This is by no means the only company to pay large fees to ‘thought leaders’. The US state of Minnesota, e.g., which requires pharmaceutical companies to disclose payments to individual physicians, reported payments up to US\$76,350 for advisory board membership and US\$334,180 for consulting activities (Ross et al., 2007).

It can be very flattering as well as lucrative to be recognised as a local, national or international expert or ‘rising star’ in one’s field, and to be invited onto advisory boards and speakers’ bureaus. Clinicians justify this work as reflecting their expertise and their own opinions. Nevertheless, they are part of a marketing plan, the effectiveness of which depends in no small part on message delivery by a seemingly neutral clinical expert.

The companies also provide substantial amounts of money to subsidise continuing medical education (CME), (Lexchin, 1993) professional conferences and professional journals (Smith, 2003). As Relman (2003) notes, since many jurisdictions require that doctors undertake postgraduate education as a condition of keeping their license, regular attendance at CME meetings is an integral part of doctors’ lives. Over 60% of the cost of CME in the US is paid for by the pharmaceutical and medical device industries. In 2006, these industries spent US\$1.45 billion on accredited CME (Hébert, 2008). Would the general public be shocked to learn, one wonders, that continuing education of doctors is not paid for by the doctors themselves but, instead, by pharmaceutical companies or, often, by for-profit firms hired by pharmaceutical companies?

Can industry funding predict research results?

Health professionals also receive funding from pharmaceutical companies to carry out research. These relationships can raise a number of ethical concerns, especially if the sponsor is involved in the design and analysis of clinical trials and reporting of results.

One of the most influential studies of how researchers' objectivity might be compromised by pharmaceutical industry sponsorship appeared in the *New England Journal of Medicine* in January 1998. Stelfox and colleagues (1998) set out to examine published articles on the safety of calcium channel antagonists. Their goal was to answer the question: to what extent is there an association between industry support of medical research and the research findings of investigators? Stelfox divided authors according to their relationships with pharmaceutical companies and then, independently, classified their research findings on the medicine's safety as "supportive", "critical" or "neutral". The conclusion reached by Stelfox et al. must be of serious concern to every supporter of industry university partnerships: "*Our results demonstrate a strong association between authors' published positions on the safety of calcium channel antagonists and their financial relationships with pharmaceutical manufacturers.*"

It may be worth spelling out just how influential pharmaceutical company sponsorship appears to have been: "*Ninety-six per cent of supportive authors had financial relationships with the manufacturers of calcium channel antagonists, as compared with 60 per cent of the neutral authors and 37 per cent of the critical authors.*"

Box 1: The 'Olivieri case': a cautionary tale about sponsored research

"The issue is not about whether their inconvenient findings were correct. It is about individual conscience in conflict with corporate greed. It is about the elementary right of doctors to express unbought medical opinions and their duty to acquaint patients with the risk they believe to be inherent in the treatments they prescribe."

– John Le Carré, *The Constant Gardener*, 2001

The Olivieri case raises questions about the influence of pharmaceutical industry sponsors on investigators' ethical obligations to disclose risks to clinical trial participants, and researchers' ability to publish findings that are counter to the financial interests of sponsors. It has implications not only for academic freedom, but also the integrity of the scientific literature on the safety and effectiveness of medicines.

In 1995, Nancy Olivieri was the lead researcher in a study of a new medicine for thalassemia, a hereditary form of anaemia. Deferiprone was the first oral treatment for thalassemia, an important potential advance over subcutaneous infusions. The trial was carried out at a University of Toronto teaching hospital where Dr Olivieri was a clinical faculty member. The sponsor was a Canadian pharmaceutical company, Apotex.

During the trial, Dr Olivieri and a colleague became concerned about risks from iron accumulation in the livers of some patients on deferiprone. They wanted to carry out more monitoring and to warn patients of this potential risk. Apotex officials disagreed with their

concerns, threatened legal action, stopped the trial and removed Dr Olivieri from a second deferiprone safety trial in Europe.

In the bitter controversy that followed, neither the university nor the hospital supported Dr Olivieri against Apotex. She was initially removed from her clinical faculty position, but was later reinstated after an independent inquiry found no evidence of wrongdoing. In 2002, she and her colleagues reached a mediated settlement with the hospital and university, providing them with substantial redress for grievances over unfair treatment. A settlement against Apotex remains in dispute, more than ten years later.

For an in-depth discussion of this and a related case, see:

Schafer A (2004). Biomedical conflicts of interest: a defence of the sequestration thesis—learning from the cases of Nancy Olivieri and David Healy. *Journal of Medical Ethics*;30:8–24. doi: 10.1136/jme.2003.005702.

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Baylis J (2004). The Olivieri debacle: where were the heroes of bioethics? *Journal of Medical Ethics* 2004; 30: 40-49.

College of Physicians and Surgeons of Ontario. CPSO Complaints Committee Decision and Reasons (2001). Complaint by Dr. L. Becker against Dr. N. Olivieri. Issued December 19, p. 17 (<http://www.dal.ca/committeefinquiry>, accessed 17 April 2009).

Frumkin H (1998). Right, wrong, and occupational health: lessons learned. *International Journal of Occupational and Environmental Health*;4:33-35.

Healy D Review: Shuchman M (2005). The drug trial. Nancy Olivieri and the science scandal that rocked the Hospital for Sick Children, Random House, Canada in *Monash Bioethics Review* Vol. 24 No. 4.

Le Carré J (2001) *The Constant Gardener*, Penguin/Viking, p506.

Nathan D, Weatherall D (2002). Academic freedom in clinical research. *New England Journal of Medicine*;347:1368-70.

Olivieri NF, Brittenham GM, McLaren CE et al. (1998). Long-term safety and effectiveness of iron-chelation therapy with deferiprone for thalassemia major. *New England Journal of Medicine*;339:417-23.

Schafer A (2004). Biomedical conflicts of interest: a defence of the sequestration thesis—learning from the cases of Nancy Olivieri and David Healy. *Journal of Medical Ethics*; 30:8-24.

Thompson J, Baird P, Downie J (2001). The Olivieri report: The complete text of the report of the independent inquiry commissioned by the Canadian Association of University Teachers. Toronto: Lorimer, (<http://www.dal.ca/committeefinquiry>, accessed 17 April 2009).

Washburn J (2005). *University inc.: The corporate corruption of higher education*. New York: Basic Books.

It should be noted, however, that there is a *caveat* in the Stelfox study: they were unable to establish a timeline. Did the authors first have a financial relationship with the company and then write the positive article or did they initially write a positive article and then develop the financial relationship? Obviously neither is acceptable but from the point of view of research integrity, the first is probably worse than the second.

More recently, Bero and colleagues (2007) examined the influence of funding sources on study methods and outcomes for 192 studies comparing statins (cholesterol-lowering medicines) with other statins or different therapies. Studies funded by the manufacturer of the test medicine were 20 times as likely to report results favourable to the test medicine than studies funded by the manufacturer of the comparator (95% confidence interval 4-93). Studies with adequate blinding were also less likely to report favourable results than those that were not blinded or in which blinding was inadequate.

Lexchin and colleagues (2003) carried out a meta-analysis of studies that examined the relationship between industry funding and research results. Studies funded by the industry were four times as likely as non-industry funded research to report outcomes favourable to the industry. This bias reflects a number of factors. Sismondo (2008) points out that one of these is the relationship between researchers and the sponsor: *“Sponsorship, then, creates subtle influences through the building of relationships that lead researchers to see the pharmaceutical companies with which they interact, and their products, in a more favourable light than they would otherwise.”*

A related problem is that of ‘ghost’ and ‘guest’ authorship on clinical trial reports. A ‘ghost’ author is someone who has written the report but is not listed as an author; this is often a company employee or a contract medical writer. A ‘guest’ author is listed but has not contributed; usually an academic clinician whose name may be used to lend weight and credibility to sponsored trials. Both relationships run counter to principles of accountability and responsibility of authors of published trial reports.

Several US court cases have revealed internal company documents listing trial reports with authors ‘to be determined’ (Ross et al., 2007). A contract medical writing company, Current Medical Directions, was responsible for management of 85 papers on Pfizer’s antidepressant, sertraline (Zoloft), 55 of which resulted in published reports (Healy and Cattell, 2003). Unsurprisingly, given the funding source, all of the included clinical trials and economic analyses were favourable to Pfizer.

The same bias, sometimes conscious but most often unconscious, that afflicts investigators whose research is funded by the pharmaceutical industry also afflicts doctors, pharmacists, trainee doctors and trainee pharmacists who accept gifts from industry. Unconscious bias is pervasive and has a seductive tendency to undermine a doctor’s commitment to put the patient’s interests ahead of all others. For this reason, respect for professional ethics places an obligation on all health-care practitioners not to put themselves in conflict of interest situations.

Conflicts of interest

Health-care professionals are understandably concerned with advancing their own careers. Closely related to this, they are also concerned to promote the well-being of their families, which hinges to some considerable extent on their income. None of these motivations is illegitimate. But the essence of being a health-care professional is that you commit yourself to put the life and health of your patients first, ahead of every other consideration.

When patients consult a health-care professional, they should be able to trust the independence and objectivity of the professional's judgement. The doctor-patient relationship depends heavily upon patient trust in the doctor's integrity and altruism (Wynia et al., 1999). The same is true of the pharmacist-patient relationship.

When doctors or pharmacists, medical students or pharmacy students, accept gifts or benefits from the pharmaceutical industry, they are putting themselves in a conflict of interest situation:

“A person is in a conflict of interest situation if s/he is in a relationship with another in which she has a moral obligation to exercise her judgement in that other's service and, at the same time, s/he has an interest tending to interfere with the proper exercise of judgement in that relationship.” (Davis, 1982).

Gifts create a sense of obligation, often unconscious, to 'return the favour' (see Chapter 2 on influence techniques). Since the doctor may also hope to receive future gifts, perhaps fairly substantial ones, from this company or from other pharmaceutical companies, self-interest reinforces the principle of reciprocity, and both conspire to bias the doctor's judgement and to distort his/her clinical practice. If doctors understood this clearly, they would never permit themselves to compromise the integrity of their judgement. If patients understood this clearly, they would be much less tolerant of the practice whereby their physician or their pharmacist was beholden to the pharmaceutical industry.

Box 2 lists four key principles of bioethics that underlie health professional-patient relationships. A tension exists between adherence to these ethical principles and financial links between health professionals and the pharmaceutical industry. Similar tensions exist in the link between the industry, medical and educational institutions and research.

Codes of conduct

Restrictions on gifts are generally covered under industry self-regulatory codes (PhRMA, 2002) (see Chapter 7). However, these codes leave an enormous loophole in the form of an exemption for so-called educational or research activities. Additionally, they often allow small gifts or gifts that are related to patient care. For the most part, it is the companies themselves which decide what counts as education or research.

As described, most health-care professionals sincerely believe they are unaffected by gifts. But the companies know better. When they invest so many billions of dollars buying gifts and other benefits for doctors and pharmacists their goal is clearly to increase sales of their high-profit-margin products. And this strategy works. A number of published studies have demonstrated that free gifts induce physician reliance on pharmaceutical sales representatives as a source of ‘objective’ information (Brennan et al., 2006). When doctors rely on pharmaceutical company representatives for their information about new medicines they are much more likely to prescribe new medicines for their patients (Wazana, 2000). The prescription of expensive new patented medicines, when there are equally good or better generic medicines available, not only adds dramatically to the financial burden on patients (and the health-care system generally) but often results in sub-optimal health results.

Box 2: Key principles of bioethics

1. Respect for autonomy

Respect for autonomy requires that patients should be encouraged and assisted, whenever possible, to make informed and voluntary decisions about their health care. It is the basis for *informed consent* in interactions between health professionals and patients.

2. Nonmaleficence

This is the principle *to do no harm*. Doctors should strive not to cause needless harm or injury to the patient, either through the treatment that is provided or by not providing needed care.

3. Beneficence

Health-care providers have a duty of care to benefit patients to the maximum extent possible in the circumstances. This goal applies both to individual patients, and to the good of society as a whole, for example, in efforts to prevent antibiotic resistance.

4. Justice

Justice in health care is usually defined as *distributive fairness*: to provide to each according to his or her needs, regardless of ability to pay. It supports the sharing of resources to provide health care for all.

(Adapted from: <http://depts.washington.edu/bioethx/tools/princpl.html>)

Vioxx: did conflicts of interest affect the benefit/harm appraisal?

Vioxx (rofecoxib) became a blockbuster product after a clinical study, known as the VIGOR Trial, was published in the *New England Journal of Medicine* (Bombardier et al., 2000). This trial demonstrated that patients who took Vioxx for arthritic pain suffered somewhat fewer stomach bleeds than patients who were given the generic medicine naproxen. Armed with this study, Merck's sales force fanned out across North America and Europe to 'educate' doctors about the advantages of this new 'miracle' anti-inflammatory medicine. Vioxx was heavily promoted to doctors and to consumers (through direct-to-consumer advertising, permitted in the US, but not in most other countries; see Chapter 5). This medicine, one of a class of medicines known as COX-2 inhibitors, quickly became a financial blockbuster for Merck, with annual sales in the region of US\$2.5 billion.

However, the VIGOR Trial - on the basis of which Vioxx flew into the commercial stratosphere - also revealed that the patients who received Vioxx suffered five times as many heart attacks and strokes as those who were randomised to naproxen. One would think that this life-threatening adverse side effect would have inhibited doctors from prescribing Vioxx to any of their patients or would have led doctors to prescribe Vioxx only to the small group of patients who were at extremely high risk of stomach bleeds and extremely low risk of heart attack and stroke. Sadly, no such inhibition occurred. Doctors wrote millions of prescriptions for Vioxx. The sales juggernaut did not grind to a halt until Merck removed Vioxx from the market. This happened only after a trial meant to test Vioxx as a preventative medication for bowel cancer confirmed, instead, that Vioxx caused a significant level of heart disease.

We now know that - notwithstanding the early evidence of elevated risk of serious adverse consequences - Merck instructed its sales reps to mislead doctors about the safety of Vioxx. They code-named their 'educational' campaigns 'Offense' and 'XXceleration' (FxClub.com, 2006). The company's representatives distributed pamphlets that ignored the cardiovascular results from the *New England Journal of Medicine* VIGOR Trial (Curfman et al., 2005, 2006) and instead presented a range of scientifically inferior studies (with inadequate subject numbers and/or inferior design) which purported to show that Vioxx users were at **lower** risk for heart attacks rather than, as was the really the case, at much **higher** risk. Had doctors been properly informed about the evidence, they would have limited their prescribing of Vioxx. The VIGOR study was itself later exposed as underreporting the data on the cardiovascular risks associated with Vioxx (Curfman et al., 2005).

This evidence of deliberate pharmaceutical company manipulation of doctors - under the banner of 'education' - only emerged (in documents submitted to the US Congress) after Vioxx was withdrawn from the market (Brownlee and Lenzer, 2005). On 30 September 2004, after more than 80 million patients had taken this medicine and annual sales had topped US\$2.5 billion, the company withdrew the medicine because of an excess risk of myocardial infarctions and

strokes (Topol, 2004). Tragically, by the time the product was withdrawn, it is estimated that tens of thousands of patients had already died unnecessarily from heart attacks and strokes induced by Vioxx (Graham et al., 2005).

In this connection, it may be worth quoting a typical passage from the compelling testimony offered by Dr David Graham of the US Food and Drug Administration (FDA) at a US Congressional hearing:

“Let me begin by describing what we found in our study, what others have found, and what this means for the American people. Prior to approval of Vioxx, a study was performed by Merck named 090. This study found nearly a 7-fold increase in heart attack risk with low dose Vioxx. The labelling at approval said nothing about heart attack risks. In November 2000, another Merck clinical trial named VIGOR found a 5-fold increase in heart attack risk with high-dose Vioxx. The company said the drug was safe and that the comparison drug naproxen, was protective. In 2002, a large epidemiologic study reported a 2-fold increase in heart attack risk with high-dose Vioxx and another study reported that naproxen did not affect heart attack risk. About 18 months after the VIGOR results were published, FDA made a labelling change about heart attack risk with high-dose Vioxx, but did not place this in the “Warnings” section. Also, it did not ban the high-dose formulation and its use. I believe such a ban should have been implemented.” (Graham, 2004).

Conclusion

The experience with Vioxx raises questions about pharmaceutical industry marketing practices, but also about grossly inadequate performance by the regulatory authority. These questions have been extensively discussed in both the medical and the general media. Millions of patients received this medicine before it was withdrawn from the market despite the predominance of evidence indicating that the risk-benefit ratio of this medicine was significantly unfavourable. Although the evidence that harms outweighed benefits was present from the outset in the medical literature, it was widely ignored by physicians, with the honourable exception of a hardy minority of independent clinicians, who issued appropriate warnings long before the product was finally withdrawn in 2004 (Wright, 2002).

Less has been said about the role of health professionals. Did gifts, free samples, speakers’ honoraria and a host of other financial relationships between health professionals and the manufacturer play a part in stimulating prescriptions of this medicine? No one would suggest that physicians knowingly prescribed an unnecessarily harmful product to patients because of a free dinner or round of golf. However, as this chapter points out, acceptance of pharmaceutical industry gifts can subvert professional practice in a variety of ways, many unconscious. Ultimately,

it is the patient who suffers. As Dana and Loewenstein (2003) point out, “*Pharmaceutical companies know that gifts influence physicians, which is why many restrict their own employees from accepting even small gifts.*” Moreover, when patients discover the full extent of the gift relationship which exists between physicians and the pharmaceutical industry, a second major casualty is likely to be the bond of trust between doctor and patient.

In short, doctors and other health-care providers should recognise the applicability of the old saying, “There is no such thing as a free lunch”. Accepting gifts or other benefits from pharmaceutical companies and their representatives carries a heavy ethical price, namely, the sacrifice of one’s professional integrity. Ethical health-professionals-in-training should say “no” to all pharmaceutical company gifts and benefits and should continue to say “no” when they become fully qualified health professionals. At the same time, one should recognise that saying “no” when one’s fellow students are saying “yes” carries risks. One not only feels badly when one loses the material rewards that come to those who say “yes”, but one risks being seen as a threat by one’s colleagues. Those who publicly reject illegitimate benefits risk being seen as killjoys. Critics of pharmaceutical company marketing may become estranged from the very people with whom they need to form bonds of mutual support and community. Thus, when one is considering taking a stand on principle one ought also to consider the possibilities of collective action. Self-education, followed by discussion and dialogue with colleagues, has the possibility of leading to a group response. At the end of the day, one has to act according to one’s conscience; but if one is able to act collectively with like-minded others, then the impact of one’s action is likely to be exponentially greater.

Student exercises

1. Debate on ethical conflicts among health professionals

Divide students into debating teams of 4 to 6 people. The first debate will be on the following question:

Team 1: *There is no ethical conflict in physicians and pharmacists accepting money from pharmaceutical companies.*

Team 2: *It is ethically unacceptable for physicians and pharmacists to accept money from pharmaceutical companies.*

Students should try to debate each side of this question regardless of their initial opinions. They can meet as a team to discuss how they will approach the debate and divide the content they will cover among team members. For example, one person might want to deal with small gifts or free lunches, another with being a member of a company advisory board, etc., yet another with sponsored research or institutional support.

Debate of this topic should include citation of some highly publicised cases of the interactions of industry with research scientists who have raised issues of uncertainty.

Background reading:

Schafer A (2004). Biomedical conflicts of interest: a defence of the sequestration thesis-learning from the cases of Nancy Olivieri and David Healy. *Journal of Medical Ethics*, 30(1):8-24.

Rennie D (1997). Thyroid storm. *Journal of the American Medical Association*, 277(15):1238-43.

Moynihan R (2003). Who pays for the pizza? Redefining the relationship between doctors and drug companies. Part 2: Disentanglement. *British Medical Journal*, 326:1189-1192.

Topol EJ (2004). Failing the public health-rofecoxib, Merck, and the FDA. *New England Journal of Medicine*, 351(17):1707-9.

Katz D, Caplan A, Merz J (2003). All gifts large and small: toward an understanding of the ethics of pharmaceutical industry gift-giving. *American Journal of Bioethics*, 3(3):39-46.

Dana J, Loewenstein G (2003). A social science perspective on gifts to physicians from industry. *Journal of the American Medical Association*, 290(2):252-5.

2. Questions on the Olivieri case

“My ethical obligation as a clinical researcher was to inform patients and the trial ethics committee of any perceived risks. As the physician responsible for the care of many of these patients, I also had duty to ‘do no harm’. When I indicated my intention to inform patients and their parents, regulatory agencies and the scientific community, of my concerns, the company disputed both the risk associated with the drug, and the need to inform patients.”

– Nancy Olivieri, personal communication

- If a clinician suspects that a medicine is leading to harm to patients during a clinical trial, must they inform the patients even if they are not sure?
- What steps can regulatory agencies, academic institutions and journals take to ensure that all of the results of a sponsored clinical trial – both beneficial and harmful – are reported in published articles?
- If industry sponsors stop studies when suspected harmful effects begin to emerge, how is the scientific literature as a whole affected? What does this mean for the information on benefits and harmful effects of medicines that physicians and pharmacists are able to access?

3. This situation happened to a leading researcher in her field, in a wealthy industrialised country. How do you think it might have differed if she was just starting her career? What if she were based in a developing country?

4. In press coverage of ‘the Olivieri case’, the public hospital and university involved came under greater criticism than Apotex. Do you agree with this? Why or why not?

5. Do you know of a similar case involving researchers from your own country or region?

6. Discussing conflict of interest policies

In this exercise, students should break into teams that will interview medical or pharmacy faculty officials about institutional conflict of interest policies.

They can either use the PharmFree scorecard developed by the American Medical Student Asso-

ciation (AMSA) or use this scorecard as a model to develop their own, more locally appropriate scorecard. For information on the AMSA rating system, see: <http://amsascorecard.org/methodology>

They should report on the results of these interviews, their faculty's letter grade and any recommendations they have for a change in policies.

Background reading:

Brennan, TA, Rothman DJ, Blank L et al. (2006). Health industry practices that create conflicts of interest. A policy proposal for academic medical centers. *Journal of the American Medical Association*, 295:429-433.

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Chapter 7

Regulation of pharmaceutical promotion

Why does regulation matter?

Lilia Ziganshina and Joel Lexchin

In the 1940s, the synthetic oestrogen, diethylstilbestrol (DES) was advertised around the world to “prevent miscarriages” and in healthy pregnancies “to make babies stronger”. The medicine was ineffective and women who took it ended up with a higher risk of breast cancer and their daughters, exposed *in utero*, developed reproductive tract abnormalities and, in some cases, a rare form of vaginal cancer (Giusti et al., 1995). In the 1970s, advertisements in Canadian medical journals told doctors that if children were “picky eaters” or “troublemakers”, they needed Atarax, a sedating medication (Canadian Family Physician, 1973). In 1990, the Medical Lobby for Appropriate Marketing (MaLAM, now renamed Healthy Skepticism) documented E. Merck’s promotion of Ilvico S to prevent colds and influenza in children under five. Ilvico S is an irrational combination of an antihistamine, a decongestant, vitamin C, phenazone and sodium salicylate (MaLAM, 1990). In the 1990s, Parke-Davis’ sales representatives illegally promoted gabapentin (Neurontin) for a wide range of unapproved conditions (Harris, 2004). At the time, gabapentin was only approved in the US as an additional epilepsy treatment for patients whose primary treatment failed to adequately control the disease.

All of these situations occurred because of inadequate regulation of pharmaceutical promotion. Health professionals are exposed to many types of promotion in their daily work. To varying degrees, regulations exist to govern these activities in order to ensure proper prescribing and to protect public health. This chapter uses specific examples of the intersection between pharmaceutical promotion and patient care to examine how well the current regulatory environment is meeting these goals.

Aims of this chapter

This chapter describes existing regulations and ethical codes for pharmaceutical promotion and provides an overview of the research evidence on the effectiveness of regulation. By the end of the session based on this chapter you should be able to:

- Describe how regulation of pharmaceutical promotion works in practice within two key regulatory models: direct government regulation and industry self-regulation;
- Compare national regulations with the World Health Organization's (WHO) *Ethical Criteria for Medicinal Drug Promotion*;
- Critically evaluate various codes or guidelines and identify strengths and weaknesses;
- Describe monitoring and enforcement systems in your country;
- Analyse specific promotional activity you encounter in terms of whether or not it breaches national laws, the WHO Ethical Criteria or professional codes.

Why regulate pharmaceutical promotion?

The pharmaceutical industry provides a valuable and legitimate contribution to society. At the same time, the pharmaceutical industry is a business and its profits are heavily dependent on marketing. The greater the volume of medicines sold, the greater the return on investments. Promotion is a key factor driving sales volumes. As the examples in the introduction show, when product sales are given priority over public health, promotion can lead to over-prescribing as well as poor quality prescribing and medicine use. This, in turn, leads to an increased risk of adverse effects and higher health-care costs. Prescribers often find themselves trapped between patients' needs and health-care priorities on the one hand and promotional influences on the other. Dual allegiances and conflicts of interest can cloud judgement and cause distortions in both the delivery of health care and the conduct of research in medicine.

Physicians, pharmacists, researchers, educators, managers and administrators need practical guidance on how to understand and manage their interactions with industry. At the same time, the pharmaceutical industry needs guidance about how to implement its marketing practices so that health outcomes are enhanced. The key ethical basis for any guidance is the understanding that the values of clinical care, of the welfare of society and of science should prevail over commercial imperatives and monetary concerns (World Medical Association, 2004).

A legal framework for regulation

Provisions in law governing pharmaceutical promotion usually include two key criteria concerning the information provided in advertising:

- It must be consistent with approved product information; and
- It must not be deceptive or inaccurate.

When a pharmaceutical product is approved for marketing, it is accompanied by approved product information. This specifies the use or uses for which the medicine has been approved (indication), dosage and administration, precautions and warnings and information on contra-indications, adverse effects and interactions with other medicines.

For manufacturers' advertising to be consistent with approved product information, it must stick to approved indications and conditions of use. For example, if a medicine has only been approved for epilepsy, a manufacturer may not advertise it for bipolar disorder or depression. Physicians, on the other hand, can legally prescribe a medicine for whatever use they wish, within restrictions that may be imposed by employers and institutions. Prescribing for an unapproved use is called 'off-label prescribing'. This is often legitimate. For example, for many illnesses, there are no medicines approved for use in children. A manufacturer may apply for approval for an additional indication for its medicine. However, until that use is approved, the company cannot legally promote the medicine for that indication. A medicine may be approved for different uses in several countries, which also leads to variations in the promotional claims that can be made legally in different countries.

In practice, when regulators decide whether advertising is deceptive or accurate, they often base the decision primarily on whether it is consistent with approved product information. Sometimes key public health concerns remain unaddressed. For example, advertising of newer, broad-spectrum antibiotics for everyday problems may lead to unnecessary prescribing and contribute to the unnecessary development of antibiotic resistance. These advertisements may be technically consistent with product labelling but be highly inadequate from a public health perspective.

Beyond prohibition of 'off-label' and deceptive advertising, national laws may also prohibit specific activities such as direct-to-consumer advertising (DTCA) of prescription medicines. Promotional activities such as gifts to physicians and pharmacists in exchange for prescriptions or attaining specific pharmacy sales volumes may be covered under other laws that are not specific to pharmaceutical marketing, such as anti-kickback or anti-corruption legislation.

Regulatory standards can also go beyond the presence or absence of information. For example in the US, a 'fair balance' is required of benefit and risk information. In practice, this means that information on the harmful effects of a medicine must be present in every part of the advertisement. In countries without this provision, the advertising copy does not always contain information on a medicine's risks.

Key differences in regulation

One of the differences in regulation of pharmaceutical promotion between countries results from their different capacities to regulate medicines. In 2004, a survey of national governments by the WHO found that fewer than one-sixth of countries had a well-developed pharmaceutical regulation system and one-third reported that they had little to no regulatory capacity (World Health Organization, 2004). Slightly less than half of the countries (89) reported that they regulated pharmaceutical promotion in some way. However, the amount of staff time or effort devoted to this work can differ enormously.

Self-regulation versus government regulation

In many countries, most active regulation is carried out through voluntary codes and guidelines. Although governments in industrialised countries have the legislated authority to control promotion most have ceded nearly all day-to-day control over some or all aspects of pharmaceutical promotion to voluntary national industry associations. This approach is called self-regulation.

Under self-regulation, regulatory activities are usually delegated to pharmaceutical or advertising industry associations or to organisations that include representation from a range of affected sectors ('multi-stakeholder groups'). These associations develop their own codes of standards and may pre-approve advertisements. They usually have formal procedures in place to respond to complaints about advertising or promotional activities. Many of these complaints come from competing companies. A key issue is whether breaching the voluntary industry code is equivalent to breaking the law. The problem here is that wording often differs and self-regulatory codes are not technically part of the law. Although governments can step in if a serious violation occurs, this rarely, if ever, happens.

An example of self-regulation and enforcement can be found in the UK. The British Medicines Act includes regulation of pharmaceutical promotion and the country's Health Minister is responsible for enforcement. However, this responsibility has been delegated to the Association of the British Pharmaceutical Industry (ABPI). The justification for this delegation is the industry's expertise and willingness and the Department of Health's ability to save money and staff time.

In a few countries, including France and the US, the government directly regulates pharmaceutical promotion. In the US, the Food and Drug Administration's Division of Drug Marketing, Advertising and Communication (FDA DDMAC) employs approximately 40 staff. By law, it cannot insist on pre-approval of advertising but companies must submit advertisements when they begin a campaign. In 2005, DDMAC staff examined some 53,000 promotional materials (Committee on the Assessment of the US Drug Safety System, Baciu, Stratton and Burke, 2006). If an advertisement is found to violate US law, DDMAC sends an 'Untitled Letter' to the company asking it to stop running the advertisement immediately and explaining why the advertisement was found to be illegal. More

serious offences merit a second stage ‘Warning Letter’, which may require costly campaigns to correct misinformation, such as running corrective advertising or a ‘Dear Health Professional’ letter sent to all doctors. DDMAC’s Untitled and Warning Letters are posted on the FDA’s website (see: <http://www.fda.gov/cder/warn/warn2006.htm>). However, in 2002, the US General Accounting Office (the research arm of the US Congress) reported that recently introduced internal administrative procedures had resulted in a much slower regulatory response. This was especially problematic for DTCA on television. “*Without more timely action ... DTC advertisements that DDMAC (the relevant FDA division) has identified as misleading can remain on the air too long.*” (United States General Accounting Office, 2002).

Five key steps in regulation

Whether regulation of pharmaceutical promotion is carried out directly by government or through industry self-regulation, there are five key components:

- National laws and regulations;
- The application of the law through codes and other standards;
- Monitoring of pharmaceutical promotion to ensure consistency with legal or other standards;
- Law enforcement with adequate sanctions to prevent violations; and
- Evaluation of regulatory effectiveness.

Even countries with adequate resources for regulatory oversight vary enormously in the extent to which they carry out any or all of these steps. There may be a law and a national code, but little enforcement and no sanctions for violations. In other cases, a functioning regulatory system is in place but there is no evaluation of regulatory effectiveness, for example, in ensuring that promotional claims support rational medicine use and public health goals. Ideally regular or ongoing evaluations should lead to changes in standards and the process of regulation, and these changes should, in turn, be evaluated. In practice, this rarely happens.

Regulatory oversight: far from perfect

The following section describes four hypothetical situations involving medicine promotion that you might encounter as a practicing physician or pharmacist. The first two involve forms of promotion that ‘fall between the cracks’ and are not covered by international industry codes or national regulation, although they involve common practices. The second two relate to the effectiveness of monitoring and enforcement. All could negatively affect patient care. In each case, existing approaches to regulation fail to provide adequate protection. Each example is presented with background information on the relevant regulatory code.

Situation 1: not covered in international industry standards

You work in a developing country without its own regulatory code. Under these circumstances, the only oversight of alleged unethical promotion is through the code developed by the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), if the company involved is an IFPMA member. One day at the hospital, you notice that a sales representative working for a major multinational company is accompanying doctors on their rounds and is instructing them on how to treat individual patients. You file a complaint with the IFPMA but your complaint is rejected because the latest version of the IFPMA code that became effective on 1 January 2007 does not have any clauses dealing with the activity of sales representatives (IFPMA, 2006).

Background: history and evolution of the IFPMA code

Initially pharmaceutical companies voluntarily introduced ethical regulations in response to an emerging and growing public concern about the harmful effects of unethical pharmaceutical promotion on public health. In 1981, countries ratified the International Code of Marketing of Breastmilk Substitutes. In the same year, a network of consumer health organisations, Health Action International (HAI), called for a code of marketing for pharmaceuticals, particularly raising concerns about examples of unethical marketing in developing countries. The IFPMA voluntary code was introduced shortly thereafter the same year. HAI described the IFPMA code as a bid to prevent WHO or national pharmaceutical regulatory agencies from taking stronger measures to control pharmaceutical promotion (Health Action International, 1987), and was highly critical of the code's content because of the weakness of standards and lack of active enforcement procedures. (Health Action International, 1988).

IFPMA member companies include all of the major multinationals as well as larger national companies and account for about 80% of world trade in pharmaceuticals by value. In countries without a national system of pharmaceutical regulation, companies that have endorsed the IFPMA Code recognise this as the primary standard governing pharmaceutical promotion. A substantial proportion of the IFPMA's 70 member companies and associations have their own national or regional voluntary codes. In this case, national or regional standards take precedence over the IFPMA Code, whether these standards are stronger or weaker.

Situation 2: covered in international standards that are not applied

While watching TV, you see an advertisement for a new medicine. Although the advertisement does not name the medicine, it does name the disease for which it is indicated and the advertisement uses a word play on the name of the product and shows the packaging. After watching this advertisement, you are sure that patients will be able to identify the new medicine and you are

concerned that they will ask you to prescribe it. In your view, the new medicine is no better than existing medicines and you feel that your time with patients would be better spent on matters other than discussing this new medicine.

You decide to file a formal complaint with your country's authority that regulates television advertising and base your complaint on a provision in the WHO Ethical Criteria that states "*They [advertisements to the public for prescription drugs] should not generally be permitted for prescription drugs or to promote drugs for certain serious conditions that can be treated only by qualified health practitioners.*" (World Health Organization, 1988). Your country's government had recently voiced its support for these criteria at a World Health Assembly. However, your complaint is not upheld. You are told that these guidelines only apply to low-income countries and that the advertisement is legal because it did not state the name of the medicine.

Background: WHO Ethical Criteria

In 1986, five years after the first IFPMA Code was developed, a second international standard was developed for pharmaceutical promotion: the WHO *Ethical Criteria for Medicinal Drug Promotion* (published in final form in 1988). The Ethical Criteria were developed following the WHO Conference of Experts on the Rational Use of Drugs, held in Nairobi in November 1985 and were part of WHO's revised drug strategy, which highlighted the need not only to make sure that medicines are available to those that need them, but that guidance is available to ensure appropriate use.

The WHO Ethical Criteria define promotion as "*all 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.*" They were developed as the result of a consensus involving health professionals, drug regulatory agencies, consumers and the industry, and so represent a broader viewpoint on appropriate marketing practices than either industry or professional codes.

The main objective of the Ethical Criteria is to support and encourage the improvement of health care through the rational use of medicines. The Ethical Criteria do not have legal standing, but are intended for use as general principles to be adapted by national governments developing legislation and as a standard for voluntary code development. They also provide an international ethical standard against which regulatory procedures and promotional activities may be compared.

Some key provisions of the WHO Ethical Criteria include the principle that promotion should not be disguised as an educational or scientific activity, that undue advantage should not be taken of people's concern for their health and that generally DTCA of prescription medicines should not be permitted.

Issues addressed by the WHO Ethical Criteria are:

- Advertising to physicians and other health professionals;
- Advertisements in all forms to the general public;
- Medical representatives;
- Free samples;
- Symposia and other scientific meetings;
- Post-marketing scientific studies, surveillance and dissemination of information;
- Packaging and labelling;
- Information for patients: package inserts, leaflets and booklets; and
- Promotion of exported drugs.

Lists are also provided of information that should be included in all advertising and promotion, including, for example, the medicine's brand and generic name, the name of the manufacturer and its approved indications. The aim is to ensure advertising provides a basic minimum of product information.

The WHO Ethical Criteria provide a broad set of principles that could be applied to many forms of promotion in both higher- and lower-income countries. Although successive World Health Assemblies, which include all UN Member States, have passed resolutions expressing support for the WHO Ethical Criteria, this international standard remains underused and in many parts of the world – especially industrialised countries – largely unknown.

Some aspects of pharmaceutical promotion have changed radically since 1988, when the WHO Ethical Criteria were developed. For example, the Internet was not commonly used at that time, and there was less use of clinical experts as 'key opinion leaders' as part of a marketing plan for a specific brand. However, the principles of the Ethical Criteria – for example, that promotion should not be disguised or that all advertisements must include basic information, such as the generic name and adverse effects – are as applicable in all media today, including the Internet, as they were in 1988.

Situation 3: no enforcement

Your local medical association is going to mount a continuing medical education (CME) course and has sought the assistance of a pharmaceutical company in preparing the material that will be distributed at the course. The company has offered to provide slides for the speakers and you are concerned that

these slides will bias the content of the course. You consult the code that your professional association has drawn up regarding interactions with pharmaceutical companies. There you find the statement that ‘technical assistance’ from industry in preparing educational materials is acceptable as long as the company “*has no input in the actual content of the material*” (American Medical Association, 1996). You complain to the professional association, which agrees with you but the event goes ahead as scheduled with industry involvement since the professional association has no way of enforcing its code.

Background: professional association voluntary codes

Many national health professional associations have developed ethical guidelines guiding their members’ interactions with the pharmaceutical industry and participation in promotional activities. Professional organisations’ codes tend to cover a wider range of promotional activities than industry codes but generally they are voluntary and lack any means of enforcement. The ability of professional associations to limit the industry’s financial influence over their members’ activities may also be hampered because professional associations are not free from industry influences. One example of this relationship was the heavy industry presence at the annual meetings of the American Psychiatric Association (APA) where companies paid the APA about US\$50,000 per session to control which scientists and papers were presented and to help shape the presentations (Vedantam, 2002). Unfortunately, so many academic physicians depend on the pharmaceutical industry for research funding that they tend to be reluctant to speak out about promotional abuses (Shapiro, 1997). Medical and pharmacy student associations also frequently take grants from pharmaceutical companies to support their activities.

Ambiguous standards can also create a barrier to effective implementation. For example, the American Medical Association’s Code of Medical Ethics provision that CME faculty may accept ‘technical assistance’ from industry in preparing educational materials as long as the company “*has no input in the actual content of the material*” makes strict implementation of the ‘no input’ rule almost impossible. Even speakers’ slides could be considered ‘technical assistance’. The extent of the problem surrounding industry influence over CME should not be underestimated; Arnold S Relman, former editor of the *New England Journal of Medicine* described existing CME as, “*a continuation of pharmaceutical marketing activities*”. (Relman, 2001).

Guidelines on gift-giving can be similarly ambiguous. In 1986, the Royal College of Physicians of London published the report *The relationship between physicians and the pharmaceutical industry* (Royal College of Physicians, 1986). The report tacitly approves the acceptance of trivial gifts, but emphasises that the costs of any gift, including teaching aids, are passed on to the public. One of the often quoted phrases is that “*doctors should avoid accepting any pecuniary or material inducement that might compromise, or be regarded by others as likely to compromise, the independent exercise of their professional judgement and practice.*” This recommendation is hard to implement in a meaningful way since individual doctors will have vastly different

perceptions of what “*might compromise, or be regarded by others as likely to compromise ... their professional judgement and practice.*” (Bennett and Collins, 2002).

Professional organisations’ ethical guidelines in principle represent a positive step forward in controlling pharmaceutical promotion and its harmful consequences on the public. However, without enforcement mechanisms or monitoring of their application, these voluntary codes have limited effects and may provide false reassurance. Additionally, if the professional associations are themselves financed by the pharmaceutical industry, and are unable to ensure independence of financed activities such as CME, they may be equally unable to oversee the independence of their membership. There is much scope for improvement, not only in the standards and types of activities covered by professional codes, but also in their application.

Situation 4: the price of doing business

A pharmaceutical company in your country is promoting a medicine with advertisements that make exaggerated claims about effectiveness and leave out information about serious, and possibly deadly, side effects. You are concerned that this type of advertising can cause serious harm to patients and complain to the national industry association. The association finds that the company is indeed violating the industry’s voluntary code and requires the company to stop running the advertisements and issue a corrective notice in next month’s national medical journal. The company runs a quarter-page announcement, which is published on one of the journal’s back pages. However, the advertisement ran in several journals for a few months and it is very unlikely that the corrective notice reached all of those who were initially exposed.

Background: national industry codes

Over 30 national industry associations have self-regulatory codes governing member companies’ promotional practices (Putzeist, 2009). These vary in terms of standards and approaches, and in the types of sanctions applied in cases of code violations, with some industry associations levying fines and sometimes, as in the given example, requiring corrective actions. This includes, for example, the UK, Australia and Malaysia’s national industry associations (Putzeist, 2009).

The longest history of industry self-regulation comes from the UK and it provides the best example of the evolution of national industry self-regulation. How promotion is controlled in the UK is important because it is taken as a standard, especially in those countries with weaker regulatory systems.

The ABPI code was critically analysed in a 1990 publication that demonstrated systematic failures (Herxheimer and Collier, 1990). Only one sanction against a company had been levied

in a 30-year period and there was virtually no adverse publicity for breaches. The authors judged that, “*the present system is unacceptable even for matters that fall outside the Medicines Act.*”

In response to this analysis, on 1 January 1993 the ABPI established the Prescription Medicines Code of Practice Authority (PMCPA) with the aim of setting up ‘arm’s length’ enforcement. It includes some members from outside of industry (see: <http://www.pmcpa.org.uk>). The ABPI Code has been revised several times since then. In 2006, the ABPI introduced additional changes to enforcement procedures, including stronger sanctions and publication of advertisements in the medical and general press describing serious offences (Prescription Medicines Code of Practice Authority, 2006). Box 1 includes excerpts from a press report describing a 2006 UK Code violation in which physicians were invited by sales representatives to sports events and to a lapdancing club.

Box 1. Example of a UK code violation

Drug firm censured for lapdancing junket

Sarah Boseley, health editor, *The Guardian* (UK), Tuesday, 14 February 2006

[Excerpts]

One of the world's largest drug companies has been disciplined by the industry's UK watchdog after admitting that its staff entertained doctors to greyhound racing, lapdancing and Centre Court tickets at Wimbledon.

The Association of the British Pharmaceutical Authority (ABPI) ruled that the scale of the hospitality to doctors who might be influenced to prescribe Abbott Laboratories' drugs breached its code of practice. It suspended the company, which made \$3.4bn (£2bn) profit last year on worldwide sales of \$22.3bn, from its board of management for six months.

An anonymous whistleblower triggered the ABPI investigation when he complained that drug reps had taken 27 doctors to the greyhound track in Manchester in January 2004 and 36 others in September. He also complained that two Abbott employees had taken a senior doctor to a lapdancing club, where one of them, a senior manager, borrowed £1,000 for the evening out from the other, a rep.

...The greyhound racing outings had not been approved by head office, it [Abbott] said, because the cost had not exceeded £40 a head or £2,000 in total...

Abbott said ... it had a "zero tolerance policy" for breaches. The allegations related to "a small number of employees" who had resigned or had their employment terminated.

(Boseley, 2006)

Conclusion

Currently many countries do not adequately regulate pharmaceutical promotion because they lack the resources needed for pharmaceutical regulation in general. Other countries have advanced medicine regulatory systems but do not treat regulation of pharmaceutical promotion as a priority. Many activities are delegated to the pharmaceutical and advertising industries for self-regulation. This is problematic for two reasons: the lack of direct relationship between regulatory codes and the law itself; and the inherent conflict of interest in self-regulation. Of particular concern is the link between the effects of promotional activities – stimulation of medicine use – and public health. In many cases, laws and regulatory codes make no reference to the WHO Ethical Criteria and/or aims to promote more rational use of medicines.

Even in countries with direct government regulation of pharmaceutical promotion, legal standards that exist routinely fail to be applied. Most medical, pharmacy and other health professional associations with voluntary codes of practice do not actively implement these codes.

Two international regulatory standards exist: the IFPMA *Code of Pharmaceutical Marketing Practices* and the WHO *Ethical Criteria for Medicinal Drug Promotion*. The former is limited to pharmaceutical manufacturers who are members of IFPMA; the latter is a broader, inclusive international code with a public health orientation. Unfortunately, however, its implementation remains far from adequate. This can be understood in part to be a question of political will, as the WHO Ethical Criteria are a general set of principles that can be used to develop legislation or regulatory standards, rather than having a legal status.

What can be done?

Health professionals can take an active role in their own medical associations to ensure that high ethical standards exist both for the association's activities and the activities of members. An individual can also set his or her own ethical guidelines for practice and can report illegal marketing activities to the relevant regulatory agency.

In Annex 1 of this chapter, you will find a comparison of the WHO Ethical Criteria and the IFPMA Code. You may want to compare the regulatory procedures and codes in your own country against these standards.

Annex 2 describes consumer and health professional organisations that are actively working to improve the quality of pharmaceutical promotion, the ethical standards governing interactions between health professionals and patients and the role of national governments in the regulation of pharmaceutical promotion. Most are international organisations that welcome collaboration. If you are interested in working towards improved regulation of pharmaceutical promotion, you may want to get in touch with one or more of these organisations.

Annex 3 presents an argument for and against industry self-regulation of pharmaceutical promotion. You may want to take a look at these arguments and explain how you believe promotion would be best regulated.

In their involvement in promotional activities and interactions with pharmaceutical manufacturers, health professionals are bound by voluntary codes, professional standards and fiduciary responsibilities to their patients. Behind the scenes, laws governing the promotion of medicines determine the types of messages and activities that are considered acceptable. The extent to which these laws govern (or fail to govern) everyday activities may come as a surprise, especially where few resources are available for enforcement or allocated to this work. This chapter provided an overview of the link between national laws and promotional activities aimed at health professionals. As a practitioner, you may at times be faced with promotional activities that concern you. Knowing the legal and regulatory framework in which they occur can help you figure out how to respond, whether it means making a complaint to the regulatory authority, avoiding activities that appear not to be in your patients' best interests or supporting more ethical promotional practices.

Student exercises

1. Looking at regulatory codes

In Annex 1 of this chapter, you will find a comparison of the WHO Ethical Criteria and the IFPMA Code. Compare the regulatory procedures and codes in your own country against these standards. Do you feel that pharmaceutical promotion is adequately regulated to ensure that promotional messages support appropriate prescribing and that promotional activities are in keeping with high standards of professional practice? Why or why not?

2. Debate the pros and cons of self-regulation.

3. Are violations of codes in your country publicised? If so, is the level of publicity adequate in your opinion? If not, what could be done to improve the situation?

4. Find some examples of violations of a code used in your country and look at the penalties that were imposed. Do you think these penalties were adequate?

5. Describe the five components related to regulation of pharmaceutical promotion in your country: 1) the law; 2) regulatory codes; 3) monitoring of promotion; 4) enforcement; and 5) evaluation. Discuss any gaps, strengths and weaknesses.

6. Draft a code of conduct that would apply to the organisation or institution where you plan to work once you have graduated.

7. Develop a plan for monitoring compliance with and enforcement of these guidelines.

Annex 1

Comparison of key provisions in the WHO Ethical Criteria and the IFPMA Code

Comparison criteria	WHO Ethical Criteria, 1988	IFPMA Code, 2007
Who drafted the document?	Developed on the basis of a consensus involving health workers, drug regulatory agencies, consumers and the industry.	Drafted by an industry-selected task force.
Definition of “promotion”	<i>“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.”</i>	<i>“Any activity undertaken, organized or sponsored by a member company which is directed at healthcare professionals to promote the prescription, recommendation, supply, administration or consumption of its pharmaceutical product(s) through all media, including the internet.”</i>
Advertisements to the general public	<i>“should not generally be permitted for prescription drugs or to promote drugs for certain serious conditions that can be treated only by qualified health practitioners... advertisements should not be directed at children.”</i>	Not regulated in the Code.
Standards of promotion and requirements for scientific evidence of the claims	<i>“...be reliable, accurate, truthful, informative, balanced, up-to-date, capable of substantiation and in good taste. They should not contain misleading or unverifiable statements or omissions likely to induce medically unjustifiable drug use or to give rise to undue risks.”</i>	<i>“Promotional information should be clear, legible, accurate, balanced, fair, objective and sufficiently complete to enable the recipient to form his or her own opinion of the therapeutic value of the pharmaceutical product concerned.”</i>
Communication to the public	Not present in the WHO Ethical Criteria; not considered by WHO to be appropriate.	Not regulated in the Code.
Pharmaceutical sales representatives	<i>“...should not offer inducements to prescribers and dispensers. Prescribers and dispensers should not solicit such inducements. In order to avoid overpromotion, the main part of remuneration of medical representatives should not be directly related to the volume of sales they generate.”</i>	Not regulated in the Code.
Continuing Medical Education, Hospitality and promotional items	No requirements for continuing medical education (CME) programmes. Sales representatives: <i>“...should not offer inducements to prescribers and dispensers.”</i>	Not regulated in the Code. <i>“All Events should be held in an appropriate venue that is conducive to the scientific or educational objectives and the purpose of the Event or meeting. Companies should avoid using renowned or extravagant venues.”</i> <i>“No stand-alone entertainment or other leisure or social activities should be provided or paid for by member companies. At Events, entertainment of modest nature which is secondary to refreshments and/or meals is allowed.”</i>

Annex 2

Consumers and professionals promote ‘healthy skepticism’

This section provides information on a few non-profit organisations that are working to improve the regulation of pharmaceutical promotion.

BEUC – European Consumers’ Organisation

Consumer organisations have played an important role in drawing attention to problematic pharmaceutical promotion, helping to stimulate public awareness of unethical activities and to lobby governmental institutions to implement proper regulatory strategies. For example, the European Consumers’ Organisation (Bureau Européen des Unions de Consommateurs or BEUC) (see: <http://www.beuc.org>) in Brussels advocates for maintaining the current ban on the advertising of prescription medicines directly to the public in the European Union.

Health Action International (HAI)

Health Action International (HAI) is an informal network of approximately 200 consumer, health, development action and other public interest groups and individuals involved in health and pharmaceutical issues in some 70 countries around the world (see: <http://www.haiweb.org>). HAI actively promotes more rational use of medicines through research, education, action campaigns, advocacy and dialogue. HAI has been very active in drawing public attention to the serious inadequacies of industry self-regulation of pharmaceutical promotion, criticising the IFPMA Code and its revisions. Like BEUC, HAI has actively campaigned to retain government bans on direct-to-consumer advertising (DTCA). This manual is a HAI initiative carried out in collaboration with the WHO’s Department of Medicines Policy and Standards to confront the unethical promotion of medicines.

No Free Lunch

NoFreeLunch is an independent, not-for-profit organisation based in New York as the Corporation for Non-Promotion-Based Medicine. The members include physicians, pharmacists, dentists, nurse practitioners, physician assistants, medical ethicists and others. Funding comes from membership fees, donations, and sales of NoFreeLunch products. No other outside funding is received. The mission of this voluntary group of health-care providers is to encourage physicians to practice medicine on the basis of scientific evidence rather than on the basis of pharmaceutical promotion. NoFreeLunch discourages the acceptance of all gifts from industry by health-care providers,

trainees and students with the goal of improved patient care (see: <http://www.nofreelunch.org>). NoFreeLunch groups now exist in France, Italy, the UK and Russia as well as in the US.

Healthy Skepticism

Another independent, nongovernmental organisation with an international membership drawn mainly from health-care professionals, Healthy Skepticism is based in Australia (see: www.healthyskepticism.org). Its main aim is to improve health by reducing harm from misleading pharmaceutical promotion. Healthy Skepticism's core funding source is subscriptions so as to ensure that it remains controlled by individual health professionals and members of the public who have an interest in improving health.

PharmFree

The American Medical Student Association's (AMSA) national PharmFree campaign (see: <http://www.amsa.org/prof/pharmfree.cfm>) aims to educate students, physicians and the public about the professional, ethical and practical consequences of the current medicine-industry relationship. AMSA is working towards developing educational tools that highlight how pharmaceutical companies undertake their marketing campaigns. In addition, it encourages medical schools, residency programmes and academic medical centres to create 'pharm free' policies that define and limit the relationship between medical students, residents and sales representatives, believing that there is no role for the biased information distributed by representatives at centres where medical knowledge is both created and disseminated. AMSA has developed a 'score card' to grade medical faculties' conflict of interest policies, and is working in this and other ways to provide members with the tools to bring about needed changes in medical schools, residency programmes and hospitals.

Annex 3

Debate on self-regulation of promotion

The case for self-regulation by the pharmaceutical industry

International Federation of Pharmaceutical Manufacturers & Associations (IFPMA)

The pharmaceutical industry is committed to benefiting patients by supporting the appropriate use of prescription medicines. Self-regulation, operated through international and national industry codes, makes an important contribution to ensuring good practice in the promotion of medicines.

The industry has an obligation and responsibility to provide accurate information about its medicines and has a legitimate right to promote them. The International Federation of Pharmaceutical Manufacturers & Associations (IFPMA) website (www.ifpma.org) provides links to various codes of practice, including its own Code of Pharmaceutical Marketing Practices which outlines minimum standards throughout the world. It has recently been substantially revised and national rules must reflect its requirements. Many national codes are more restrictive than that of the IFPMA.

Key requirements are that promotion has to be accurate, balanced, fair, objective and based on up-to-date, relevant evidence. Codes also impose restrictions relating to meetings, gifts (promotional aids), hospitality and several other areas. Codes are almost invariably wider in their scope than national legislation. Many companies have their own codes of conduct containing additional restrictions.

Any health professional who is concerned about any promotional activity should contact the national trade association which will either deal with their complaint or provide advice regarding available options.

The experience from the UK and many other countries is that self-regulation is extremely effective. Companies are committed to compliance and when complaints arise they are dealt with fairly and effectively. It is very important that material in breach of a code is removed from use quickly. Code processes generally take just a few weeks. One of the most effective sanctions is publication of decisions. The UK makes public very detailed reports of the outcome of every case.

Codes of practice operate through adjudication bodies that often include independent health professionals. The principles of the codes are applied and judgements made on what is right, sensible and appropriate. In the UK, professional associations' input is important in ensuring that the regular code updates always reflect current accepted good behaviour.

The role of health professionals is important. European law makes it an offence both to offer, and for health professionals to ask for or to receive, inappropriate gifts or hospitality. Requirements for health professionals are covered in their own professional codes and these should support the principles of the IFPMA Code.

Self-regulatory codes, compared with legislation, are wider in their scope, often quicker in their application and more responsive to current good practice. They do, however, need legislation to back them up. The IFPMA-associated codes apply to multinational companies but some local manufacturers, particularly in developing countries, are not covered by codes and thus legislation is needed.

There is major change underway with self-regulatory codes being strengthened around the world. It is worth trying the new systems to see whether concerns are satisfactorily resolved.

The case against self-regulation by industry

Joel Lexchin

Governments in nearly all developed and developing countries have ceded control of promotion to voluntary codes operated by the pharmaceutical industry. As Lexchin and Kawachi argue (1996), the problem with voluntary regulation is that trade associations have not made systematic efforts to either monitor the advertising practices of their members or to enforce compliance. Far from being anti-competitive, many misleading advertising tactics are good for business.

A British parliamentary committee investigating the pharmaceutical industry heard evidence that led it to state: “*The examples cited to us of breaches of advertising regulations, cover-up of negative medicines information and provision of misleading information to prescribers suggest that self-regulation is not working satisfactorily*” (House of Commons Health Committee, 2005).

When industrial associations draw up their codes of practice they deliberately make them vague or do not cover certain features of promotion to allow companies wide latitude and the sanctions for violations are either non-existent or weak and ineffective. These problems can be seen in the codes from the International Federation of Pharmaceutical Manufacturers & Associations (IFPMA), the Pharmaceutical Research and Manufacturers of America (PhRMA) and Canada’s Research-Based Pharmaceutical Companies (Rx&D).

The PhRMA Code lacks any sanctions. The latest version of the IFPMA Code retains adverse publicity as its only sanction. Although the Rx&D code does provide for fines, the maximum amount after three violations is CAN\$50,000 a trivial amount for companies that spend tens of millions or more annually promoting their products. Furthermore, the IFPMA and Rx&D decisions about whether or not the codes have been broken are made either entirely by industry personnel or with only token representation from outside the industry.

The new version of the IFPMA Code offers protection for companies wishing to present exaggerated benefits or downplay safety issues. Clause 4.1 states “*It is understood that national laws and regulations usually dictate the format and content of the product information communicated on labelling, packaging, leaflets, data sheets and in all promotional material. Promotion should not be inconsistent with locally approved product information.*” (IFPMA, 2006). In practice, this could mean that if weak national regulatory systems allow claims based on dubious science or do not require detailed safety information then companies are under no obligation as far as the code is concerned to provide this level of detail. There is nothing in the Rx&D Code that explicitly requires company sales representatives to supply safety information to Canadian doctors. The PhRMA code allows companies to offer doctors “modest” meals “*in a venue and manner conducive to informational communication and provide scientific or educational value*” (PhRMA, 2002). What a “modest” meal and “a conducive manner” are lack any definition.

Poor control over promotion has been linked to poor prescribing in numerous studies. While voluntary self-regulation spares governments the direct expense of setting up a regulatory system, the indirect costs from the public health perspective are substantial.

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Chapter 8

Using unbiased prescribing information

Andy Gray, Bob Goodman, José M Terán Puente and Barbara Mintzes

The previous chapters discuss a range of promotional techniques, as well as some ways to avoid undue influence of the promotion of medicines on professional practice. A key strategy is to rely only on independent and unbiased information sources as a basis for prescribing and dispensing decisions. Secondly, it is important to know how to judge the strength of this evidence and its applicability: is the design of a study strong enough to support a claimed effect? Is it relevant to your patients? Is adequate information provided on harmful as well as beneficial treatment effects?

This chapter presents basic principles of critical appraisal of clinical trials and concludes with a list of independent information sources as well as criteria you can use to choose information providers. As a busy health professional, you will not always have time to read original studies in order to decide whether a medicine will or will not be useful for your patients. It is also important to be familiar with high-quality, unbiased sources of brief, summarised reviews of the research evidence.

Aims of this chapter

After reading this chapter you should be familiar with:

- The five steps in evidence-based medicine;
- Principles of critical appraisal of studies assessing medicinal treatments;
- Key criteria by which to judge research study quality;
- Sources of reliable, unbiased information on medicines.

Evidence-based medicine and prescribing decisions

Evidence-based medicine aims to base diagnostic and treatment decisions on the full body of existing scientific evidence. Sackett and colleagues (1996) define it as: “...*the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients.*” They stress the need to integrate individual, clinical expertise with the best available external, clinical evidence. Practising evidence-based medicine involves five steps:

1. Converting the need for information (about prevention, diagnosis, prognosis, therapy or causation) into a clearly stated, answerable question.
2. Finding the best evidence with which to answer that question.
3. Critically appraising that evidence for its validity (truthfulness), impact (size of the effect), and applicability (usefulness in the practitioner’s clinical practice).
4. Integrating the critical appraisal with clinical expertise and with the patient's unique biology, values and circumstances.
5. Evaluating the effectiveness and efficiency of the first four steps and continually improving them.

One of the foundations of evidence-based medicine is the **systematic review**, which aims to combine all of the existing scientific knowledge about the effects of a specific medical intervention or pharmacotherapy, in order to answer a precisely defined research question. Often a systematic review will also include **meta-analysis**, a statistical technique that is used to pool research results from included individual trials in order to obtain a quantitative estimate of a treatment’s effects that reflects all of the existing research evidence. Sometimes meta-analysis is not possible because the existing trials differ too much in methods, patient population or evaluated outcomes. When meta-analysis is possible, it provides a powerful tool to obtain a more precise estimate of a treatment’s effects than an individual trial can show, including less common effects and effects in different subgroups of patients. As with any other study design, consideration must be given to actual and potential conflicts of interest that may affect the integrity of the analysis.

Like individual clinical trials, systematic reviews and meta-analyses vary in quality. Some key studies may have been left out, for example. Trials of such poor quality that the results are unlikely to be valid are included nevertheless. Sometimes a systematic review fails to include harmful effects of medicines, leading to a biased view of treatment benefits. Additionally, if negative trials remain unpublished and inaccessible to reviewers, publication bias can lead to inaccurate systematic reviews.

One of the best sources of up-to-date, high-quality, systematic reviews and meta-analyses is the Cochrane Library of Systematic Reviews, produced by the Cochrane Collaboration, a global, non-profit network of researchers who evaluate health-care interventions, including pharmaco-

therapy. The Cochrane Collaboration has developed a standardised set of methods for systematic reviews and training for reviewers, as well as actively testing, discussing and revising methods as the science of systematic reviews improves.

Box 1: Educational material on evidence-based medicine

A number of websites provide evidence-based medicine toolkits and tutorials, including:

- The Centre for Evidence-Based Medicine (Oxford) <http://www.cebm.net/index.asp>
- The Centre for Evidence-Based Medicine (Toronto) <http://www.cebm.utoronto.ca/>
- The Evidence-Based Medicine Toolkit <http://www.med.ualberta.ca/ebm/ebm.htm>

Limits to the available evidence

“Evidence-based medicine is valuable to the extent that the evidence base is complete and unbiased. Selective publication of clinical trials — and the outcomes within those trials — can lead to unrealistic estimates of drug effectiveness and alter the apparent risk–benefit ratio.”

(Turner E et al., 2008)

Well-conducted systematic reviews are an important information source because they combine all of the available clinical trial information that addresses a specific question. However, sometimes the type of evidence needed is not available.

There is often a large gap between the situation faced by an individual patient and the body of available research evidence. For example, studies may have been carried out for too short a time. A systematic review of trials of stimulant medicines for attention deficit disorders in children reported an average treatment duration of three weeks (Shachter et al., 2001). Long-term effectiveness remains largely unknown. One 14-month study failed to show an advantage for drug treatment over behavioural therapy or usual care, based on blinded classroom observations (MTA, 1999). However, many children are prescribed these medicines for several years.

Sometimes clinical trial participants are very different – usually younger and healthier – than those commonly prescribed a medicine. The patient in front of you may look more like people who were systematically excluded from clinical trials of a medicine’s effects than trial participants. For example, often elderly people and those with serious health problems are systematically

excluded. There may only be placebo-controlled trials with no comparative trials against other active treatments available, making it impossible to know whether a new medicine is better – or worse – than standard treatment. If the medicine has been compared with other treatments, non-equivalent doses may have been used.

Finally, the available published studies may represent only a subset of the scientific evidence about a specific medicine's effects. For example, Turner and colleagues (2008) found that whereas nearly all published studies (94%) reported that antidepressants were more effective than placebos in treating depression, the picture was very different if all trials, both published and unpublished, were examined. In this case, only 51% – just over half – found the medicines to be better than placebo. This difference reflects both a serious *publication bias* and *reporting bias*. Trials in which the medicines looked worse tended not to be published. If a trial was published, the results were often published in a way that made them look more positive than they were.

A second analysis looked at all studies comparing statins (medicines used to lower cholesterol) to one another or to other cholesterol-lowering therapies (Bero et al., 2007). In the 95 industry-funded trials identified, which company sponsored the trial was a strong predictor of which product was found to be superior.

In summary, although the aim of evidence-based medicine is to base treatment decisions on scientific evidence, there are many shortcomings in the scientific evidence, its public availability and its applicability to the situation faced by individual patients.

It is important to keep in mind how strong or weak a body of evidence is, whether there are important gaps in knowledge, and whether the available studies are relevant to your patient. A consistent bias in published clinical trial evidence is that often less evidence is available on harmful than beneficial effects of medicines (Papanikolaou, PN, Ioannidis JP, 2004). This is, in part, simply because not enough people have been included in clinical trials to test whether a rare, serious, harmful effect occurs more often on the medicine than on placebo or comparative treatments. In this case, 'absence of evidence of harm' does not mean the same thing as 'evidence of no harm'.

The truth, the half-truth and nothing like the truth

Promotional materials are not limited to paid advertisements in journals or glossy materials provided by sales representatives. Richard Smith (2005), former editor of the *British Medical Journal*, has gone so far as to call medical journals part of the marketing apparatus used by the pharmaceutical industry. He is critical of journals' role in publishing and disseminating biased trial reports that help to stimulate sales. He suggests that "*journals should critique trials, not*

publish them". Box 2 lists methods companies use to get favourable trial results that are then reported in medical journals.

Box 2. How to get the results you want from a clinical trial

- Compare your medicine to an inferior treatment;
- Compare your medicine to too low a dose of a competitor (for more effectiveness);
- Compare your medicine to too high a dose of a competitor (for fewer side effects);
- Use too small a sample to show differences;
- Use multiple endpoints and publish only those that look best;
- Do multicentre trials and publish results only from centres with the best results;
- Conduct subgroup analyses and publish only those that are favourable;
- Present results that are most likely to impress—for example, reduction in relative rather than absolute risk.

(Adapted from Smith R, 2005)

At the market launch of the Cox-2 inhibitors rofecoxib (Vioxx) and celecoxib (Celebrex), there were high hopes that these medicines would prove safer than other arthritis medicines because of a lower risk of serious gastrointestinal bleeding. The first trials testing this hypothesis were published after both medicines had begun to achieve 'blockbuster' sales, based, in large part, on a promise of greater safety.

What happened when study results proved differently? The published clinical trial reports of both the Vioxx Gastrointestinal Outcomes Research (VIGOR) trial (Bombardier et al., 2000) and the Celecoxib Long-Term Arthritis Study (CLASS) trial (Silverstein et al., 2000) claimed safety advantages. In both cases, this was based on incomplete reporting of clinical trial data.

The VIGOR trial aimed to assess rates of serious gastrointestinal bleeding and found a lower rate with rofecoxib than naproxen. However, more patients on rofecoxib experienced serious cardiovascular events. The authors argued that this difference was due to the cardio-protective effect of naproxen and the published report mainly discussed gastrointestinal bleeding, although more patients were affected by the increased cardiovascular risks.

In late 2004, rofecoxib was withdrawn globally because of increased risks of heart attack and stroke. Soon after, the journal editors published an 'expression of concern' (Curfman et al., 2005) because three heart attacks among rofecoxib users were not included in the VIGOR report or the manuscripts they had reviewed. The study's academic authors argued in a rebuttal that

they had acted correctly because of a pre-specified study protocol. Curfman and colleagues point out the larger picture: *“Because these data were not included in the published article, conclusions regarding the safety of rofecoxib were misleading.”* (Curfman et al., 2006).

In a similar case, data published on the CLASS study (Silverstein et al., 2000) differed from the data presented to the US Food and Drug Administration (FDA) (Hrachovec and Mora, 2001; Wright et al., 2001). Trial results were reported at six months and did not refer to the full, longer study period. The first six months looked better for celecoxib. However, when the full 12-month trial data were examined, most ulcer complications had occurred in the second six months, meaning that there was no significant safety advantage (Jüni, 2002). Again, the authors defended their work, but did acknowledge that *“we could have avoided confusion by explaining to the JAMA editors why we chose to inform them only of the 6-month analyses, and not the long-term data that were available to us when we submitted the manuscript.”* (Silverstein et al., 2001).

Interpreting the numbers

In Box 2, Smith mentions the use of relative rather than absolute risk differences as a common misleading presentation of data. When only relative risks are reported, a small difference in a rare event can be made to look clinically significant. The following example illustrates this practice and also the way in which an alternative metric, the **number needed to treat** (NNT) can be calculated.

Table 1 compares the results of two imaginary trials (‘Trial 1’ and ‘Trial 2’) on the effects of intensive versus standard insulin treatment on diabetic nephropathy. It illustrates how different relative versus absolute risk reductions can look.

Here are the results of Trial 1:

- **28 of 1,000** patients on intensive insulin developed diabetic nephropathy;
- **96 of 1,000** patients on standard insulin developed diabetic nephropathy.

The **absolute risk reduction** is calculated by subtracting the event rate in the experimental group from the event rate in the control group. As Table 1 illustrates, in Trial 1, the absolute risk reduction is $9.6\% - 2.8\% = 6.8\%$. In a two-year trial, it would mean that around 7 fewer patients on intensive therapy out of each 100 patients treated would experience nephropathy over a two-year period.

Imagine that only one-tenth as many people developed diabetic nephropathy over a two-year period. This is the situation in Trial 2, (the right-hand column):

- 28 of 10,000 patients on intensive insulin developed diabetic nephropathy;
- 96 of 10,000 patients on standard insulin developed diabetic nephropathy.

The absolute risk reduction is $0.96\% - 0.28\% = 0.68\%$. This is much less impressive, and a physician would probably be much less likely to recommend intensive treatment. Out of every 100 people treated, one fewer patient would develop diabetic nephropathy each two years.

Number needed to treat (NNT) is another way of expressing the same results and using the concept of absolute risk. The focus is on the individual patient's probability of benefit. The NNT shows the number of patients with diabetes who need to be treated with the intensive regimen in order to avoid 1 additional case of diabetic nephropathy. It is calculated by taking the reciprocal of the absolute risk reduction:

For Trial 1: $NNT = 1 \div 0.068$, or ~ 15 .

In other words, 15 patients need to be treated for 1 to benefit. For Trial 2: 147 patients must be treated for 1 to benefit.

If **relative risk reduction** is used instead, these differences disappear and the results look far more impressive for both trials. Relative risk reduction is a measure of the difference between the two rates 'relative to' the rate for standard treatment:

Trial 1 $(9.6-2.8) \div 9.6 = 71\%$

Trial 2 $(0.96-0.28) \div 0.96 = 71\%$

It is not hard to guess why this measure is often used to advertise benefits: "*reduce your patients' risk of diabetic nephropathy by 71%*". This is accurate – both for Trial 1 and Trial 2 – but without mentioning the absolute differences it can also be highly misleading. Table 1 summarises the measures for absolute risk reduction, numbers needed to treat, and relative risk reduction for these two imaginary trials.

Table 1: Why report absolute risk reductions? An illustration

Comparisons	Trial 1		Trial 2	
	Intensive insulin therapy	Standard insulin therapy	Intensive insulin therapy	Standard insulin therapy
Trial results (n of N) n= number with nephropathy N = total number of participants	28 of 1,000 (0.028)	96 of 1,000 (0.096)	28 of 10,000 (0.0028)	96 of 10,000 (0.0096)
Absolute risk reduction (ARR)	standard - intensive = ARR 0.096- 0.028 = 0.068		standard – intensive = ARR 0.0096-0.0028 = 0.0068	
<i>Expressed as percentage</i>	9.6% - 2.8% = 6.8%		0.96% - 0.28% = 0.68%	
Number needed to treat (NNT)	1/ARR = NNT 1/0.068 = ~15		1/ARR = NNT 1/0.0068 = 147	
Relative risk reduction (RRR)	(standard – intensive)/ standard = RRR (0.096 – 0.028)/0.096 = 0.708		(standard – intensive)/ standard = RRR (0.96% – 0.28%)/0.96 = 0.708	
<i>Expressed as percentage</i>	71%		71%	

For a physician or pharmacist making treatment decisions it is always important to know not just the relative differences between two approaches to treatment, but also absolute differences and how likely a patient is to benefit. When this probability is very small sometimes medicine treatment may be as likely or almost as likely to lead to harm. Allenso-Coello and colleagues (2008) use the example of the hormonal medicine raloxifene for prevention of osteoporosis. An advertisement claimed a 75% relative risk reduction for vertebral fractures (see Chapter 3). In the population group targeted, fracture rates are expected to be less than 1% per year. Allenso-Coello et al. calculate the number needed to treat as 133 (95% confidence interval 104 to 270) for 3 years to prevent one fracture. Raloxifene also leads to an increase in thromboembolic events (deep-vein thrombosis and pulmonary embolism). With an absolute risk increase of 0.7%, the number needed to harm is 143 for 3 years. The number needed to harm is the number of patients that would have to receive this medicine in order for one additional person to develop the adverse effect of interest. An independent bulletin points out that the magnitude of benefit is similar to the magnitude of harm (Therapeutics Initiative, 2000).

If the benefits of medicines are reported only as relative risk reductions and harmful effects only as absolute risk increases, it is very hard to compare the effects directly, or to know that sometimes – as in the case above – the likelihood of benefit and harm are very similar.

Critical appraisal of studies of medicinal treatments

The term ‘critical appraisal’ refers to methods used to evaluate the strength of a study’s design, the way the study was carried out, and the reporting of results, in order to judge the results’ validity. One rule for critical appraisal is to pay close attention to the methods section of a clinical trial report and not too much attention to the study abstract, which is often misleading. Unfortunately, busy clinicians often do exactly the opposite. Critical appraisal of a clinical trial’s results, and its relevance to your patients, starts with a few key elements:

- **Type of studies:** evidence of benefit must be based on the strongest possible research evidence, generally double-blind, randomised, controlled trials.
 - Was selection truly random? Sometimes methods are used that allow some selection of participants for different treatment groups.
 - Were some patients screened out in a ‘run in’ period (for example, those who responded less well to treatment or better to placebo); this creates a biased subset of trial participants.
 - Were patients, clinicians and assessors adequately ‘blinded’ to treatment allocation? Methods should be described in detail and ideally the adequacy of blinding tested by asking patients and clinicians to guess what treatment they are on.
 - Is the sample size adequate? The sample size calculation should be described in the trial.
- **Type of participants:** these should be similar to the types of patients encountered in normal clinical care. For example, if a medicine is often used by the elderly and they were excluded in a trial, this is a problem, or if patients in a trial are much healthier (for example, if patients with co-morbidities were unnecessarily excluded) or much more ill than those encountered in clinical care.
- **Types of comparisons:** the study should compare a new medicine with standard treatment for the same condition or with a placebo, only if there is no standard treatment. If a medicine is in an existing class with a specific mechanism of action, it should be compared with other medicines in the class. The dose should also be comparable.
- **Accounting for all patients in the trial:** analysis should be by ‘intention-to-treat’, and include all patients randomised to each treatment arm, regardless of whether they discontinued early or not.
- **Type of outcome measures:** the main focus should be on health effects of importance to patients’ lives. Serious morbidity and mortality are given priority over symptom-free, physiological effects.
- **Funding source and conflicts of interest:** if the study was funded by a pharmaceutical company, were any procedures in place to prevent sponsor involvement in study design, analysis of data and reporting?

Box 3: Useful websites on evidence-based medicine and critical appraisal skills

Centre for Evidence-Based Medicine (CEBM), Oxford, UK

<http://www.cebm.net/index.aspx?o=1011>

CEBM tools and worksheets for critical appraisal

<http://www.cebm.net/index.aspx?o=1157>

The 'evidence-based toolkit' from the University of Alberta, Canada

<http://www.ebm.med.ualberta.ca/>

Similar resources from the University of Toronto

<http://www.cebm.utoronto.ca/>

Organisations that carry out systematic reviews of clinical evidence

National Institute for Clinical Excellence (NICE), UK

<http://www.nice.org.uk/>

Scottish Intercollegiate Guidelines Network

<http://www.sign.ac.uk/>

US Agency for Healthcare Research and Quality (AHRQ)

<http://www.ahrq.gov/>

and the AHRQ web portal for clinical guidelines

<http://www.guideline.gov/>

The Cochrane Collaboration – an international organisation that carries out systematic reviews of health care interventions (includes database of systematic reviews)

(Source: <http://www.cochrane.org/>)

The use and abuse of statistics in advertising

It is useful to know some of the common tricks that may be used in advertising and promotion to misrepresent the scientific evidence. Someone glancing at an advertisement or other promotional materials may not immediately notice them, but once alerted, they become much more obvious. Box 4 is an overview of some of the more common techniques used, produced by a regional drug and therapeutics committee in the UK.

Box 4: The Hitch-hikers' guide to promotional drug literature

1. **Beauty is only skin deep** – be wary of skilful and seductive graphics designed to grab your attention and distract from the actual content. Look out for irrelevant photographs, e.g. advertisers are more likely to use glamorous, well-dressed women to sell oral contraceptives, and harassed mothers to sell antidepressants.
2. **What's the point** – strip away the multicoloured hype and ask yourself: what does the advert really say? Does it actually say anything? Is it merely a gimmick to reinforce a brand name? Is the drug really new, or the consequence of “molecular roulette”?
3. **Examine the claims** – check the original evidence on which the claim is based. If possible, compare statements, quotations and conclusions with the original article. Direct misquotation is not unknown, nor is quoting out of context, nor citing of studies with inadequate methodology.
4. **The great picture show** – these are the favourite tools of the advertiser – points to check: (i) make sure the axes start at zero. Axial distortion may make an insignificant difference “look significant”; (ii) Lines of graphs should not be extended beyond plotted points, and that there is an indication of variance (e.g. standard error bars); (iii) “Amputated” bar charts (similar effect to (ii)); (iv) Logarithmic as opposed to numerical plots.
5. **“Lies, damned lies and statistics”** – always be suspicious of statistics. Most readers have only a very basic knowledge of statistics. Beware of BIG percentages from small samples. “p” values are only worthwhile if data have been properly and accurately collected in a well-designed trial and the correct statistical test used for analysis.
6. **Non sequiturs** – this involves positioning two irrelevant statements in a manner implying a relationship – commonly, pharmacokinetic data from single dose studies in young healthy volunteers and the implication that this will apply to elderly patients with multiple pathology in a chronic dosage schedule.
7. **References** – if there are any – examine the list of references carefully. Be suspicious if references are old or from obscure or unfamiliar foreign journals (some journals exist only to publish drug company sponsored papers). “Data on file”, “Symposium proceedings”, “To be published” or “Personal communication” should also ring warning bells. Remember an isolated quote taken out of context can alter the real conclusion of the reference.

A scanned image of the original version published in the Essential Drugs Monitor No. 17, 1994, can be accessed at: <http://www.healthyskepticism.org/library/EDM/17/Page24.pdf> (West Lothian Drug and Therapeutics Committee, 1994)

Conclusion

This chapter has provided a brief introduction to evidence-based medicine, including some of the difficulties involved in interpreting clinical trial reports and techniques that can be used to misrepresent or to more accurately represent results. We would also like to conclude with lists of resources and a positive, alternative approach to the most common treatment decisions you will encounter.

Develop a personal formulary

Nobody has time to look up all the evidence on all available treatments each time a patient comes in for care or to search the Cochrane Library or another information source for the most relevant systematic reviews. In reality, doctors see many patients for many of the same health problems, day after day. Although there are differences between patients both in general health and treatment preferences, it is possible to develop a list of medicines and other treatments that can be helpful to most patients with a specific condition, most of the time. In primary care, around 50 to 100 medicines can meet nearly all of patients' health needs. It is especially useful to develop a personal list of medicines to treat the most commonly encountered health problems in most patients.

Box 5: Five key steps required for rational prescribing decisions

1. Define the patient's problem.
2. Specify your treatment objective (i.e. what you are trying to achieve, in how long?)
3. Make an inventory of possible treatments. This can include drug and non-drug options, information and advice, watchful waiting and the option not to treat.
4. Choose your P-treatment (personal treatment) based on efficacy, safety, suitability and cost.
5. Verify that the 'P-treatment' is appropriate for this patient.

(de Vries et al., 1994)

Resources

Some sources of independent information on medicines

Below are a few examples of English-language, non-promotional information on medicines. Sources will, of course, vary depending on where one is practising (as approved medicines and regulatory agencies will also vary), so it is not the intention here to review and compare the world's sources of unbiased pharmaceutical information, only to give a very small sampling. Note that none of these sources comes with a free lunch.

International Society of Drug Bulletins

Founded in 1986, ISDB is a network of drug bulletins and journals whose members are “*financially and intellectually independent of the pharmaceutical industry.*” The aim of ISDB is to assist in the development of drug bulletins and facilitate cooperation of bulletins in different countries. For more information, visit: <http://www.isdbweb.org>

The Medical Letter

Published in the US since 1959, it is one of the better known bulletins in this country. Independent of the pharmaceutical industry, it gives practical, concise recommendations, accompanied by information on cost, adverse effects and comparisons with other medicines. In addition to a paper version, it is available online and for PDA. It is available by subscription, see:

<http://medletter.com>

Prescrire International

This is the English-language version of the French drug bulletin *La revue Prescrire*. Prescrire provides independent information on new medicines and indications, adverse effects, cost comparisons, as well as treatment guidelines. It is available by subscription and is an ISDB member, see: <http://www.prescrire.org>

Drug and Therapeutics Bulletin

Started in 1963, this is a monthly UK publication giving independent evaluations of, and practical advice on, individual treatments and the management of disease. It is available by subscription, see: <http://www.dtb.org.uk>

Prescriber's Letter

This independent monthly newsletter is published in the US. It is available as a printed newsletter, by subscription, with online and PDA versions, see: <http://www.prescribersletter.com>

Therapeutics Letter

This publication was established in 1994 by the Department of Pharmacology and Therapeutics at Canada's University of British Columbia "*to provide physicians and pharmacists with up-to-date, evidence-based, practical information on rational drug therapy.*" It is available free of charge. The letter is an ISDB member, see: <http://www.ti.ubc.ca/>

Martindale Complete Drug Reference

First published in 1883, this reference book covers medicines, veterinary and investigational agents, herbal medicines, as well as toxic substances. It is available in online and PDA versions (although it is not free), see: <http://www.medicinescomplete.com/mc/>

Worst Pills Best Pills

Produced by the Public Citizen Health Research Group, this is the only US bulletin that is a member of ISDB. It is primarily intended for patients. The newsletter is available online and on paper, by subscription, see: <http://worstpills.org>

Guides to critical appraisal of the research evidence

Montori VM et al. (2004). Users' guide to detecting misleading claims in clinical research reports. *British Medical Journal* 329:1093–1096.

Guyatt G et al. (1998). Interpreting treatment effects in randomised trials. *British Medical Journal*, 316:690–693.

Greenhalgh T (1996). Is my practice evidence-based? *British Medical Journal*, 313(7063):957-958.

Greenhalgh T (1997). How to read a paper. The Medline database. *British Medical Journal*, 315(7101):180-183.

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Greenhalgh T (1997). How to read a paper. Statistics for the non-statistician. I: Different types of data need different statistical tests. *British Medical Journal* 315(7104):364-366.

Greenhalgh T (1997). How to read a paper. Statistics for the non-statistician. II: "Significant" relations and their pitfalls. *British Medical Journal* 315(7105):422-425.

Greenhalgh T, Taylor R (1997). Papers that go beyond numbers (qualitative research). *British Medical Journal*, 315(7110):740-743.

Greenhalgh T (1997). How to read a paper. Papers that tell you what things cost (economic analyses). *British Medical Journal*, 315(7108):596-599.

Greenhalgh T (1997). How to read a paper. Papers that report drug trials. *British Medical Journal*, 315(7106):480-483.

Greenhalgh T (1997). Papers that summarise other papers (systematic reviews and meta-analyses). *British Medical Journal*, 315(7109):672-675.

Greenhalgh T (1997). How to read a paper. Papers that report diagnostic or screening tests. *British Medical Journal* 315(7107):540-543.

Student exercises

1. Assessing advertisements

Select an advertisement from a medical journal or news magazine, and as a group, critically examine the advertisement by using the elements listed in “The Hitch-hiker’s Guide to Promotional Drug Literature” (see Box 4). In particular:

- a. Check if any statistics are quoted or graphically represented. Were these done appropriately?
- b. Check if the results are represented as a relative risk reduction or an absolute risk reduction – if an RRR was presented, can the ARR and NNT be calculated?
- c. Check if the research cited is retrievable from your library. Was it quoted as “data on file”? If so, what does this mean?

Share your results with the class and discuss how this would affect your view of the medicine being advertised.

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Chapter 9

Promotion, professional practice and patient trust

Dee Mangin

This chapter describes the wider context of promotion: the effects on discriminatory prescribing, on the health of patients individually and collectively and on the relationship between a clinician and a patient.

At the heart of this manual is the patient. Patients have a right to good care and providing it should be the aim and the responsibility of all health-care practitioners. This begins with the individual sitting with a clinician in a consultation – the patient is often worried, sometimes frightened, but almost always trusting that the health professional will provide advice based on the best available information. Above all, patients expect to be protected from unnecessary harm. Good care entails giving advice that is informed by both science and wisdom, which requires seeking out sources of good science on the harmful as well as the beneficial effects of the treatments available.

Prescribing and dispensing decisions must always balance the potential for benefit against the possibility of harm. It is important that in our desire to help patients who are suffering we do not add to their burden by inflicting the harms of medicines unnecessarily on them. It is easy to confuse the practice of medicine with the giving of medicines. However, good care also requires considering the effect of not doing anything or of using non-pharmacological treatments. Sometimes giving a medicine is not the wisest choice and the best course is to use other treatment options, or no intervention at all. Where effective treatments are not available, good care includes giving patients information and a sense of competence in coping or adjusting to illness so that life remains worth living. The giving of hope, appreciation of context, trust and reassurance are fundamental components of this interaction with patients. While patients should and do take an active role in their own care, and in deciding whether or not to take a professional's advice, good care also means not always giving patients what they request – particularly if their expectation is generated by misleading advertising.

Discriminatory prescribing

Giving a medicine is one of the riskiest things you will do for patients. Promotion, whether direct or indirect, is aimed at increasing the use of newer, patented medicines. Being an early adopter of new medicines is not necessarily in patients' best interests, considering the often relatively small benefits and how little is known about unknown rare and long-term harms of newly introduced medicines. In minimising potential harm, adopting a 'precautionary prescribing' approach is safer.

Another key concept is that of discriminatory prescribing. The good prescriber is one who is discriminatory – who knows when to suggest a particular medicine, but most importantly when *not* to. Phillipe Pinel, a psychiatrist in 18th-century Paris, one of the earliest exponents of an evidence base to medicine, understood the concept of discriminatory prescribing well: *“It is an art of no little importance to administer medicines properly: but, it is an art of much greater and more difficult acquisition to know when to suspend or altogether to omit them.”* (Pinel, 1809).

Not prescribing is often the best decision, for example, where the natural history of the illness is more acceptable than the hazards of treatment or where the effect of the medicine is so modest that it is clinically insignificant. Similarly, pharmacists and other dispensers need to know when and when not to recommend pharmaceutical treatment in response to patients' requests for advice, particularly in environments where prescription-only status is poorly enforced.

Misleading promotion: a note of caution

Why is developing a strategy for dealing with promotion important? The difficulty for physicians and pharmacists is that sources of independent evidence that should form the basis for good care are overwhelmed by the volume of promotional material. In the UK, for example, the pharmaceutical industry has a marketing budget of £1.65 billion – 300 times more than the UK National Health Service spends on independent information to health professionals (House of Commons Health Committee, 2005). To use medicines in a rational way requires access to sources of independent evidence on the effects of medicines, an understanding of the commercial biases that occur during the generation of that evidence and the ability to recognise and take account of the effects of misleading promotional material and activities.

The 'benefits' of indiscriminate prescribing and dispensing resulting from misleading promotion go directly to pharmaceutical companies and health professionals, but it is patients who bear the risks. Sometimes, they will be mortal ones. The case study of the Cox-2 inhibitor rofecoxib described in this manual is a stark, recent example of this – the risks of this medicine were known for four of the five years that it was promoted.

There are many other examples. In 1997 a new medicine, troglitazone, was introduced for the treatment of Type 2 diabetes and was promoted to the US public. It was quickly linked to severe liver damage and, by the end of 1997, was implicated in 6 deaths and 135 cases of severe liver toxicity. This led to its withdrawal from the UK market by the UK Medicines Control Agency at the end of 1997, just six weeks after it was made available. Despite this, it continued to be advertised to consumers and health professionals in the US. By the time it was finally withdrawn from the US market, troglitazone was named as the probable cause of 391 deaths, 63 from liver failure. (Meek, 2001; Gale, 2001). Troglitazone had not been proven to save lives or reduce the complications of Type 2 diabetes. At the time of approval, the pharmaceutical company's chief executive was quoted as telling investors he saw the medicine as a "billion dollar blockbuster". This was correct. Rezulin (troglitazone) generated sales totalling US\$2.1 billion for the company in its first three years on the US market (Willman, 2000). Since then, two newer forms of the glitazone medicines have been introduced – rosiglitazone and pioglitazone. Despite lowering glycated haemoglobin, there is no evidence that this drug group extends lives or reduces the complications of Type 2 diabetes. One of the main aims of diabetes treatment is preventing myocardial infarction (MI, better known as heart attack). Recent evidence indicates that rosiglitazone increases the risk of myocardial infarction (RR 1.42 95% CI 1.06 to 1.91) and doubles the risk of heart failure (RR 2.1 95% CI 1.5 to 2.9) (Singh et al., 2007). It is estimated that in 2006 there were 3.5 million users of rosiglitazone in the US alone, and that at a conservative estimate, this would result in 4,000 excess myocardial infarctions and 9,000 excess heart failure events (Singh et al., 2007). At the time of publication, rosiglitazone was still licensed for treatment.

Promotion and chronic conditions

Chronic conditions such as diabetes represent a large potential market for pharmaceutical companies, and long-term exposure to medicines for patients. Direct-to-consumer and associated direct-to-physician advertising are largely focused on a small number of medicines for chronic conditions (General Accounting Office, 2002). These medicines are new and still under patent (General Accounting Office, 2002). When prescribing and dispensing a long-term medicine for a chronic condition, there should be reasonable certainty that, on balance, it will relieve the burden of disease, not add to it. Similarly, when changing a medicine, there has to be clear evidence of clinical advantage for the patient, particularly if the medicine is newer and therefore more expensive while having less long-term safety data available. This is especially important for prescribing and dispensing of medicines for chronic conditions. Promotional pressure often exists to provide newer, more expensive medicines when patents expire on medicines a patient is currently taking. There are a number of examples where such promotion has led to widespread use of more costly medicines that are clinically identical to the parent medicine from which they were derived. This is illustrated in the case study of omeprazole and esomeprazole (Nexium)

in Chapter 2. Other examples include citalopram and escitalopram, loratadine and des-loratadine. These are all single enantiomers of the racemic medicine that they have replaced. (An isomer has the same chemical formula, but only one specific configuration in space.) While there are instances in which new single enantiomers may bring improvements, in many cases, effects on the body are identical (Therapeutics Initiative, 2002).

Clinical decision-making carries an additional responsibility when introducing preventive treatments. There is an ethical difference between offering treatments when patients seek help for relief of their symptoms and making recommendations for treatments for prevention of future illness in people who currently think of themselves as well. When offering treatment to relieve symptoms we rely on the best available evidence with an awareness of its gaps, biases and uncertainties and some guidance from the patient's individual response to that treatment. For preventive treatments, a greater burden of proof is needed that the treatment has a high likelihood of altering the natural history of that disease and that any improvement to the future health and well-being of the person in front of us is meaningful to them. It is important here to be aware of the role of promotion in constructing not only how we understand the effects of medicines, but also our understanding of disease and risk. For example, rating scales that have little meaning in health terms are often used to evaluate disease outcomes. Sometimes natural physiological processes, such as a gradual decrease in bone density as people age, are misrepresented as diseases. The phrase 'disease mongering' is used to describe this process of medicalisation (see Chapter 5).

Many people can be described as 'at risk' of chronic diseases so the potential for market expansion for pharmaceutical companies promoting treatments for prevention is enormous. The promotion of statins in populations who do not stand to benefit has resulted in the unnecessary exposure of large numbers of people to the potential harms of these medicines. There is no evidence that statins used for primary prevention protect women against non-fatal myocardial infarction or fatal heart disease, yet these medicines are promoted indiscriminately for both men and women (Eisenberg & Wells, 2008). Evidence for primary prevention with statins in the elderly is also lacking, yet these medicines are used indiscriminately in this group and are recommended for use in the elderly in treatment guidelines (Mangin et al., 2007). In addition, using these medicines for prevention in the population over 75 has other ethical implications. It appears that introducing this preventive intervention beyond the average lifespan, even in groups that do show cardiovascular benefit, has unintended effects on their health and lives. Looking at the balance of overall benefits and harms, we may be simply changing a patient's cause of death with medicines rather than improving or extending his or her life. An elderly person who is told that a medicine will "*reduce the risk of heart attack and stroke by...*" may make a different decision when the rider is added "*however you will not extend your years of life and you will increase your risk of being diagnosed with and dying of cancer by the same amount.*" The potential harms are not just those related to the medicines themselves or to patients with chronic disease. Preserving health also means avoiding unnecessary medical care and medicalisation among the healthy.

These examples show how promotion influences the landscape you work in and how it may compromise good care, discriminatory prescribing and dispensing and the ethical practice of medicine.

Promotion and clinical practice

Promotion of pharmaceuticals is designed to drive prescribing decisions in order to stimulate sales. This manual describes examples of a range of promotional techniques used by pharmaceutical companies to influence the prescriptions you write and dispense for your patients. The description includes the carefully constructed links in the chain of commercial influence on clinical practice that begins with control of research design and interpretation as well as publication decisions and the development of treatment guidelines based upon that research. A study published in the *Journal of the American Medical Association* (2002) showed that four out of five experts responsible for clinical practice guidelines have financial relationships with pharmaceutical companies, and the majority of these experts “had relationships with companies whose drugs were considered in the guideline they authored.” (Choudhry, 2002). This is compounded by the level to which opinion influences these guidelines. A recent review of the American Heart Association and the American Cardiology Association guidelines showed that of 2,711 recommendations, half were based on level C (expert opinion) evidence while only 1 in 10 was based on strong (level A) evidence (Tricoci, 2009). Promotion continues with attempts to directly influence your clinical practice through advertising and sales representative visits and indirect marketing techniques. Added to this is the effect of promotion on the beliefs and desires of all of us, both doctors and patients, through direct and disguised direct-to-patient advertising.

Pharmaceutical companies’ primary responsibility is quite appropriately to maximise profits for shareholders. The purpose of regulation is to ensure that these interests do not override the values of good clinical care and the interests of individuals and society. Regulation to protect patients from harmful products and misleading claims has failed to control the negative influence of promotion on patients and on the credibility of the medical profession. This is because adequate regulatory frameworks either do not exist, are inadequately monitored and enforced or are compromised by conflict of interest or because promotional activities are not recognised as such. This is most obvious in the case of heavily-promoted medicines with a greater potential for harm than benefit. However, much more commonly, a medicine does have some useful effects in a particular group of patients, but promotion creates adverse effects by extending treatment into populations in which pharmaceutical treatment is not indicated, or in which benefits do not outweigh harm for this particular medicine.

The responsibility of health professionals

Pharmaceutical companies are simply fulfilling their role as commercial businesses in trying to sell more medicines to more people in order to increase profits for shareholders. They have some products that are helpful in life-transforming ways for some people, but pharmaceutical companies, through their marketing departments, are fundamentally traders trying to increase profit rather than being altruistic organisations trying to improve health. It is our failure as health professionals to recognise this fact and respond appropriately to promotion and poor science that results in harm to patients. Some potential ethical ‘red flags’ have been highlighted in this manual to help you see when you or those who might influence you, are in situations likely to lead to a direct conflict of interest. The challenge for you now is how you will deal with this in order to provide the best possible care for your patients. All of us are vulnerable to conflicts of interest and the influence of promotion – they are designed to act through our own most basic desires and sense of entitlement, altruism, obligation and reciprocity. This is well understood by the pharmaceutical marketing industry.

Health professionals usually believe that while others are influenced by promotion they personally are not. This is an illusion. *“To do the bigger scams you need the victims to trust their own capabilities and experience,”* a fraud expert said, commenting on the particular vulnerability of doctors to being misled because they thought they were doing good (Malvern, 2008).

As you have read, this attempt to influence your behaviour begins during your student years, with direct as well as indirect promotion using sales representatives, sponsored education, gifts and modelling from your colleagues and teachers. Until now, there has been little help within the medical and pharmacy curriculum to assist students in dealing with this ‘hidden curriculum’. The aim of this manual has been to improve your understanding and awareness of the ways in which you will be influenced. If you think that after using this manual you are immune to this influence then it has failed in its intent. We will all experience situations that create conflicts of interest. We are all subject to the effects of conflicts of interest and promotion. The important thing is how to ensure that the care and the trust of our patients is not compromised. This involves personal approaches to mitigate the effects of promotion as much as possible and to understand the ways in which we are influenced. It also involves thinking proactively about the potential for conflicts of interest and how to manage them while being open and honest about their influence.

The characteristics that define a profession are clearly described (Downie, 1990). One of these has direct relevance to promotion: a credible profession should be independent of the influence of the state or commerce (Downie, 1990). While it is not possible to escape influence, the current entanglement between health professionals and pharmaceutical companies has been and continues to be deeply corrosive to the practice of medicine. More money is spent by pharmaceutical companies on promotion than on research and development, so much of the cost of medicines

to patients, health-care agencies and governments goes towards paying for this promotion (General Accounting Office, 2002). The rise of the corporate model of health care may have helped promote entanglement and validate the passage of large sums of money as well as other ties between pharmaceutical companies and health professionals. These ties are increasingly coming under public scrutiny. There are calls to mitigate the effects of promotion with disentanglement and increased transparency in research and development of guidelines as well as disentanglement of professionals from pharmaceutical company promotional activities. This requires social change and improvements in research transparency, regulatory oversight and institutional policies, as well as individual responses. These will not work unless individual prescribers and dispensers act from early in their training to make sure these principles are incorporated into the framework of professional practice. Students groups such as the American Medical Student Association are becoming increasingly active in this area.

Society aims to improve each individual's experience of life by minimising the burden of suffering due to ill health. Clinicians can contribute to this by providing the highest quality individual health care, but this on its own will be overwhelmed if the system within which such care is provided is flawed. It is equally important to advocate as professional groups for ongoing improvement in the systems within which this care is provided – structural therapeutics. This advocacy is an important part of physicians' role in not just 'doing no harm' but in ensuring that the promise of the benefits of improved medical care and advances in science are realised.

Student exercises

1. Dealing with promotion and conflicts of interest

There are a range of options for engaging with the pharmaceutical industry and dealing with promotion. The aim of this final section is to help you to begin thinking about the approaches you will take in recognising and dealing with the effects of different promotional strategies and ethical dilemmas in your professional life. This exercise will give you the basis of a personal approach to promotion.

- Compile a list of promotional strategies and ethical conflicts you are likely to encounter once you are in professional practice;
- Think about the risks and benefits you perceive from each for you and for your patients;
- Assess whether there are alternative ways of achieving these benefits; and
- Plan your strategy for dealing with each one.

Fill in the table below about five key promotional strategies.

Promotional strategy / conflict of interest	Risks and benefits for you and your patients	Alternative way of getting the same benefits	Your personal strategy
1.			

Promotional strategy / conflict of interest	Risks and benefits for you and your patients	Alternative way of getting the same benefits	Your personal strategy
2.			
3.			
4.			
5.			

2. Independent information

An important step in minimising the harmful effects of promotion is the development of positive strategies to improve prescribing. What resources are available in your country? Where can you get independent, unbiased, comparative information about medicines? Are there similar resources available for patients?

Discuss this with your professors, fellow students, librarians and others who you believe may know what resources are available. Access the suggested resources and list the three you believe will be the most useful, either for you or your patients.

- a. What are the positive characteristics that made you choose them?
- b. How do you think you might use each of them (or already use them)?
- c. Are there any drawbacks or gaps in information?

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Doctors and pharmacists play a key role in ensuring the rational use of medicines. As gatekeepers to care, they need to assess different treatment options, including pharmacotherapy, and consider each for potential benefit and harm. However, in recent years, growing concern has focussed attention on the relationship between health-care professionals and the pharmaceutical industry - particularly the industry's influence on prescribing and dispensing decisions using a range of promotional tools, which can influence rational treatment choices.

In 2005, a World Health Organization (WHO)/Health Action International (HAI) cross-sectional, international survey of educational initiatives on pharmaceutical promotion found that whilst many schools and colleges included this topic in their curriculum, most spent less than one day on it. The survey showed that although medical and pharmacy educators recognise the need for education on pharmaceutical promotion and sometimes do their best to incorporate it into their work, it is mostly limited.

This draft manual is a first step in addressing the need for medical and pharmacy professionals to reconsider their central role as a target for pharmaceutical marketing. Its nine chapters explore a spectrum of related topics, providing a resource for curriculum development that will help tomorrow's doctors and pharmacists be better prepared to face the promotional activity to which they will be exposed. In addition, it emphasises the importance of analysing information about medicines so that health professionals can make rational choices that will contribute to the health of patients.