Editorial

Advertising to doctors is an effective way for pharmaceutical companies to ensure that their products are prescribed.[1] (See Figure 1)

An Australian, Dr Peter Mansfield's website: <www.healthyskepticism.org> has provided most of the material for this article. I'd recommend browsing the site, and signing up for e-mail alerts of new articles published periodically on the site.

Increasingly the bulk of the revenues of larger pharmaceutical companies are coming from one or two unique preparations for which they have the patented and sole rights for a limited time. With the expiry of patents and the increasing numbers of generic alternatives, more and more research is being done on substances which have minor variations from the original molecule. Many of these new substances have minimal, if any, improvement in efficacy compared with the original. The focus of much new pharmaceutical research has therefore shifted to safety (tolerability) studies, often including quality of life (QoL) variables. Many QoL instruments and variables in studies undertaken in South Africa are not necessarily validated for this country. It is reported that the SA Medicines Control Council has received research protocols containing QoL questions such as: 'How short of breath do you become while shovelling snow?'[2]

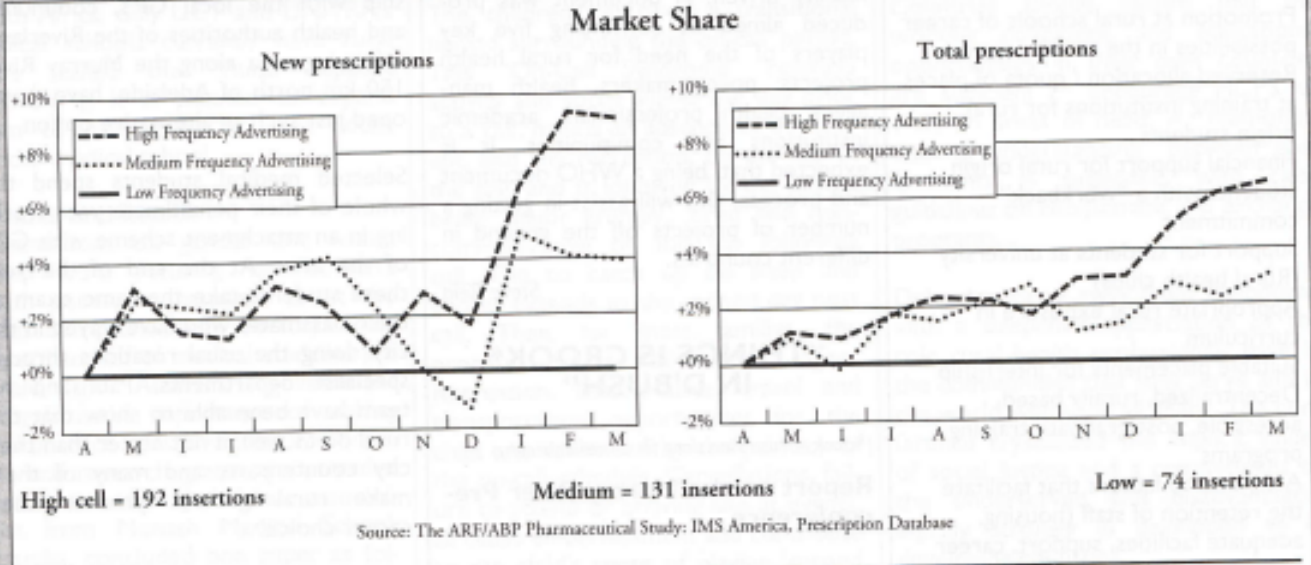

Figure 1: Response of doctors to different levels of intensity of advertising.

Although there are apparently flaws in the above study, it certainly suggests that frequent repeated exposure to printed promotional material, such as journal advertising, is very effective.

As an independent peer-reviewed, science-based publication, South African Family Practice is caught in a 'Catch-22' situation. We need the support of advertisers in order to continue our publication (as well as the membership fees of members of the Academy!), and yet we need to retain a healthy scepticism about the validity of certain advertising claims. The advertisers in turn need our continued support in terms of our prescribing of their products.

Further pressure is being exerted on family physicians to prescribe certain 'brand names' within the context of the increasing availability of cheaper generic alternatives. The decisions of medical funding organisations not to fund brand name drugs if generic alternatives are available, puts pressure on medical representatives to ensure that their assigned doctors prescribe brand name products (even if patients have to make out of pocket contributions).

Roy Jobson

1. Mansfield P. How does pharmaceutical company promotion affect prescribing? International Conference on Improving Use of Medicines (ICIUM), Thailand. Poster presentation, April 1997.
2. Registrar of the SA Medicines Control Council. (Personal communication).

PERSUADING DOCTORS WHAT TO PRESCRIBE

An analysis was undertaken by the Medical Lobby for Appropriate Marketing (MaLAM) of pharmaceutical advertising of asthma drugs as published in two New Zealand medical magazines: *New Zealand Doctor* and *New Zealand GP*, during 1999 – 2000.[1]

The relevant advertisements were identified, and the articles quoted in the advertisements were obtained and checked. Medline searches for relevant meta-analyses or randomised controlled trials were performed, and New Zealand GPs and respiratory specialists consulted.

(References to the individual articles on which the conclusions of the second opinions are based are not included – they can be found on the website.)

The main advertising claims are quoted in Table 1. Generic names have been substituted for the original brand (trade) names used in the advertisements.

Table 1: Summary of claims made in asthma advertisements	
Claim 1	Fluticasone offers superior asthma control, compared with other inhaled steroids.
Claim 2	Studies in children have shown low potential for side effects such as growth impairment and cortisol suppression (when using fluticasone).
Claim 3	Turbuhaler (delivering budesonide) may reduce the medication needed for asthma control by up to half.
Claim 4	[The manufacturer] reports that 600 GPs (20 per cent) prescribed montelukast in the first two weeks it came on the market.
Claim 5	[T]he idea behind the free month's supply of montelukast is to let patients 'try before they buy'. Auckland GP [Dr X] prescribed the drug for about 20 patients and takes it himself. 'It's fast acting – you notice in a day or two. If its useless, you risk nothing, it's a generous offer from the company. One woman can barely afford it but her asthma was so bad, and the drug made such a dramatic improvement, now she's paying for it.'
Claim 6	Less exacerbations (with salmeterol).
Claim 7	A proven reduction in exacerbation rates (with eformoterol).
Claim 8	When inhaled long-acting ß2-agonists are out of the question, just add bambuterol.

In reaching their conclusions, the doctors offering the second opinions considered the promotion technique(s) used in the advertisements, the evidence cited in the references, and the information from the medline searches. It must be noted that this was the evidence available at the time of the original preparation of the critique in February 2001. Subsequently published studies or systematic reviews may provide alternative perspectives.

Claim 1: Fluticasone offers superior asthma control, compared with other inhaled steroids.

On the available evidence fluticasone is not superior to beclomethasone via a spacer. Although fluticasone is about twice as potent per mg as beclomethasone, this would not necessarily make it 'superior' to a higher (equipotent) dose of beclomethasone.

Claim 2: Studies in children have shown low potential for side effects such as growth impairment and cortisol suppression (when using fluticasone).

Firstly, the problems with the actual wording: there is a hanging comparator. No comparator is stated in regard to the word 'low'. What is the lower potential compared with? Secondly, the advertisement exaggerated the safety claims. It was concluded that adrenal suppression may be equal or worse with fluticasone than with beclomethasone via spacer. The manufacturers cited one study which found that fluticasone had fewer adverse effects than an equipotent dose of beclomethasone. In contrast a meta-analysis found a significantly greater potential for adrenal suppression with fluticasone compared to other inhaled steroids. An earlier meta-analysis found that fluticasone was superior to budesonide but no better nor worse than beclomethasone. It was also found that use of spacers may decrease adrenal suppression with beclomethasone, but may increase it with fluticasone.

Claim 3 (Budesonide via) Turbuhaler may reduce the medication needed for asthma control by up to half.

The assessor's opinion was that this claim was based on studies in which the wrong comparative doses were used (800mg budesonide a day vs 1500mg of beclomethasone a day). The highest efficacy of beclomethasone is at 1000mg per day, so increasing the dose above this is illogical. Furthermore the studies were too short (two months) and had too few participants to draw reliable conclusions.

Although the Turbuhaler mechanism is more convenient, a concern was expressed by the assessor about patients getting less steroid than they needed when deteriorations in their asthma led to lower inspiratory flow rates than

required to activate a Turbuhaler. Also, humid weather or breathing on the device may cause the powder to clump.

Claim 4: [The pharmaceutical company] reports that 600 GPs (20 per cent) prescribed montelukast in the first two weeks it came on the market.

This claim has no scientific component, it is purely 'social pressure'. It capitalises on doctors' time constraints in not being able to adequately read and appraise journal articles for themselves. An impression that many of our colleagues are using a product, makes it more likely that we ourselves will use it too.

Claim 5: [T]he idea behind the free month's supply of montelukast is to let patients 'try before they buy'. Auckland GP [Dr X] prescribed the drug for about 20 patients and takes it himself. 'It's fast acting – you notice in a day or two. If its useless, you risk nothing, it's a generous offer from the company. One woman can barely afford it but her asthma was so bad, and the drug made such a dramatic improvement, now she's paying for it.'

When patients do well on free samples of a drug, the tendency is to believe that it was necessarily the drug which led to the improvement. This is called the *post hoc ergo propter hoc* (after that, therefore because of that) fallacy. Asthma is not a static condition, and variations in control are dependent on many factors – including something as mundane as the weather. A patient who is improving anyway and takes the free sample will most likely attribute the improvement to the new drug. The woman mentioned by Dr X above may well have achieved better asthma control with oral prednisolone followed by inhaled beclomethasone, than with montelukast. The available evidence is that inhaled beclomethasone (200µg bd) is more effective than montelukast (10 mg daily). How well montelukast compares with inhaled steroids in the long term for preventing adverse events, including deaths, was not known at the time of the assessment.

Claim 6: Less exacerbations (with salmeterol).

Note the appearance of the hanging comparator again: 'less'. We are left to wonder, 'less than what?' A meta-analysis of trials of salmeterol vs increasing the dose of inhaled steroid found no significant difference in exacerbation rates during the first 6 months. (The reference in the advert was to a trial which compared salmeterol to salbutamol and to placebo.) It is possible that preventable deaths could occur by changing the $ß_2$-agonist, when in fact the patient should be receiving an inhaled steroid.

Claim 7: A proven reduction in exacerbation rates (with eformoterol).
Here we have a variation in wording of the hanging comparator: 'a reduction in'. We are not told with what therapeutic option the reduction is compared. In consulting the study quoted it turns out to have been compared to placebo! The same study showed that a low dose inhaled steroid combined with eformoterol was significantly less effective than the same inhaled steroid at a higher dose.

Claim 8: When inhaled long-acting $ß_2$-agonists are out of the question, just add bambuterol.

At the time of the survey, no evidence to support the use of bambuterol could be found. (No indication that this drug is registered in South Africa could be found.)

The study authors conclude that **in every case** the claims are misleading because of failure to disclose problems. (my emphasis). The promotional (advertising) techniques included:

- hanging comparators
- exaggeration
- claims made on the basis of personal data collection (via an 0800 telephone line)
- flawed studies
- social pressure
- use of the word 'new'
- 'free' samples
- *post hoc ergo propter hoc*

The findings in terms of the scientific validity of the claims in Table 1 are summarised in Table 2.

Table 2: Conclusions of second opinions in selected asthma advertisements

Claim 1	Fluticasone efficacy is not superior to beclomethasone via spacer.
Claim 2	Adrenal suppression may be equal or worse with fluticasone than with beclomethasone via spacer.
Claim 3	Turbuhaler (delivering budesonide) is not superior to beclomethasone via spacer. It is more convenient but may be less reliable.
Claim 4	This claim has no scientific merit.
Claim 5	Montelukast is faster (in onset) but less effective than steroids.
Claim 6	Adding salmeterol rather than increasing steroids has not been shown to lead to fewer minor exacerbations, but may lead to more severe exacerbations.
Claim 7	Adding eformoterol rather than increasing steroids has not been shown to lead to fewer minor exacerbations, but may lead to more severe exacerbations.
Claim 8	Evidence to support the use of bambuterol could not be located.

I quote Dr Mansfield's results section from his poster presentation in full.[2]

More frequent and/or intense exposure to promotion correlates with increased prescribing volumes and more expensive and less appropriate prescribing.

Promotion may mislead by use of false statements, omission, fine print, poor quality evidence, "red herring" surrogate endpoints, statements of relative risk, ambiguity or widened indications. The methods of influence used by "drug reps" include gifts, appeals to authority, social validation, commitment consistency and liking. Advertisements link drugs with images that appeal to desires, and then repetition takes those links to the top of the mental agenda.

In considering selected asthma advertisements (excluding 'advertorials') in the four editions of Volume 7 (2001) of the *South African Respiratory Journal*, the following examples were located. The original references were not obtained (as in the New Zealand survey), so the comments are based only on the text of the advertisements, and the titles of the references.

1. Salmeterol and fluticasone propionate in a fixed combination '*provides sustained bronchodilation and controls inflammation*'. The title of the single reference: 'Salmeterol/fluticasone propionate combination therapy 50/250µg twice daily is more effective than budesonide 800µg twice daily in treating moderate to severe asthma.' From the title alone, it is clear that this study is flawed. One would have expected the addition of a bronchodilator to the budesonide arm of the trial.
2. The final edition of 2001 has a variation in the above advert. It includes two additional references, and the text is changed to *Superior asthma control in one from day one*. Note the appearance of the hanging comparator ('superior') once more. We are not told what it is superior to – but the title of the first article gives us a clue: 'Salmeterol and fluticasone propionate combined in a new powder inhalation device for the treatment of asthma. A randomised, double-blind, placebo-controlled trial.' Does this mean that the combination has simply been shown to be superior to placebo? Or was it a trial mainly testing the delivery method?
   The title of the third reference reads: 'Fluticasone proponiate/salmeterol combination provides more effective asthma control than low-dose inhaled corticosteroid plus montelukast.' One would have to read the original article to determine whether or not the combination of low-dose inhaled corticosteroid plus montelukast is a logical comparator, and what dosages were used, etc. However as montelukast is primarily an anti-inflammatory agent rather than a bronchodilator, the comparison does seem somewhat dubious.
3. Formoterol *reduces the incidence of severe exacerbations by 63% when added to 400µg bd budesonide*. This is yet another version of the hanging comparator. The title of the reference: 'Effect of inhaled formoterol and budesonide on exacerbations of asthma' does not help clarify where the 63% reduction comes from. Is this based on the patients' own past history of severe exacerbations, or compared to the use of budesonide alone? The text of the advertisement and the title of the article are not consistent with each other.
4. Formoterol *a potent bronchodilator provides greater broncho relaxation than salmeterol a partial agonist*. The reference number has an asterisk; and below the list of claims, in small print, the asterisk refers to: '*In vitro* data'. The title of the article confirms that guinea-pig trachea and human bronchus have been tested *in vitro*. The pictures accompanying the advertisement, incongruously however, are of highly trained athletes. The use of *in vitro* or animal studies in advertising is one of several types of 'Poor Quality Evidence' listed by Mansfield.[2]
5. The fluticasone advertisement in all four editions appears to have avoided the errors of its New Zealand counterpart. However, it would require careful reading of the actual references to confirm this. It was notably the only advertisement amongst those selected to contain a reference from a South African journal.

An article by a former drug company employee is revealing. Twenty-three different strategies for increasing prescriptions of drugs are listed. This article can be found on the healthyskepticism.org website at <http://www.healthyskepticism.org/editions/IN9903.htm>. The names of the employee and the company have been omitted. Only the first of these strategies called 'profiling' is included here.

Doctor profiles

The author indicates that pharmaceutical companies profile doctors in several ways. When that friendly 'drug rep' visits, s/he is not only presenting information, but gathering information which remains with the company even if the 'rep' leaves. The author states: 'Doctors' profiles will contain minutiae, from the names of their family members to their golf-handicap, to the foods they like or dislike, to the clothes that they wear!' Furthermore, doctors are classified into various personality types. The system this particular writer refers to is the 'eagle-owl-dove-peacock' classification. 'Eagle' doctors are egotistical and domineering; 'owl' doctors want information and are very analytical; 'dove' doctors are the friendly sort who get on well with everyone; and 'peacock' doctors are social butterflies/extroverts.

Dr Mansfield uses a different classification of doctors (Table 3) in the poster referred to previously.[2] I'm sure South African companies have their own indigenous classifications. Which Australian category do you think you would fall into? It might be illuminating to ask a medical representative what kind of 'animal' they think you are!

Table 3: Personality types of doctors as classified by some pharmaceutical companies

Species	Description	Concerned about:
Sheep	conservatives	maintaining conformity
Wolves	entrepreneurs	making money
Bunnies	progressives	caring for patients
Dodos	burned out	survival

Several years ago, Prof Bruce Sparks wrote an article in similar vein describing Medical Representatives from a family physician's perspective. This article is still used by certain South African drug companies in the training of their representatives.

Not only is data collected about our personality types, but more insidiously, also our prescribing preferences in terms of different products. We may then be classified as A,B or C prescribers of that company's products. For example, 'A' doctors are high volume prescribers; while 'C' doctors are those not worth targeting. Ever wondered why some of your colleagues end up being pampered by a particular company while you are not? The A,B,C classification is based on the principal that 80% of the market for a product comes from 20% of prescribers. Those classified as 'A' need to be kept on this level and so are targeted by the representatives to attend meetings etc. The 'B' group are those targeted with a view to converting them to 'A' types.

Conclusion:

This article has focused on the use of words and the scientific 'endorsement' of advertisements. The use of pictures and other mechanisms of attracting doctors' attention have not been considered – although they are probably even more powerful and have more impact on the average doctor than the text and references.

References:

1. Medical Lobby for Appropriate Marketing (MaLAM). A Second opinion on Drug Promotion for Doctors in NZ. Healthy Scepticism NZ. September/October 2001 Vol 19 No 9/10. <http://www.healthyskepticism.org/editions/IN0112.htm> [accessed 28/04/2002]

2. Mansfield P. How does pharmaceutical company promotion affect prescribing? International Conference on Improving Use of Medicines (ICIUM), Thailand. Poster presentation, April 1997.