Evaluating promotional material from industry: an evidence-based approach

In this article, the authors illustrate how the principles of information mastery, described in a previous article (PJ, 5 February, p148), may be used to evaluate promotional material produced by the pharmaceutical industry.

Medicines are big business. The NHS currently spends around £10bn a year on pharmaceuticals, equating to roughly £30m a day.¹ This expenditure is increasing both in the UK and throughout the world. Although a lot of resources are invested in research and development, the pharmaceutical industry spends far more on marketing and administration of its products (on average around 35 per cent of sales) than on trying to discover new ones.²

To put this into context, figures from the US make interesting reading. For example, in 2000, Merck spent $161m advertising Vioxx (rofecoxib). This was more than PepsiCo spent advertising Pepsi ($125m) and Anheuser-Busch spent advertising Budweiser ($146m) in the same period.³

The pharmaceutical industry employs various strategies to interact with health professionals. The method health professionals are most familiar with is face-to-face visits from pharmaceutical sales representatives. Many less direct methods of drug promotion are also used, such as direct mailing, advertising in medical journals and newspapers, and sponsorship of medical conferences and products. For a smaller proportion of health professionals, interaction with the industry may occur through involvement in clinical trials or advisory groups.

A more subtle form of drug promotion is raising public awareness of a disease through campaigns in the general media or through support of self-help groups (disease-awareness campaigns).⁴ These are often sponsored by a pharmaceutical company that markets (or is about to launch) a product available to treat the particular condition. Although companies are not being asked to advertise a prescription only medicine (POM) direct to the public in the UK, public awareness campaigns serve to encourage both existing and potential patients to seek these new treatments. An excellent recent example of this was given in the BMJ concerning the use of a testosterone patch for female sexual dysfunction.⁵ In particular, the subtlety involved in this approach should be noted and is neatly summarised by the comment that “...then it won’t be seen as the company pushing its product, it will be seen as health education”.

Do not believe all you read and hear

Although much of the promotional information health care professionals receive from the industry is based on good evidence, this is not always the case. A study reviewed all advertisements for antihypertensives and lipid-lowering drugs published in six Spanish medical journals in 1997.⁶ Of 125 references cited to support advertisements, the authors of the study were unable to retrieve 23 of the references from monographic works and non-published “data on file”. In 45 claims, the promotional statement was not supported by the reference, most frequently because the advertising slogan recommended the drug in a patient group other than that assessed in the cited study.

Furthermore, an analysis of the accuracy of information provided by pharmaceutical representatives found that one in 10 statements — all of which favoured their product — were at odds with their company’s own literature.⁷ Importantly, only one in four health professionals was aware that the information provided by the drug representative was incorrect.

Pharmaceutical representatives are effective at delivering key messages

In our previous article (PJ, 5 February, p148), readers were introduced to the “usefulness equation” as a way of evaluating medical information.⁸

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\text{Usefulness} = \frac{\text{relevance} \times \text{validity}}{\text{time to locate and interpret information}}
\]

When the usefulness equation is applied to information provided by pharmaceutical representatives, work (the time needed to locate and interpret the information) is low, since the representative usually delivers the information direct to the health professional, often accompanied by food and other goodies (pens, pads, etc). However, as demonstrated by the earlier evidence, the relevance and validity of the information often remains uncertain. Some commonly misused shortcuts for choosing therapies are shown in Panel 1.
In order to determine the relevance and validity of promotional material, a number of factors need to be considered. A selection of the most important and commonly seen factors are discussed below. Further sources of information are given at the end of this article.

What sort of evidence is available?

Many claims made by the pharmaceutical industry, particularly for new drugs, are based on the results of trials that use surrogate endpoints and give rise to disease-oriented evidence (DOE). Surrogate endpoints are variables that are relatively easily measured in trials and are used to predict a rare or distant outcome of a therapeutic intervention, but in themselves are not a direct measure of either harm or clinical benefit. Surrogate endpoints are commonly used in trials because the size, duration in practice, therefore, cost of the trial can be reduced.

For example, claims may be made that an antibiotic provides “better penetration into sputum” or the latest antihypertensive gives “better 24-hour blood pressure control”. Although these factors may be of interest, to base or change clinical practice on the basis of DOE is inappropriate and may even be dangerous (PJ, 5 February, p148). It often requires a leap of faith to assume that these surrogate markers of efficacy will translate into actual clinical benefits for the patient when the drug is used in practice.

Results from research studies that health professionals (and their patients) should care about are those that measure outcomes that produce tangible benefits to patients and so give rise to patient-oriented evidence that matters (POEMs), eg, whether a patient lives longer, suffers less pain or has an improved quality of life as a result of taking the drug.

Consider the marketing of cyclo-oxygenase-2 inhibitors: much of the early advertising of these drugs focused on the finding that, compared with traditional non-steroidal anti-inflammatory drugs, these drugs caused fewer ulcers as detected via an endoscopy. This is disease-oriented evidence (DOE) since these ulcers do not consistently translate into pain or more serious ulcers, and are not indicators of true harm, such as a perforation, symptomatic ulcer or a bleed (any of which would be POEM). Indeed, once such evidence was published, close scrutiny of the two major trials for drugs in this class — rofecoxib (VIGOR) and celecoxib (CLASS) — showed these drugs produced an increased risk of serious adverse effects compared with traditional NSAIDs (a 1.5 per cent and 1.0 per cent absolute risk increase, respectively) — a factor which was not always apparent from reviews of these interventions or in their promotional materials.

Does trial population reflect real life?

Patients included in clinical trials are often carefully selected, do not have co-morbidities and their characteristics may not reflect the “typical” patient who will ultimately use the drug in real life.

For example, a study from Canada analysed the characteristics of patients enrolled into trials of NSAIDs and found that only 2.1 per cent of subjects recruited were aged 65 years or more, despite NSAIDs being much more commonly used in the elderly in practice.12 It is also extremely important to have evidence of the use of these agents in the elderly since they are more likely to experience an adverse effect compared with a younger, fitter population. Another example to remember is that of antidepressants, where studies are often performed in highly selected hospital-based populations. The applicability of these data to patients seen in primary care is, therefore, questionable.

Choice of comparator drug and dose?

The choice of drug used for comparison or the dose can influence the likely outcome of a clinical trial. Researchers may use a comparator drug that is not generally regarded as the standard therapy for a given condition or choose a suboptimal dose of the comparator drug.

For example, in the two largest studies of meloxicam,14,15 a relatively low dose of meloxicam (7.5 mg daily) was used and one of the studies used piroxicam as the comparator agent.16 Piroxicam is widely considered to be one of the NSAIDs with a greater tendency to cause gastrointestinal toxicity.17 This has the effect of minimising the risk of side effects from meloxicam (by using a relatively low dose) but potentially maximising the harms seen in the comparator arm (by using one of the more GI-toxic NSAIDs). In short, one can question whether such studies are making a fair comparison.

Relative risk vs absolute risk reduction?

Relative risk reductions always sound more impressive than absolute risk reductions and are therefore more attractive, particularly when describing the benefits of a product. Many practitioners are confused by these terms and it may be best explained in terms of buying a lottery ticket. The chance (“absolute risk”) of winning the lottery jackpot by buying one ticket is about 1 in 14 million. By buying two lottery tickets, the chances (relative risk) of winning the jackpot are doubled (ie, increased by 100 per cent) but the absolute risk of winning is only slightly higher at 2 in 14 million (or 1 in 7 million). Hence, even by doubling the relative risk, the absolute risk is still extremely small for rare events — like winning the lottery jackpot.

An example of how the results of studies are sometimes miscommunicated to others is provided by the CURE (Clopidogrel in Unstable Angina to Prevent Recurrent Events) study.18 This study received much publicity when first published and had a website dedicated to the findings (www.thecurestudy.com) containing a PowerPoint presentation available for health care professionals to download.

The results suggested that taking clopidogrel in combination with aspirin reduced the risk of having subsequent cardiovascular events compared with aspirin used alone. This was consistently reported as equivalent to a 20 per cent relative risk reduction without reference to the absolute risk reduction produced (actually a 2.1 per cent absolute risk reduction).19

The harms associated with the combination of clopidogrel with aspirin were also highlighted in the results but were reported as showing a 1 per cent increase in serious bleeds in those taking the combination. This is of course the absolute risk increase — the relative risk increase in bleeds was 38 per cent, but was not communicated in the findings in this way. This makes interpretation of the clinical significance of the risks and benefits of this intervention difficult without an appreciation of the differences between relative and absolute risk. We are not suggesting that this was an attempt at duplicity on the part of the manufacturers, but it shows how results of studies may be presented in an accurate way while the implications of such results may be misleading to the unwary.

One method often used to try to convey a balanced report of the harms and benefits of an intervention is the number needed to treat (NNT) or the number needed to harm (NNH). Here, the absolute risk differences between the intervention and the control groups are used to estimate the number of people that need to be treated with an intervention to prevent (or cause) an event. In the CURE study for example, the NNT to prevent one cardiovascular event was about 50, while the NNH to cause a major bleed was 100. Put another way, if 100 people similar to those in the study were to receive clopidogrel plus aspirin rather than aspirin alone, two of them would have a cardiovascular event prevented while one would have a major bleed caused. The website www.nntonline.net gives an excellent explanation of how this tool can be used to communicate the results of trials to others effectively, including patients.

Statistical vs clinical significance?

Statistical significance and clinical significance do not necessarily mean the same thing, and caution is required when promotional material states the results of a study are “significant”. Statistical significance simply means that the results were unlikely to have occurred by chance. Whether a statistically significant intervention is deemed clinically significant will depend on the size of the effect being measured and whether it provides any meaningful benefit to the patient. It is also determined by whether the intervention is warranted or justified in routine practice.

For example, a Cochrane review into the use of antibiotics to treat sore throat found that those taking antibiotics endured symp-
Other factors to consider

Health professionals should be aware of the potential for publication bias. For a number of reasons, studies showing positive differences between interventions are more likely to be published than those showing no difference or inferiority of the study drug. Furthermore, studies with positive findings can sometimes lead to multiple publications, particularly in multicentre trials.

These factors can lead to problems where a meta-analysis is performed (where data from small similar studies are combined to increase the “power” of the study so that stronger conclusions may be drawn). Where positive publication bias exists, results from the trials showing a positive result are more likely to be included, or one set of study participants may be included in the analysis twice. This may lead to an overestimation of treatment effects. The latter was seen in a meta-analysis of trials of ondansetron for prevention and treatment of postoperative nausea and vomiting.

It should also be remembered that clinical trials are not like real life since patients in trials are generally more likely to be motivated to remember to take their medicines and are usually more intensively monitored than they are in routine clinical practice. These factors require consideration because trial results may exaggerate the benefits of an intervention that is simply not realistic or achievable for the majority of patients when incorporated into their busy daily lives.

Of course there are many other considerations to take into account when appraising clinical trials. Sources of further information are given at the end of this article.

STEPS

So how can we attempt to walk through this minefield? Use STEPS. The STEPS acronym gives five simple and valid reasons for consideration when deciding the benefits and harms of one drug over another:

Safety If possible, determine safety from real-life comparison studies since these will better reflect the patient population that will ultimately use the drug. Specifically, check for adverse effects that would place patients at significant risk, eg, cardiovascular events, liver and renal toxicity, seizures and bone marrow suppression.

Tolerability Tolerability will question whether the drug produces effects that will affect compliance. A more reliable indicator than trying to compare lists of side effects is to compare dropout rates from clinical trials.

Effectiveness Effectiveness is basically determined by asking the question: “Does the drug work in the real world?” To help answer this question, one should look for head-to-head trials that compare the new drug with the current standard therapy used at a dose that is known to be effective. (Note: comparing the relative response rates or the incidence of adverse effects of two drugs using data from different trials may not give valid comparisons if the populations studied were different.)

Price Include all costs when making a comparison between a new drug and alternative therapy. This may include the costs of additional visits to titrate doses or maybe the cost of biochemical tests to monitor therapy.

Simplicity of use Think of the patient. Factors that may be important in the simplicity of use include the availability of the drug as a liquid formulation, the frequency of administration (since compliance with drugs taken once a day is generally better than for those requiring administration four times a day), or the ease of use of a delivery device.

The practical application of these five criteria can be seen in Panel 2.

How do we relate this to patient care?

A similar set of criteria to consider when making a prescribing decision was defined by Nick Barber in 1995 in the BMJ.\(^{21}\)

- Effectiveness
- Safety
- Cost
- Patient factors

Although this framework is only rarely used consciously, every single clinical decision that is ever taken is a balance between four factors, which have their roots in medical ethics — beneficence, non-maleficence, justice and patient autonomy.

It is not enough merely to understand the likely relative risks and benefits in a given population. Health care professionals must be skilled in relating and communicating this to a patient in terms they can understand. This also requires an appreciation of the fact that patients or fellow health professionals may not share the same values as you do — some may be particularly risk averse, while others may accept a much higher degree of risk set against another potential benefit. Only then are we likely to be able to allow patients to reach informed decisions about their treatment plans.

Final thoughts . . .

By focusing on the points above and applying STEPS, health professionals have a simple and objective method to review quickly the quality of information provided by the pharmaceutical industry. When used in combination with an effective method of finding valid and relevant information, as discussed in our previous article (PF, 5 February, p148) health professionals will be better placed to make an informed judgement regarding advertising claims. Health professionals should insist on having sufficient information to substantiate any claims made about products. For example, where the benefits of a new drug appear to be based on data derived from studies using surrogate endpoints, health professionals may wish to request further patient-oriented evidence to justify these claims.

The pharmaceutical industry can undoubtedly be extremely helpful in highlighting and providing new and important information to health professionals. However, by adopting these simple techniques, health professionals will be able to integrate their expertise with the wishes of their patients and the best available evidence, and so always ensure that they get the most from their interactions with the pharmaceutical industry — while also effectively managing their information load.
DECLARATION OF INTEREST Jonathan Underhill is involved in the organisation of two information mastery conferences being run by the NPC in conjunction with the founders of information mastery and POEMS. Scott Pegler is the distributor for InfoPOEM Inc in the UK and Ireland.

References

Useful resources
- No Free Lunch. www.nofreelunch-uk.org
- National Electronic Library for Health (NeLH) gives access to Cochrane, Clinical Evidence, MeReC, Drug and Therapeutics Bulletin, Bandolier, etc. www.nelh.nhs.uk
- An Introduction to Information Mastery. www.poems.msu.edu/infomastery
- InfoPOEMS. www.infopeoms.com
- National Prescribing Centre. www.npc.nhs.uk
- Clinical Evidence. www.clinicalevidence.org
- Effective Health Care Bulletin. www.york.ac.uk/inst/crd
- Cochrane Collaboration. www.cochrane.co.uk
- National Institute for Clinical Excellence. www.nice.org.uk
- United Kingdom Medicines Information. www.ukmi.nhs.uk
- Centre for Evidence Based Medicine. www.cebm.net