prevention programmes are based. The model presented here suggests that the driving force for the increasing prevalence of obesity in populations is the increasingly obesogenic environment rather than any "pathology" in metabolic defects or genetic mutations within individuals. A paradigm shift to understanding obesity as "normal physiology within a pathological environment" signposts the directions for a wider public health approach to the obesity pandemic.

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How to read a paper

Papers that report drug trials

Trisha Greenhalgh

This is the sixth in a series of 10 articles introducing non-experts to finding medical articles and assessing their value

Unit for Evidence-Based Practice and Policy, Department of Primary Care and Population Sciences, University College London Medical School/ Royal Free Hospital School of Medicine, Whittington Hospital, London N19 5NF

Trisha Greenhalgh, *senior lecturer*

p.greenhalgh@ucl.ac.uk

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"Evidence" and marketing

If you prescribe drugs, the pharmaceutical industry is interested in you and is investing a staggering sum of money trying to influence you. The most effective way of changing the prescribing habits of a clinician is through personal representatives (known in Britain as "drug reps" and in North America as "detailers"), who travel round with a briefcase full of "evidence" in support of their wares.[1]

Pharmaceutical "reps" do not tell nearly as many lies as they used to (drug marketing has become an altogether more sophisticated science), but they have been known to cultivate a shocking ignorance of basic epidemiology and clinical trial design when it suits them.[2] It often helps their case, for example, to present the results of uncontrolled trials and express them in terms of before and after differences in a particular outcome measure.[3] The recent correspondence in the *Lancet* and *BMJ* on placebo effects should remind you why uncontrolled before and after studies are the stuff of teenage magazines, not hard science.[4-12]

Summary points

Pharmaceutical "reps" are now much more informative than they used to be, but they may show ignorance of basic epidemiology and clinical trial design

The value of a drug should be expressed in terms of safety, tolerability, efficacy, and price

The efficacy of a drug should ideally be measured in terms of clinical end points that are relevant to patients; if surrogate end points are used they should be valid

Promotional literature of low scientific validity (such as uncontrolled before and after trials) should not be allowed to influence practice

Making decisions about treatment

Sackett and colleagues have argued that before giving a drug to a patient the doctor should:

- identify, for this patient, the ultimate objective of treatment (cure, prevention of recurrence, limitation of functional disability, prevention of later complications, reassurance, palliation, relief of symptoms, etc);

- select the most appropriate treatment, using all available evidence (this includes considering whether the patient needs to take any drug at all); and
- specify the treatment target (to know when to stop treatment, change its intensity, or switch to some other treatment).[13]

For example, in treating high blood pressure, the doctor might decide that:

- the ultimate objective of treatment is to prevent (further) target organ damage to brain, eye, heart, kidney, etc (and thereby prevent death);
- the choice of specific treatment is between the various classes of antihypertensive drug selected on the basis of randomised, placebo controlled and comparative trials—as well as non-drug treatments such as salt restriction; and
- the treatment target might be a phase V diastolic blood pressure (right arm, sitting) of less than 90 mm Hg, or as close to that as tolerable in the face of drug side effects.

If these three steps are not followed (as is often the case—for example in terminal care), therapeutic chaos can result.

Surrogate end points

A surrogate end point may be defined as a variable which is relatively easily measured and which predicts a rare or distant outcome of either a toxic stimulus (such as a pollutant) or a therapeutic intervention (a drug, surgical procedure, piece of advice, etc) but which is not itself a direct measure of either harm or clinical benefit. The growing interest in surrogate end points in medical research, and particularly by the pharmaceutical industry, reflects two important features of their use:

- they can considerably reduce the sample size, duration, and, therefore, cost, of clinical trials; and
- they can allow treatments to be assessed in situations where the use of primary outcomes would be excessively invasive or unethical.

In the evaluation of pharmaceutical products, commonly used surrogate end points include:

- pharmacokinetic measurements (for example, concentration-time curves of a drug or its active metabolite in the bloodstream);
- in vitro (laboratory) measures such as the mean inhibitory concentration of an antimicrobial against a bacterial culture on agar;
- macroscopic appearance of tissues (for example, gastric erosion seen at endoscopy);
- change in levels of (alleged) serum markers of disease (for example, prostate specific antigen[14]);
- radiological appearance (for example, shadowing on a chest *x* ray film).

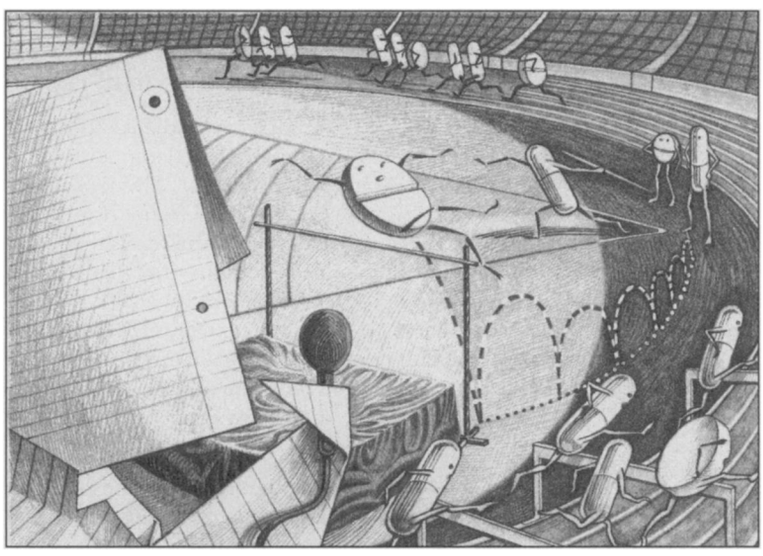
But surrogate end points have some drawbacks. Firstly, a change in the surrogate end point does not itself answer the essential preliminary questions: "what is the objective of treatment in this patient?" and "what, according to valid and reliable research studies, is the best available treatment for this condition?" Secondly, the surrogate end point may not closely reflect the treatment target—in other words, it may not be valid or reliable. Thirdly, overreliance on a single surrogate end point as a measure of therapeutic success usually reflects a narrow clinical perspective. Finally, surrogate end points are often developed in animal models of disease, since changes in a specific variable can be measured under controlled conditions in a well defined population. However, extrapolation of these findings to human disease is likely to be invalid.[15-17]

Features of the ideal surrogate end point

- The surrogate end point should be reliable, reproducible, clinically available, easily quantifiable, affordable, and show a "dose-response" effect (the higher the level of the surrogate end point, the greater the probability of disease)
- It should be a true predictor of disease (or risk of disease) and not merely express exposure to a covariable. The relation between the surrogate end point and the disease should have a biologically plausible explanation
- It should be sensitive—a "positive" result in the surrogate end point should pick up all or most patients at increased risk of adverse outcome
- It should be specific—a "negative" result should exclude all or most of those without increased risk of adverse outcome
- There should be a precise cut off between normal and abnormal values
- It should have an acceptable positive predictive value—a "positive" result should always or usually mean that the patient thus identified is at increased risk of adverse outcome
- It should have an acceptable negative predictive value—a "negative" result should always or usually mean that the patient thus identified is not at increased risk of adverse outcome
- It should be amenable to quality control monitoring
- Changes in the surrogate end point should rapidly and accurately reflect the response to treatment. In particular, levels should normalise in states of remission or cure

The features of an ideal surrogate end point are shown in the box. If the "rep" who is trying to persuade you of the value of the drug cannot justify the end points used, you should challenge him or her to produce additional evidence.

One important example of the invalid use of a surrogate end point is the CD4 cell count in monitoring progression to AIDS in HIV positive subjects. The CONCORDE trial was a randomised controlled trial



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comparing early and late start of treatment with zidovudine in patients who were HIV positive but clinically asymptomatic.[18] Previous studies had shown that starting treatment early led to a slower decline in the CD4 cell count (a variable which had been shown to fall with the progression of AIDS), and it was assumed that a higher CD4 cell count would reflect improved chances of survival.

However, the CONCORDE trial showed that, although CD4 cell counts fell more slowly in the treatment group, the three year survival rates were identical in the two groups. This experience confirmed a warning that was issued earlier by authors suspicious of the validity of this end point.[19] Subsequent research in this field has attempted to identify a surrogate end point that correlates with real therapeutic benefit—that is, delayed progression of asymptomatic HIV infection to clinical AIDS, and longer survival time after the onset of AIDS.[20 21] Using multiple regression analysis, investigators in the USA found that a combination of markers (percentage of CD4:C29 cells, degree of fatigue, age, and haemoglobin concentration) was the best predictor of progression.[20]

Other examples of surrogate end points which have seriously misled researchers include ventricular premature beats as a predictor of death from serious cardiac arrhythmias,[22 23] blood concentrations of antibiotics as a predictor of clinical cure of infection,[24] and plaques seen on magnetic resonance imaging in monitoring the progression of multiple sclerosis.[25]

Before surrogate end points can be used in the marketing of pharmaceuticals, those in the industry must justify the utility of these measures by showing a plausible and consistent link between the end point and the development or progression of disease. It would be wrong to suggest that the pharmaceutical industry develops surrogate end points with the deliberate intention to mislead the licensing authorities and health professionals. However, the industry does, theoretically, have a vested interest in overstating its case on the significance of these end points. Given that much of the data relating to the validation of surrogate end points are not currently presented in published clinical papers, and that the development of such markers is often a lengthy and expensive process, one author has suggested setting up a data archive that would pool data across studies.[26]

How to get evidence out of a drug rep

Any doctor who has ever given an audience to a "rep" who is selling a non-steroidal anti-inflammatory drug will recognise the argument that "this NSAID reduces the incidence of gastric erosion in comparison to its competitors." The question to ask the rep is not "what is the incidence of endoscopic signs of gastric erosion in volunteers who take this drug?" but "what is the incidence in clinical practice of potentially life threatening gastric bleeding in patients who take this drug?" Other questions, collated from recommendations in *Drug and Therapeutics Bulletin*[27] and other sources,[1 3] are listed below.

- See representatives only by appointment. Choose to see only those whose product interests you, and confine the interview to that product
- Take charge of the interview. Do not hear out a rehearsed sales routine but ask directly for the information below
- Request independent published evidence from reputable, peer reviewed journals
- Do not look at promotional brochures, which may contain unpublished material, misleading graphs, and selective quotations
- Ignore anecdotal "evidence," such as the fact that a medical celebrity is prescribing the product
- Using the STEP acronym, ask for evidence in four specific areas:
  - *Safety*—the likelihood of long term or serious side effects caused by the drug (remember that rare but serious adverse reactions to new drugs may be poorly documented)
  - *Tolerability*—best measured by comparing the pooled withdrawal rates between the drug and its most significant competitor
  - *Efficacy*—the most relevant dimension is how the product compares with your current favourite
  - *Price*—should take into account indirect as well as direct costs
- Evaluate the evidence stringently, paying particular attention to the power (sample size) and methodological quality of clinical trials, and the use of surrogate end points. Do not accept theoretical arguments in the drug's favour ("longer half life," for example) without direct evidence that this translates into clinical benefit

Checklist for evaluating information provided by a drug company

- Does this material cover a subject which interests me and is clinically important in my practice?
- Has this material been published in independent peer reviewed journals? Has any significant evidence been omitted from this presentation or withheld from publication?
- Does the material include high-level evidence such as systematic reviews, meta-analyses, or double-blind randomised controlled trials against the drug's closest competitor given at optimal dosage?
- Have the trials or reviews addressed a clearly focused, important and answerable clinical question which reflects a problem of relevance to patients? Do they provide evidence on safety, tolerability, efficacy and price?
- Has each trial or meta-analysis defined the condition to be treated, the patients to be included, the interventions to be compared and the outcomes to be examined?
- Does the material provide direct evidence that the drug will help my patients live a longer, healthier, more productive, and symptom-free life?
- If a surrogate outcome measure has been used, what is the evidence that it is reliable, reproducible, sensitive, specific, a true predictor of disease, and rapidly reflects the response to therapy?
- Do trial results indicate whether (and how) the effectiveness of the treatments differed and whether there was a difference in the type or frequency of adverse reactions? Are the results expressed in terms of numbers needed to treat, and are they clinically as well as statistically significant?
- If large amounts of material have been provided by the representative, which three papers provide the strongest evidence for the company's claims?

- Do not accept the newness of a product as an argument for changing to it. Indeed, there are good scientific arguments for doing the opposite[28]
- Decline to try the product via starter packs or by participating in small scale, uncontrolled "research" studies
- Record in writing the content of the interview and return to these notes if the "rep" requests another audience

In conclusion, it is often more difficult than you are being led to believe to weigh the potential benefits of a drug against its risks to the patient and cost to the taxpayer.[29] The difference between the science of critical appraisal and the pharmaceutical industry's well rehearsed tactics of marketing and persuasion should be borne in mind when you are considering "evidence" presented by those with a commercial conflict of interest.

I am grateful to Dr Andrew Herxheimer for advice on this article.

The articles in this series are excerpts from *How to Read a Paper: the Basics of Evidence Based Medicine.* The book includes chapters on searching the literature and implementing evidence based findings. It can be ordered from the BMJ Publishing Group: tel 0171 383 6185/6245; fax 0171 383 6662. Price £13.95 for UK members, £14.95 for non-members.

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When I use a word...
Buyers and sellers

These articles about words elicit an interesting postbag. I have recently been asked by F J Langfield of Frenchay in Bristol if I can remind him of the word for the inverse of a monopoly. A monopoly is defined in the *Oxford English Dictionary* as "the condition of having no competitor in the sale of some commodity or in the exercise of some trade or business." What then do you call the condition in which you have no competitor in the *purchase* of some commodity?

Well monopoly comes from two Greek words, μόνος (monos) single and πωλέω (poleo) I sell—monopoly, one seller. So what we want is a word meaning one buyer. Attic Greek had more than one word meaning I buy, but the relevant one is ὀψωνέω (opsoneo), and the word we want is monopsony.

Monopsony was first coined in the 1930s, but in contrast to monopoly it is used almost exclusively by economists. For instance, in an article entitled "How to Pay for the National Health Service" (*Roy Soc Health J* 1971;91:217-21) Michael H Cooper, a social economist, defined a monopsony as "a consumer so large that it can exert pressure on price merely by the threat of withdrawing its custom." One familiar instance is the government as a purchaser of healthcare. Other current or past examples of monopsonies, or at least oligopsonies, include the diamond trade, dominated by de Beers as both buyer and seller, the tobacco industry, and academic specialist book publication.

Opsonins are substances that combine with bacteria or other foreign cells, making them more susceptible to phagocytosis. To understand the genesis of the term opsonins (which we now call members of the complement group), we must explore the origins of ὀψωνέω more closely. It originally meant to buy ὄψον (opson), cooked meat or fish, non-staple food as opposed to bread, consequently anything eaten with bread to give it flavour, and hence seasoning or sauce. So, as Shaw put it in the preface to his play *The Doctor's Dilemma* (1906), "the white corpuscles or phagocytes which attack and devour disease germs for us do their work only when we butter the disease germs appetisingly for them with a natural sauce which Sir Almroth [Wright] named opsonin [in *Proc Roy Soc* 1903;72:366]." According to Wright's alter ego in the play, Sir Colenso Ridgeon, "To inject a vaccine into a patient without first testing his opsonin is as near murder as a respectable practitioner can get." An opinion on which he seems to have had a monopoly.

Jeff Aronson, *clinical pharmacologist, Oxford*

We welcome filler articles up to 600 words on topics such as *A memorable patient, A paper that changed my practice, My most unfortunate mistake,* or any other piece conveying instruction, pathos, or humour. If possible the article should be supplied on a disk.