

## If it doesn't work, stop it

### "Ineffective" treatments might be in a patient's best interests

EDITOR—To have a themed issue (28 February) on negative trial results was innovative but risks returning to a dichotomous view of outcomes that should have been abandoned with hypothesis testing. Even means and confidence intervals ignore the wide range of responses likely to be experienced by individual patients.

Much of this variation probably represents measurement error or intraindividual variability, but some will be due to true heterogeneity in response. Given a symmetrical distribution of outcomes, 50% of patients will benefit from a treatment with a convincingly null effect (mean zero and confidence interval excluding clinically significant harm or benefit). Most individual beneficial responses to an "ineffective" drug will be small, but some could be large enough to be clinically worthwhile even when the confidence interval for the mean apparently excludes significant gains. An equal number of patients will of course suffer detriment. The only difference between effective and ineffective treatments is that the proportion of patients gaining clinically important benefit is greater and the proportion suffering significant harm smaller with effective treatments.

Every treatment is experimental. When treatments of equal tolerability, safety, and cost are available only a fool would choose the "ineffective" treatment because of the smaller chance of benefit and the greater chance of harm. However, some patients might prefer to try an "ineffective" non-drug treatment to "effective" treatment based on "chemicals." This would seem rational if any harm from choosing such treatment is reversible, and it illustrates how outcomes usually measured in clinical trials might not be those of primary interest to patients. It does, however, lay on the doctor an even greater responsibility to monitor treatment and ensure any beneficial response persists. In this limited context I disagree with your urging to stop ineffective treatments.

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### Medicine is a science of prediction and intervention

EDITOR—Assessing effectiveness and benefit in epidemiological studies entails several degrees of imprecision and uncertainty at the individual level while its estimator is defined for a population. A single disease entity may have varied manifestations in different patients and divergent outcomes.<sup>1</sup>

As Anderson and Groves emphasise,<sup>2</sup> Archie Cochrane posed three key questions to ask about a healthcare intervention: "Can it work?" "Does it work in practice?" and "Is it worth it?" We usually use rules to decide between "yes," "not sure," and "no." By doing this we assume Aristotelian logic and the classic current definition that "health and disease are opposites and that they are dual and contradictory attributes."<sup>3</sup>

Why do doctors use treatments that do not work?<sup>3</sup> People usually do not require precise numerical information, and yet they are capable of making decisions. They accept noisy and imprecise input<sup>4</sup>; so do doctors.

Having a huge number of input variables (patient background, expectations, behaviour, and beliefs, disease manifestations, laboratory results, etc), doctors use "fuzzy logic" algorithms (grade of evidence, personal knowledge, cost, ritual, mystique, etc) to decide treatments. Evidence is one of the most important pieces of the complex system, but not the only one. Fuzzy logic has been developed to deal with the concept of partial truth values between completely true and completely false. It mimics human control logic and may be applied to improve knowledge in epidemiological and medical problems.<sup>1,4</sup>

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### Small question with big answers

EDITOR—Why do doctors use treatments that do not work?<sup>1</sup> A simple question with many answers.

1. Doctors are paid to do this.
2. Doctors are taught to "practise medicine" not to "help the patient." When these do not overlap doctors are guided by adherence to professionally accepted theories as much as by evidence of benefit.
3. Diffusion and uptake of knowledge have limits. Doctors are overloaded with irrelevant information but have little access to information on things that they have been doing for years but do not work.
4. There is a tension between short term relief and long term attempts to "help the patient." Some things provide instant relief

but little long term benefit (or even harm).

5. Effort must be justified. If people take a lot of effort to achieve something they tend to justify their efforts by attaching value to what they have achieved. Doctors spend years learning to offer some treatments that don't work, making it harder to accept that they may have no value.

6. The myth of the pathophysiological model is strong. Students are taught medicine as if people first

learnt how the body works, then learnt how it went wrong, and finally deduced how to fix it. This makes doctors resistant to evidence from clinical trials contradicting a cherished pathophysiological model. In reality, medical knowledge is often discovered in reverse. We first identify an illness, accidentally finding that something works to cure it. We then infer how the treatment works and elucidate the underlying disease mechanism.

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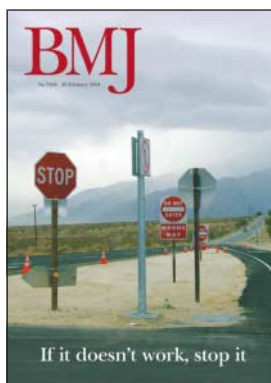
- 1 Doust J, Del Mar C. Why do doctors use treatments that do not work? *BMJ* 2004;328: 474-5. (28 February.)

### Don't just stand there, hold my hand

EDITOR—"The aphorism 'Don't just do something, stand there!' seems ludicrous."<sup>1</sup>

Does it?

Reading this reminded me of something a student wrote in a reflective piece at the



end of the University of Bristol's fifth year preregistration house officer shadowing course. She was confronted on a ward round for senior house officers with an extremely unwell, very breathless man. The house officer and senior house officer sprang into action. She looked at him and realised he was dying, and dying soon.

While everyone else examined him, gave him oxygen, and arranged investigations she looked on and wondered if she would be capable of such actions when she qualified. She also described feeling powerless, and that there was nothing she could do. She wrote: "And then the words of a particular palliative care consultant came into my mind: 'If there is nothing else to do, you can hold their hand.' So I did. He died shortly afterwards."

Sometimes there is nothing to do, or there is nothing doctors should do, in terms of management or treatment.

Medicine entails "ritual, custom, and the expectations of doctors, patients, and society."<sup>1</sup> But it also entails compassion and humanity, the ability to be with someone and to give of yourself as a human being. And that is what this student did. Sometimes the aphorism might read: "Don't just do something, hold my hand." And that would not be ludicrous.

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### I don't know

EDITOR—Alderson and Groves suggest that "what we don't know we don't know would be a good topic for a *BMJ* theme issue."<sup>1</sup> But, do you know what? It couldn't be done. For to write about what we don't know, we must surely know we don't know it first, otherwise how could it be an issue?

The only way it could work would be that those who know they don't know something, but think the rest of us don't know we don't know it, write about it so that the rest of us then also know we don't know it. Then everything in that issue will no longer be unknown unknowns, but known unknowns. Do you know what I mean?

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1 Alderson P, Groves T. What doesn't work and how to show it. *BMJ* 2004;328:473 (28 February.)

### Summary of rapid responses

EDITOR—Most of the 50 or so correspondents agreed that doctors are guilty of using treatments that don't work.<sup>1-3</sup> Some thought that patients respond very differently to the same treatment, so what works in one might

not work in another. And sometimes useless, but harmless, treatment bought much needed time for patients to heal themselves, suggested others.

But many simply felt that culture and training and peer pressure and patient expectations often got in the way of change, even when patients stand to benefit. Financial imperatives, some of which are not always obvious, also favour using treatments that don't work, suggested an ethicist in Qatar. The lack of published negative trial results didn't help much either, volunteered a professor of psychiatry from India.

Just because everyone is doing it, doesn't mean it's right, it was acknowledged. But deviating from accepted practice or long held traditions, for which a great deal of time and effort had often been invested, took considerable courage, to say nothing of persistence, suggested some correspondents. This risked not only the wrath of the profession but also the threat of litigation, which, with its propulsion towards defensive medicine and standardisation, left little room for manoeuvre.

But the risks are worth it, and must be taken in the light of proof of ineffectiveness, to avoid potential harm, warned a senior lecturer from the University of New South Wales, Australia. His examples included the failure to research polio in the early decades of the last century and the over reliance of prison smoking cessation programmes on drug treatments in this one.

A French doctor wondered if medicine is not also about "killing the patient quicker than nature would do it?" This vein of cynicism was echoed in a saying attributed to Molière: "Medicine is only for those who are fit enough to survive the treatment as well as the illness."

A few writers questioned some of the criteria for evidence based practice, which, they felt, ignored whether an effective treatment might also be a harmful one. But one retired physician pointed out that measuring harm is even more difficult than measuring benefit. And in any case, should doctors be the only judges of what is or isn't harmful for patients, she asks?

Patients' views are all too often ignored, and their expectations rarely sought, which makes doing nothing all the harder. Not least because this tactic relies on advanced communication skills to present it in a positive light—skills which many doctors simply don't possess, opined an associate director of postgraduate general practice education.

One correspondent cautioned that medicine jumped to conclusions on the basis of statistical associations. These could be both spurious and misleading, which researchers from the health think tank the King's Fund had proved. They found an association between a country's ranking for health system performance, as judged by the World Health Organization, and its international football ranking.

Several correspondents continued the theme begun by US defence secretary Donald Rumsfeld's somewhat infamous mouth-

ful of knowns and unknowns. One suggested that true knowledge was humbling, rather than a source of pride, and a spur to extend the frontiers of knowledge. Another pointed out that 25 years of medicine had convinced him that there were far more "unknown unknowns" than "known knowns." Very few of the "facts" he had been taught at medical school had retained their factual status.

But one correspondent pointed out one of the essential difficulties of admitting to unknowns. Doctors "are trained to 'know.' In medical training and practice, ignorance is so often equated with failure."

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1 Electronic responses. Why do doctors use treatments that do not work? <http://bmj.bmjournals.com/cgi/eletters/328/7438/474#responses> (accessed 15 Apr 2004).

2 Electronic responses. What doesn't work and how to show it. <http://bmj.bmjournals.com/cgi/eletters/328/7438/473> (accessed 15 Apr 2004).

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## Confidence intervals illuminate absence of evidence

EDITOR—We agree with Alderson that authors should recognise that non-significant results are compatible with a range of possible findings.<sup>1</sup> Papers in the same issue of the *BMJ* do not adhere to this good advice.

Koivunen et al concluded that adenoidectomy is not effective and cannot be recommended, yet the 95% confidence interval for further episodes of otitis media is compatible with an 18% absolute risk reduction.<sup>2</sup> The clinically important difference sought was a 25% reduction.

Karimnia et al said that hands and knees exercise with pelvic rocking did not reduce the incidence of persistent occiput posterior position at birth<sup>3</sup>; the 95% confidence interval was from 1.8% reduction to 2.5% increased risk. This trial sought a risk reduction of 2.5%.

Marre et al concluded that "low dose ramipril has no effect on cardiovascular and renal outcomes"<sup>4</sup>—the 95% confidence interval was from 15% reduction to 11% increased risk. A 20% reduction was considered clinically important.

None of these non-significant trials ruled out some treatment benefit. Others may judge that a smaller benefit would be clinically useful. Even when a clinically useful effect has been ruled out, phrases such as "is not effective," "did not reduce," and "has no effect" are not justified.

Also, confidence intervals reflect only uncertainty owing to random allocation, not that owing to failure to follow the protocol, non-random loss to follow up, and so on. True uncertainty is greater, therefore, than indicated by confidence intervals.

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Lastly, we cannot claim priority with the title "Absence of evidence is not evidence of absence": a paper with this title was published in 1983.<sup>5</sup>

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- 1 Alderson P. Absence of evidence is not evidence of absence. *BMJ* 2004;328:476-7. (28 February.)
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- 4 Marre M, Lievre M, Chatellier G, Mann JE, Passa P, Menard J. DIABHYCAR Study Investigators. Effects of low dose ramipril on cardiovascular and renal outcomes in patients with type 2 diabetes and raised excretion of urinary albumin: randomised, double blind, placebo controlled trial (the DIABHYCAR study). *BMJ* 2004;328:495-9. (28 February.)
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## Coeliac disease and schizophrenia

### Data do not support hypothesis

EDITOR—Eaton et al report a strong risk relation between schizophrenia and coeliac disease.<sup>1</sup> We do not believe that their data support this hypothesis.

They define their case sample as 7997 patients with schizophrenia, in whom they found four cases of coeliac disease. They then include the data on parents' coeliac status (eight cases) in their analysis, and this is potentially misleading. If the parents' data are excluded from the analysis the prevalence of coeliac disease in people with new onset schizophrenia is only 0.5 per 1000, which is the same as in their control group.

Eaton et al describe coeliac disease as rare in Denmark, which was the traditional view. Their sample population dated from 1981-98, when diagnostic testing for coeliac disease advanced. Recent data using endomysial antibody to screen the Danish population suggests a prevalence of 1 in 400, more akin to neighbouring Scandinavian countries.<sup>2</sup> Underascertainment of the true prevalence of coeliac disease is therefore a real possibility and a potential confounding factor.

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- 1 Eaton W, Mortensen PB, Agerbo E, Byrne M, Mors O, Ewald H. Coeliac disease and schizophrenia: population based case control study with linkage of Danish national registers. *BMJ* 2004;328:438-9. (21 February.)

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### Authors' reply

EDITOR—As noted in the original paper, we agree that coeliac disease is almost certainly underascertained in the study; but we do not agree it is a confounding factor. The question is whether the ascertainment in cases and controls, and in cases and controls with other autoimmune intestinal diseases, is differential (biased).

The numbers are small, but the logic of bias is weak in cases, and even weaker in parents. The figure of 0.5 in the table, for prevalence in controls, includes coeliac disease in controls or their parents (as noted in the table). The numbers with coeliac disease in the controls were: 27 controls, 48 mothers of controls and 18 fathers of controls (93/199 915, or 0.5 per 1000). This compares to figures given in the paper of 4, 5, and 3 in cases, mothers of cases, and fathers of cases, respectively (12/7997, or 1.5 per 1000).

We are also not yet convinced. But, we are led to direct our attention further in this area in the light of current research, including the availability of new screening tests for coeliac disease, which identify subclinical cases; prior trials of gluten withdrawal which usually identify a small proportion who respond positively<sup>3-5</sup>; and some dramatic case studies.<sup>5</sup>

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## Missing evidence that animal research benefits humans

### Evidence is all around us

EDITOR—The general inference drawn by Pound et al from six systematic studies, that animal research does not benefit humans is



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not justified.<sup>1</sup> These studies represent a very small proportion of all animal research. The correct inference from their examples (in four out of six, animal studies agreed with clinical findings) is not that animal research was "valueless" but that it was not done at the right time and was disregarded. Selective referencing (study 5) does not reflect animal research giving the wrong signals; it exemplifies the Nelson syndrome—choosing which signals to see.

The real message of the article is not about the value of animal research but about the basis of clinical trials. Before clinical trials are started, all relevant existing research should be critically assessed, locally and externally. In trials of new drugs the external assessment is carried out by the licensing authority; where trials are supported by non-industry funds (Medical Research Council, etc) this is done by the peer reviewers. More clinical research is needed but this deficiency is more an organisational problem<sup>2</sup> and not a measure of the value of animal research.

Pound et al ask where the evidence is that animal research benefits humans. That evidence is like Christopher Wren's monuments—it is all around us. Many humans are benefiting now from, say, angiotensin converting enzyme inhibitors, selective  $\beta$  agonists, neuromuscular blockers, anaesthetics, or statins. All have been introduced because animal research initially suggested benefit for a human disorder; suggestions that were subsequently fully substantiated in clinical practice.

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- 1 Pound P, Ebrahim S, Sandercock P, Bracken MB, Roberts I. Where is the evidence that animal research benefits humans? *BMJ* 2004;328:514-7. (28 February.)

- 2 Stewart PM. Improving clinical research. *BMJ* 2003;327:999-1000.

### Moratorium is unjustified

EDITOR—Pound et al take an extremely narrow approach to the question: "Where is the evidence that animal research benefits humans?" and they misinterpret their own data.<sup>1</sup> Their opening statement, that clinicians and the public often consider it axiomatic that animal research has contrib-

uted to the treatment of human disease, yet little evidence is available to support this view, is seriously misleading. There is a huge amount of evidence for the value of animal research.

The authors identified 277 reviews of animal experiments but described just six systematic reviews, conducted to discover whether animal research had informed particular clinical studies. Far from providing evidence that animal research doesn't work, five reviews showed that full analysis of the animal results predicted the ineffectiveness of the treatment being tested. But the clinical work was started before proper assessment of the animal studies.

It is imperative that animal research is properly evaluated before the results are transferred to medical practice. The relevant ethics committees and regulatory authorities should have identified that these clinical trials were based on inadequate analysis of animal experiments. The animal studies were not at fault.

Pound et al did not even consider the importance of animal studies for basic medical research. They ignored research on normal life processes and the natural history of disease, not to mention safety testing. All these make essential contributions to the development of new therapies for humans (and animals). Much of this work is required by law.

Some of the authors have called publicly for a "moratorium" on animal research.<sup>2</sup> This is totally unjustified by their results.

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1 Pound P, Ebrahim S, Sandercock P, Bracken MB, Roberts I. Where is the evidence that animal research benefits humans? *BMJ* 2004;328:514-7. (28 February.)  
2 Scientists for Accountability in Biomedical Research and Education. Press Release, 27 February 2004. www.greensolutions.moonfruit.com/download/4511247567/60e020d2721467269157f3384f557dbd00f020c0802090d070d07091/guest/4004776299/4507182560/BMJ%20Press%20Notice%20C.doc (accessed 17 Mar 2004).

## Well informed uncertainties about the effects of treatment

### "Evidence based" must not equal "judgment free"

EDITOR—"Evidence based medicine" and "evidence based policy" have done much to improve decision making. However, it is refreshing to see Chalmers reject the abuse that suggests these can simply be used to identify a "best practice" that should always be followed.<sup>1</sup>

The typical "evidence based" review identifies a large number of articles and then discards many as irrelevant and many more as methodologically unsound. The review is then based on the remaining handful and by implication all the other articles have nothing to contribute. However, detailed knowledge of the subject is

often needed to judge the worth of a paper, and even methodologically flawed articles often contribute some information to the evidence base.

Typically an evidence base shows that fewer patients will benefit if given treatment A than if given treatment B. In the absence of any other information the best bet must be to choose treatment B, but nearly always other information and judgment are required as to whether the general conclusion that treatment B is better than A applies to an individual patient.

Wise doctors and policy makers will always use the evidence base to inform their decisions. But they also exercise judgment in considering all the information, formalised and informal, available to them before reaching a decision. In an uncertain world judgment free medicine (or policy making) is as bad as or worse than evidence free.

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### Paradox exists in dealing with uncertainty

EDITOR—As inevitable and unpleasant as many uncertainties are, one can argue that patients (and their doctors) should not even strive to completely eliminate uncertainties. Although the role of scientific method is to reduce uncertainties, a total elimination of uncertainty would be undesirable, since, it has been argued, it would lead to deterministic life—meaning that all events would be known in advance, in turn implying no hope, no ethics, no freedom of choice.<sup>1</sup>

Hence, there is a paradox in dealing with uncertainty—we want to reduce uncertainty, but we do not want to eliminate it totally.<sup>1</sup> Only because we do not know what the future holds can we have our hope and choices.<sup>1</sup> In the context of informing patients about the effects of treatments, this means that the patients' basic right is whether to accept that uncertainty<sup>2</sup> exists (which in practice often means disagreement among their doctors), and the proposed method for resolution of the existing uncertainties (which can include enrolment into a clinical trial as one of the means to resolve uncertainties).<sup>3-5</sup>

Therefore, uncertainty should not be looked on as the enemy but rather as a friend (or as the opportunity). Once uncertainty is recognised and acknowledged,<sup>2-5</sup> more effective solutions for its resolution can be devised. Hence, "two cheers for uncertainty!"<sup>1</sup>

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## New system for ethics approval is unacceptable

EDITOR—Greenhalgh is right to highlight the idiocies of the new game to obtain "ethical approval" for a research project.<sup>1</sup> As a comparatively new member of a committee I hate the new system, which seems to generate far too much paper. The weight that comes through the post is overwhelming.

It seems the system is based on covering the most complex projects for drug trials in many sites and many countries. Simple projects have to fit the most complex model.

In attempting to review a project, all I need is:

- A statement of the problem to be studied and a description of the methods to be used—the introduction and methods section of the final paper
- The information sheet for patients—what patients can carry away, hopefully written in plain English
- The patients' consent form

All the rest is really to do with administration. Ethics committees do not need to review the finances of the projects or the consent and approval of departmental heads and research committees. They do not need to check on the data protection officer, the chief pharmacist, etc. Those are matters for the research worker, who is, after all, the one to carry the can.

We are confusing administration with ethics. It is time for the research workers of the world to rise: you have nothing to lose.

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1 Greenhalgh T. The new ethics. *BMJ* 2004;328:651. (13 March.)

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