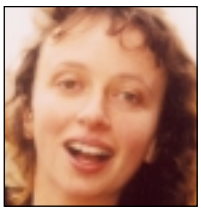
The crack in the biomedical box



ZELDA DI BLASI *on the placebo effect – the ghosts that haunt the house of biomedical objectivity.*

CROCODILE dung, lozenges of dried vipers, blisters and bloodletting. Until this century most medications were pharmacologically inert, if not harmful. Since the age of the scientific revolution the realms of magic, spirituality and superstition have been pushed aside by the rational, objective and scientific biomedical model. The discovery of penicillin, aspirin and cortisone are only a few examples of the triumph of science and rationality in the conquest of illness and the combat of quackery and charlatanism.

But, interestingly, remarkable medical achievements and scientific proof have often been obtained by using the very thing that was associated with trickery and deceit – the placebo.

The placebo as design and effect

In his classic meta-analysis of placebo-controlled trials, Beecher found that a third of patients responded positively to placebos (Beecher & Boston, 1955). This discovery prompted researchers to carry out studies on university students and in clinical populations suffering from a variety of conditions. Many undergraduates took part in drug experiments and were found to display various drug-related behaviours (e.g. alcohol-induced sexual arousal: Hull & Bond, 1986), even though the substance taken was totally drug-free. In asthma patients, airways could be dilated simply by telling people they were inhaling a bronchodilator, even when they weren't (Luparello *et al*., 1970; Neild & Cameron, 1987).

Over the past 20 years therapies have been compared using an experimental design known as the randomised controlled trial or RCT (Lilienfeld, 1982). To evaluate the specific effectiveness of a new 'active' treatment, patients are randomly allocated either to the experimental treatment or to a sham or 'inert' placebo treatment (Armitage, 1982).

Placebos were designed to simulate the treatments being investigated but had no specific therapeutic properties. For example, in pharmacology a fake drug would usually be a white sugar pill or a saline injection. In physiotherapy the ultrasound machine would be turned off for the placebo group (Hashish *et al*., 1988). In surgery, sham operations merely involve making a skin incision – this has been found to have an especially powerful placebo effect (Cobb *et al.*, 1959; Dimond, 1960). In acupuncture, patients would get their needles in the 'wrong' pressure points (Berk *et al.*, 1977). A more recent study of placebo surgery published in the *New England Journal of Medicine* found no difference between patients randomised to surgery for the knee and placebo surgery (Moseley *et al.*, 2002).

To study the direct effects of treatment on health, clinical researchers controlled for any possible experimenter bias by following very strict guidelines in the conduct of RCTs, such as double-blind designs, randomisation and power calculations (Pocock, 1983). In controlling for potential biases, researchers created a 'biomedical box' that allowed them to get rid of any possible variable that might 'threaten the fastidious detection of a predictable cause and effect outcome' (Kaptchuk, 1998, p.1723). Among these variables were placebo effects. Seen as 'noise' in the machine to be filtered out of the scientific data, placebo effects were 'boxed'.

The challenge for biomedical scientists

Are placebo effects out of their box?

WEBLINKS

National Institutes of Health – Science of placebo:
http://placebo.nih.gov

The skeptic's dictionary:
www.skepdic.com/placebo.html

Article from *Modern Drug Discovery*:
www.pubs.acs.org/hotartcl/mdd/99/aug/mysterious.html

Do placebos work?:
www.mad.scientist.org/features/placebos.html

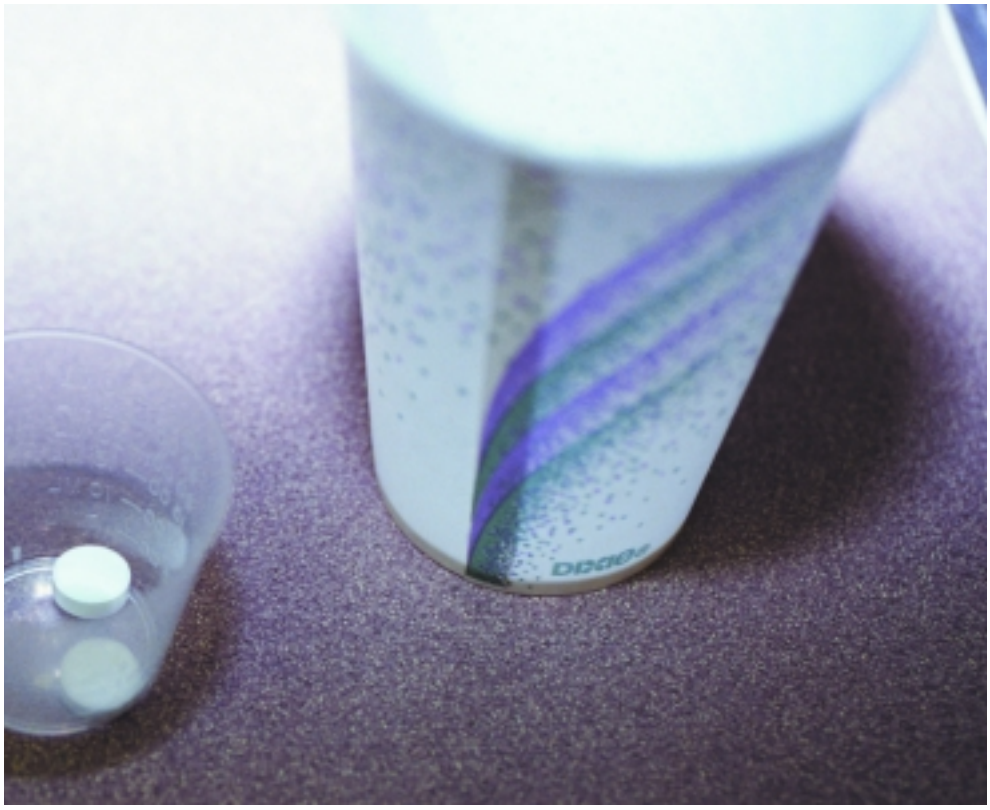
was to prove that the therapeutic intervention was better than a placebo, because if clinical trial findings showed little or no difference between the two treatments, the therapy would have to be abandoned. But despite rigorous and systematic adherence to strict clinical guidelines, placebo effects would still appear – unpredictably and uncontrollably (Hrobjartsson, 1996). This was a nuisance for scientists who had devoted time and energy to carefully developing the therapy, for healthcare practitioners who needed effective treatments, and most importantly for patients desperately seeking a relief to their symptoms.

If the treatment consisted of a placebo, there were problems even when patients *did* get better, as the medical condition of patients who responded to placebos would often be thought of as 'psychosomatic' or 'all in their head'. Furthermore, discovering that they had improved thanks to a fake therapy threatened the doctor–patient relationship, as patients might feel they had been tricked. It also risked cutting short the healing response. It is perhaps because of this that people who *do* respond to placebo treatment are often not told what they got when the study closes (Di Blasi *et al*., 2002).

Scientists, physicians and practitioners are not the only ones to be frustrated and mystified by the placebo effect. The phenomenon has been an attack on the whole scientific paradigm, clearly shaking the solid foundations of the biomedical model. Harvard historian Anne Harrington described placebos as 'ghosts that haunt our house of biomedical objectivity…and expose the paradoxes and fissures in our own self-created definitions of the real and active factors in treatment' (Harrington, 1997, p.1).

The debate hots up

Puzzled by the thought that a harmless white pill could have such overwhelming effects on the physical state of patients, biomedical researchers pulled up their sleeves to take a good look at what might be happening. In Beecher's meta-analysis no systematic strategy had been used to identify the studies. While these were selected 'at random', seven of the 15 trials had been conducted by the author himself. The trials had not been conducted prospectively to investigate placebo effects, and while some of these had both placebo and no treatment arms, the difference between these groups was not discussed. Having noted various such flaws in the evidence for placebo effects, a group of reviewers from Germany explained the effect, not as a powerful therapeutic tool, but as merely an 'illusion' created by a scientific artefact (Kienle & Kiene, 1998, 2001).



Kienle and Kiene (2001) listed a number of factors 'that cause a false impression of a placebo effect', such as natural course of disease (e.g. spontaneous improvement, fluctuation of symptoms), additional treatment, observer bias (e.g. scaling bias, conditional switching of treatment), no placebo given at all, and patient bias (e.g. polite answers, neurotic or psychotic misjudgement).

The debate became a hot topic in the media and internet discussion lists when the views of Kienle and Kiene were supported by the findings of two Danish researchers, published in the *New England Journal of Medicine*. Asbjorn Hrobjartsson and Peter Gøtzsche felt that a 'true' placebo effect should be examined by comparing the difference not between 'active treatment' and 'placebo' but between 'placebo' and 'no treatment' groups. This is because it is normal for placebo effects to be observed in randomised controlled trials when comparing an active drug with a placebo control; a waiting-list group would control for the effects of natural progression of the disease. They identified 114 such trials and found 'little evidence in general that placebos had powerful clinical effects' (Hrobjartsson & Gøtzsche, 2001). This finding delighted placebo sceptics and reinforced the view of placebos as fictitious, powerless phenomena when compared with biology and medicine. Was the biomedical box safely shut once more?

A new challenge to its solid structure came when a group of psychiatrists from Los Angeles identified brain changes in patients randomised to placebos (Leuchter *et al*., 2002). Perhaps placebo effects *were* real, and even more powerful than previously thought. Once the LA study was over and placebo responders were told about their treatment allocation, most of them relapsed and had to be put on 'active' treatment. According to a Reuters report, 'placebo responders, when told they were on a placebo, had a deterioration of their mood. Within a month, most of the placebo responders had enough depressive symptoms that they actually ended up on medications' (Fox, 2002).

Yet not all placebo responders are upset to find that their medicine was a sham. In a study conducted in collaboration with John Weinman from University College London, I interviewed a man whose heel pain had

vanished following a placebo injection. When told about his treatment allocation he excitingly replied: 'This is fantastic, this is a real discovery… Human chemistry is the most important of them all… It is the faith, the trust we put in people!'

Digging for placebo gold

Social psychologist W.J. McGuire describes 'three stages in the life of an artefact: first it is ignored; then it is controlled for its presumed contaminating effects; and finally, it is studied as an important phenomenon in its own right' (quoted in Harrington, 1997, p.2). This has been the case with the placebo effect: rather than attempting to repair the cracks of the biomedical box, some researchers have been curious to see what lay inside. And indeed, something appeared to glitter.

The possibility of striking gold moved researchers towards digging to explore what they increasingly felt was the most magical, mysterious and most widely misunderstood phenomenon in medicine. The 'gold rush' grew in the year 2000 when the National Institutes of Health (NIH) in America organised a placebo effect conference, putting forward major grants to study placebo effects (see weblinks).

Interestingly, the pharmaceutical industry has indirectly exploited the placebo effect in the form of marketing and advertising. We only need to think of the diamond-shaped sex pill Viagra to get excited! Drugs are promoted in ways that attempt to maximise their effect with allusive names such as 'Regaine' for male baldness, 'Welldorm' for insomnia, 'Marvelon' as a marvellous contraceptive (Holm & Evans, 1996). The colour of a drug has also been shown to affect its perceived effects, with red, yellow and orange pills perceived as stimulants and blue and green as tranquillising or sedative drugs (de Craen *et al*., 1996).

Despite the fact that placebo effects are basically psychological processes, psychologists were the last discipline to join the placebo gold rush (Shapiro & Shapiro, 1997). Perhaps we felt that researching placebo effects threatened the scientific soundness of the discipline, or that it risked reawakening ghosts like Freud! Rather than advancing our understanding of the mechanisms of this phenomenon, we have generally tended to adopt placebo controls in our trials to evaluate the efficacy of specific psychological therapies.

Enthusiasm in researching placebo effects dwindled when studies failed to identify a placebo-responding personality (e.g. Shapiro & Shapiro, 1997), but was reawakened yet again in the 1980s and 1990s with the boom in complementary and alternative medicine (Eisenberg *et al*., 1993; Fulder & Munro, 1983). Sceptical of the growing popularity of 'CAM', clinical researchers challenged its real worth by assigning any effectiveness to placebo effects alone (Lynoe, 1990). This left alternative practitioners with the challenge to prove that their therapy is actually more effective than a sugar pill. Interestingly, CAM practitioners are among the few health professionals to recognise that it is not their treatment alone (homeopathy, acupuncture, etc.) but also the way this is delivered (e.g. empathically, reassuringly) that is therapeutic. It is for this reason that some of the major placebo effect experts have a background in CAM research.

It is with the guidance of some of these experts that I began to examine whether the way treatment was delivered by healthcare professionals could actually affect the healing process. We conducted a systematic review of all relevant placebo-controlled randomised controlled trials conducted in patients with a physical illness. Complex psychological and psychotherapeutic interventions (e.g. training health professionals in patient-centred care or in preparing patients for stressful interventions) were excluded to focus on situational or context factors (e.g. the manipulation of treatment expectations).

We used Leventhal's self-regulatory theory (Leventhal *et al*., 1980) to guide this work. Leventhal's theory was chosen because it takes account of the dynamic nature of psychological processes, and in predicting how patients cope in reaction to a health threat it takes account of both cognitive and emotional responses. It appears to embrace various theoretical approaches commonly used to understand the mechanisms and determinants of the placebo effect, such as expectancy, anxiety, appraisal and conditioning.

Our aim was to see if healing could be 'triggered' by influencing the way patients thought ('cognitive care') and felt ('emotional care') about their illness and their treatment. For example, by giving a positive vs. a negative/neutral diagnosis or prognosis, or by increasing or decreasing expectations (e.g. 'This is a new, fast-acting drug, very effective in reducing pain' vs. 'This is a new drug which I have not found to be very effective in reducing pain').

We searched 11 electronic databases,

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including PsycLIT. Our search strategy for Medline alone included 183 search terms. Our findings, published in *The Lancet* (Di Blasi *et al*., 2001), showed that out of a total of 25 trials that met our inclusion criteria, approximately half of these studies found significant effects on patients' health status. No clear patterns emerged when clinical conditions were analysed separately. However, there were some interesting findings, though not always consistent. Systolic blood pressure was found to be higher in hypertensive patients who were told to expect this to be higher in a second assessment, than in patients who were informed that it would be low or that there would be no change. We also found that physicians who adopted a warm, friendly and reassuring manner while increasing expectations were more effective than those whose consultations were formal and did not offer reassurance.

As psychologists, you will probably wonder how some of these variables (such as 'warmth' and 'friendliness') were operationalised. Unfortunately, these studies do not go beyond giving a simple description of the intervention; for example, 'warm, a lot of verbal interaction' vs. ' neutral, minimal interaction' (Freund *et al*., 1972). Furthermore, even though 'expectancy' was the main variable being manipulated (i.e. 'high' vs. 'low') in 19 of the 25 studies, only five studies actually measured whether expectations had indeed been influenced by the intervention. When expectations were assessed, measures tended to be crude, single-item scales and administered at one point in time.

Furthermore, while the RCT is perceived to be the 'gold standard' research method in health sciences, it is limited in its application. For example, by focusing on outcomes it tends to overlook processes such as healthcare interactions, making it difficult to extrapolate on the findings. It is also important to bear in mind that human interactions are often spontaneous, creative and unpredictable. For this reason, video or tape recordings of interactions could help advance our understanding of the types of therapeutic processes that are influencing the effects of therapies and placebos.

'we need to...welcome back the discredited sister of scientific medicine'

Conclusion

In the 17th century Descartes, one of the great fathers of the Age of Science, wrote: 'there is nothing included in the concept of the body that belongs to the mind; and nothing in that of mind that belongs to the body' (quoted in Sommers, 1978). Our current system of care is founded upon this assertion. It is no wonder that four hundred years later we are finding so many cracks in our system. This artificial split cannot be sustained much longer.

With growing evidence on mind–body interactions in healing and with our current crisis in health care, a revolutionary paradigm shift needs to occur. Rather than fixing the cracks of the biomedical model, we need to break the box, remove the gap between medicine and psychology and welcome back the discredited sister of scientific medicine.

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