

## SELECTED SUMMARY

# Placebos: can you get something for nothing?

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**Daniel E Moerman. Cultural variations in the placebo effect: ulcers, anxiety, and blood pressure. *Medical Anthropology Quarterly* 2000; 14: 51-72.**

### Summary

Moerman defines the placebo effect as a meaningful and desirable psychological and physiological effect of treatment. In typical randomised control trials (RCTs) patients are randomly allocated to active treatment, placebo treatment and no treatment groups. If the placebo group does substantially better than the no treatment group, the difference is the placebo effect. Such trials show that all interventions, from a simple history taking to invasive testing, may have therapeutic value.

In a study of ultrasound therapy for swelling after extraction of the third molar, the ultrasound probe was placed on the cheek but not turned on—that is, it was a placebo. It still reduced swelling in most patients. In another study, the placebo improved the duration of exercise and functional class in patients with congestive heart failure, as compared to patients who received no treatment.

In such trials, the untreated group may also improve. Problems often do heal by themselves; these are often called “natural history effects”. It is also often the case that people seek treatment (and are enrolled in trials) when their (fluctuating) symptoms are at their worst; improvement in such patients is called “regression to the mean”.

Before the 1970s when RCTs became standard, scientific investigation led to widespread use of therapies that were only later put to the test of the RCT. Moerman cites a study where intervention once considered effective proved to be no better than a placebo in subsequent RCTs. This study examined a number of early treatments for angina pectoris. The initial 70-90 per cent success rate dropped to 30-40 per cent – the same as a placebo.

Medical students participating in a study were informed that the trial involved a stimulant and a tranquilliser. All were given a packet containing one or two red or blue capsules containing inert material. The responses of the students suggested that, in general, the red tablets acted as stimulants and the blue ones as depressants and two capsules were more effective than one. This study suggests that the colour of the capsules had some meaning: red implied “up” or “danger”, blue implied “down” or “cool”, and two meant “more than one”. A British study has shown that heavily advertised brand name aspirin is more

effective than the generic drug and a placebo with a brand name is more effective than a generic placebo.

Cultural beliefs may have a significant impact on healing. This is shown by a study that examined deaths in 28,169 adult Chinese Americans with lymphomas and 500,000 randomly selected age- and sex-matched white Americans. Chinese Americans born in an inauspicious birth year were likely to die four-six years earlier than Chinese born in other birth years or Caucasians.

The compliance of patients also influences the outcome of treatment, irrespective of whether the patient received a placebo or a drug. A study of beta-blockers to prevent myocardial infarction found that patients who took more than 80 per cent of the doses had a better outcome (15 per cent mortality) than those with poor compliance (25 per cent mortality), irrespective of whether they received a beta-blocker or a placebo. “Placebo effects are shaped by factors that influence the meanings patients attribute to their illnesses and to the treatments they receive.”

### Measuring placebo effects

In peptic ulcer disease, relief of pain does not necessarily lead to healing of the ulcer. Stress and hyperacidity do not correlate with the presence of an ulcer. Despite conflicting evidence, antacids remain the mainstay of therapy. In mid-1970s, H2 receptor blockers became the standard of care. In an analysis of 117 trials of H2 blockers from 32 countries, the mean rate for placebo healing of peptic ulcer disease was 35.3 per cent with a range of 0-100 per cent. Overall, the effectiveness of drug treatment and placebo treatment were related—when the placebo effect increased, drug effects also increased with a correlation rate of .40 ( $p = .0000$ ). As Moerman says, “This finding is highly counterintuitive for medical researchers who usually consider placebo effects as ... ‘noise’ in the system...”

How can we explain the healing of ulcers in the placebo group? Is it contact with the physician? Are ulcers cyclical and do they heal by themselves? In a Danish study of 91 patients with endoscopically proven duodenal ulcers who were receiving antacids, 32 per cent healed spontaneously in two weeks and 75 per cent in six weeks. Could the antacids have accounted for the healing? Many gastroenterologists believe that any white powder labelled as an “antacid” will relieve ulcer pain. In the 50 years before the introduction of H2 blocking agents, hourly feeding of milk and antacids (the Sippy regimen) was a standard treatment. Double-blind studies showed that this regimen

was as effective as a placebo. That antacids are not likely to be responsible for the placebo response is shown in six studies of H<sub>2</sub> blockers, where no antacids were allowed, yet healing of the ulcer occurred in 10-74 per cent of placebo patients and it averaged 39 per cent.

The author found no effect of age, gender or duration of treatment on placebo healing rates. But placebo response rates from different countries were significantly different. The average placebo healing rate was 37 per cent for all studies, but three studies from Brazil showed a rate of 7 per cent while six studies from Germany showed a rate of 59 per cent—about three times the rate in two of its neighbouring countries, Netherlands and Denmark (22 per cent).

Are the rates of placebo healing in Germany always high and in Brazil always low? The rates of placebo effect seem to vary by medical conditions within cultures. The placebo response rate in hypertension is more modest compared to peptic ulcer disease and the rate in Germany is lower than the international average. In generalised anxiety disorder trials, the decrease in anxiety by drugs versus a placebo is comparable to the ulcer data. Italians seem more resistant to placebo treatment for anxiety than others. Germans fall in the middle for anxiety and are among the lowest for treatment of hypertension. Just because placebo effects are high for one condition in some setting they need not be high for other conditions in that setting. Placebo effects vary between national cultures, they vary within them and sometimes they seem to be unaffected by national culture.

## Discussion

Doctors in India encounter a plethora of dubious alternative therapies with highly exaggerated curative properties. Numerous people swear that urine therapy, strange combinations of diets and spiritual practices, and surrender to the outlandish dictates of a guru, are highly efficacious. Are all these placebo effects? Where do Indians stand in placebo response rates for various diseases? Do regional variations exist?

Although “placebo” in Latin means “I please you”, in clinical medicine, placebo has a pejorative connotation – something given to please rather than benefit the patient (1). With increased scientific rigour in the practice of medicine, evidence-based care requires clinical practice to be supported by scientific evidence: hence RCTs. RCTs require a placebo group. It is therefore not surprising that clinicians and academics are forced to come to terms with the placebo effect. However, the placebo response challenges the underlying mechanistic cause and effect ideology of biomedicine: how can you get something for nothing? Yet, we find it very difficult to systematically use this phenomenon in our therapies. “... by focusing on placebos, we constantly have to address the moral and ethical issues of prescribing inert treatments, of lying... It seems possible to evade the entire issue by simply avoiding placebos (2).”

Several studies have shown that about half the patients seen in general practice have no diagnosis, and therefore, the treatment offered is no better than a placebo in most cases. Why not, then,

prescribe placebos deliberately—at least they will do no harm (1). “... illness is what doctors have to treat, whether by curing a disease with a specific remedy or by other means, such as using the ‘doctor as drug’ effect, or using a placebo... it is whether the patient gets better that matters, not the treatment used (1).”

While some physicians consider a placebo as the ultimate complementary medicine, others vehemently deny its existence. In 1997, the Canadian Tri-Council (comprising the Medical Research Council of Canada, the Natural Sciences and Engineering Research Council of Canada, and the Social Sciences and Humanities Research Council of Canada), worked on developing guidelines for an ethical code of conduct for research involving humans. It said, “the use of placebos in clinical trials is ethically unacceptable where clearly effective therapies or interventions are available (3).”

In an effort to debunk the placebo effect, Hrobjartsson and Gotzsche did a meta-analysis of a number of clinical trials comparing a placebo to no treatment. They concluded that in trials with subjective or objective binary outcomes, a placebo performed no better than no treatment. It was only in trials with continuous outcomes such as treatment of pain that placebos came out ahead. However, this meta-analysis has many methodological problems and mixes up patients with widely disparate diagnoses, so the comparisons have little clinical or scientific meaning (4).

Interest in the use of placebo persists. In November 2000, the US's National Institute of Health organised a three-day workshop involving physicians, biologists, behavioural and social scientists, epidemiologists and bio-statisticians to map out an interdisciplinary agenda for research on the placebo effect.

## Ethics of placebo use

The Canadian Tri-Council and the 1996 Helsinki Code frown on the use of placebos in research. However the Helsinki Code was modified in 2001 to permit use of placebos in select circumstances. This debate was reflected in the pages of this journal earlier this year (5,6).

Much of the discussion in academic circles on the ethics of placebo use is in the context of research. The use of a placebo in routine clinical practice has received far less attention. While the researcher hopes that the placebo has no clinical effect, the clinician prescribes a placebo with the expectation that it will have a clinical effect.

The two major ethical criticisms of the use of a placebo in clinical practice are:

- The physician has an obligation to heal using scientifically proven treatment.
- The physician is deceiving the patient by using a placebo.

Invalidating the first objection are studies quoted here and others that have shown that placebos do have a biologic effect that leads to the amelioration of symptoms as well as healing. As far as the science in medicine is concerned, “... science is... only

a small segment of the pathological system...which...extends far beyond those interventions ...verifiable by double-blind randomised controlled trial. ...most of pathological medicine is rational rather than scientific...derived by logical extension from...science. But when suitable findings are not available the gaps are filled by reasoning from 'authoritative' principles and 'theoretical' pathology (7)."

The second criticism assumes that only pharmacologically active therapy is ethically acceptable. However, "...the physician intervenes at many points along the bio-psycho-social continuum—through his personality, air of assurance, words of encouragement, offers of help, and resolution of uncertainty. The placebo is a deception only for those who would reduce treatment to a purely biomedical pursuit (8)." It is possible to reassure the patient and offer a placebo with a very positive slant without being deceitful. "I would like to offer you a pill which I believe can help...I do not know exactly how it works. I have other pills to offer whose mechanism is clearer, but...they may also entail more serious side effects (8)."

Lichtenberg offers the following practical guidelines for ethical use of placebo in clinical practice (8):

- "The intentions of the physician must be benevolent: her only concern the well being of the patient. No economical, professional or emotional interest should interfere with her decision.
- "The placebo, when offered, must be given in the spirit of assuaging the patient's suffering, and not merely mollifying him, silencing him, or otherwise failing to address his distress.
- "When proven ineffective the placebo should be immediately withdrawn.
- "The placebo cannot be given in place of another medication

that the physician reasonably expects to be more effective. Administration of placebo should be considered when a patient is refractory to standard treatment, suffers from its side effects, or is in a situation where standard treatment does not exist.

- "The physician should not hesitate to respond honestly when asked about the nature and anticipated effects of the placebo treatment he is offering.
- "If the patient is helped by the placebo, discontinuing the placebo in the absence of a more effective treatment, would be unethical."

When selecting between drugs with proven efficacy we select the less toxic and less expensive. When, in an RCT, a placebo has been shown to be more effective than no treatment, should we not then, with Lichtenberg's caveats in mind, offer a placebo to the patient in a clinical setting?

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