Credible placebos can produce powerful effects on some conditions, credible placebos have much smaller effects, and placebos of any kind have no effect on some conditions. Hence the significant heterogeneity in effect sizes that Hróbjartsson and Gotzsche found in their meta-analysis. The overall effect sizes they reported are arbitrary. They depend on the nature of the placebos that were used and on the kinds of conditions that were treated in the studies that were included in their meta-analysis. In fact, most of the studies they analyzed did not include conventional placebos (that is, placebo pills) at all. Thus, they tell us nothing about the power of placebos as used in clinical trials.

References


The placebo efficacy study: Problems with the definition of the placebo and the mechanisms of placebo efficacy

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Hróbjartsson and Gotzsche (2001) claim to evaluate the empirical efficacy of “placebo,” but they failed to distinguish between placebo studies that experimentally manipulate placebo mechanisms to amplify placebo efficacy and those that reduce it, and they fail to use a uniform criteria to define and identify placebo studies. Their study appears to have an important strength because it is based on research that compared a “no-treatment” control group to a placebo control group, which is rarely done in clinical trials. But, as the authors admitted, they did not verify that patients in an alleged “no-treatment” control group in fact received no treatment. If the patients in an untreated control group sought treatment outside of the trials more often than did patients in the placebo groups, the effects of placebo would be less apparent, as they
appear to be in this study. Untreated human patients are not passive chess pieces on a clinical trial chess board unless their passivity can be verified with respect to not seeking treatment outside the clinical trial. Patients with aversive clinical symptoms who know they are not receiving any treatment in the clinical trial are likely to seek help outside the clinical trial. Likewise, patients who believe they are receiving only a “placebo treatment” are not likely to take or use it enthusiastically. This study made no effort to determine if the patients in the placebo group even verbally reported that they believed they were receiving a credible therapy, much less did they attempt to verify behavioral compliance with a placebo therapy. Such verification, by at least verbal report of patient belief, has become standard in behavioral science studies of clinical efficacy comparing active therapy interventions with placebo therapies.

As noted, this study failed to pay any attention to the hypothesized theoretical mechanisms that have been empirically shown to amplify the placebo effect (Roberts et al. 1993; Turner et al. 1994; Wickramasekera 1977, 1980, 1985). This is a more serious flaw that goes to the heart of the study’s claims to evaluate the efficacy of the placebo effect. In its definition and its selection of placebo therapy groups, it ignores all the growing literature on hypothesized theoretical mechanisms (patient and therapist subjective belief in the efficacy of the therapy, conditioning and memory mechanisms, etc.) that have been empirically shown to amplify or reduce the efficacy of the placebo effect (Ader 1985, 1989, 1997; Kirsch & Sapirstein 1998; Moerman 1983; Roberts et al. 1993; Siegel 1999; Siegel et al. 1982; Turner et al. 1994; Wickramasekera 1977, 1980, 1985). Studies show a broad range of placebo effects. For example, with regard to clinical pain treated with drugs or surgery, on both objective and subjective measures of efficacy the mean placebo effects range from 20% to 100% (Turner et al. 1994). It seems likely that the explanation for such a range is at least partly due to the involvement of different possible mechanisms that enhance or diminish a placebo’s effect. The failure to consider a placebo’s relationship to such mechanisms is a major deficiency in scholarship. It is blind empiricism.

In the last 30 years, there have been at least two empirically replicated theoretical mechanisms accounting for placebo effects—first, the degree of patient and therapist belief in the efficacy of the therapy proposed (Roberts et al. 1993); second, the hypothesis that placebo responses can be conditioned (Ader 1985; Ader 1997; Hersen 1962; Wickramasekera 1977, 1980, 1985) or learned and retained in memory from previous specific therapies. The presence of these two empirically documented mechanisms has been shown to increase the efficacy of the placebo component, even of active drug therapies; their absence reduces the placebo effect. These mechanisms should have been considered in planning any serious study of placebo efficacy.

In regard to belief, Hróbjartsson and Gotzsche made no effort to determine if the patients and therapists believed that those in the placebo group were receiving an equally credible therapy. This needs to be done routinely if for no other reason than to insure patient participation and compliance with the “placebo therapy” or any other active drug therapy. Turner et al. (1994) have shown that compliance is likely to be an important factor of placebo studies, and it clearly is in testing any active drug. Roberts et al. (1993) review of five treatments (drug and surgical) that have since been abandoned (due to the results of blinded controlled randomized clinical trials) involving 6931 patients, found that when both the patient and therapist believed in the efficacy of the therapy, the mean placebo rate was 70%.

Further, it has been shown that the empirical efficacy of a placebo compared to an active therapy in drug depression studies depends on whether the placebo is “active” (produces side-effects like the active drug therapy) or inert (Greenberg & Fisher 1997). It appears that in drug therapy depression studies the efficacy of the placebo is related to the magnitude of placebo-produced side-effects (Kirsch & Sapirstein 1998). Patients who do not get “drug side-effects” come to believe quickly that they are on a placebo and not receiving the active therapy.
It has also been shown by Kirsch and Saperstein (1998), in a meta-analysis of antidepressants and other drugs, that the more powerful the drug the more powerful the placebo. This meta-analysis of 19 double-blind studies (n=2318) found that the magnitude of the placebo effect was highly related ($r=0.90$) to the magnitude of the drug effect. Evans (1974) had previously reached a similar conclusion from an analysis of six double-blind studies of other medications.

Hröbjartsson and Gotzsche claim that patients in a placebo group would think they had received treatment, but they do not provide any direct or indirect evidence to support this minimal but crucial claim of patient belief. Actual clinical practice always involves treatments that therapists have reason (based on theory or clinical observation) to believe are effective and patients believe are likely to help them. It is known that simply telling patients that they are in a clinical trial in which they may get a placebo therapy under double-blind conditions can cut in half the efficacy of a placebo therapy (Cohen et al. 1977). Hröbjartsson and Gotzsche even report a large study (Schulz et al. 1995) of 33 meta-analyses showing that blinding in clinical trials reduces the efficacy of placebo therapy.

The authors also totally ignore the large body of empirical evidence from animal and human studies that placebo effects can be conditioned through the mechanisms of learning and memory and that these effects can be amplified or reduced experimentally (Ader 1985, 1997; Hernstein 1962; Siegel 1999; Siegel & Kretzler 1997; Siegel et al. 1982; Wickramasekera 1977, 1980, 1985). This conditioned mechanism can be inferred only indirectly from conventional double-blind crossover designed studies (Ader 1989). A conditioning demonstration of placebo effects needs direct experimental manipulation of the reinforcement property of the active ingredient in a drug or therapy and the associated and inevitable learned or memory component in all blinded or unblinded clinical trials (Wickramasekera 1977, 1980, 1985).

The definition and composition of the placebo groups in this study ignored the above empirical evidence bearing on the belief and conditioning mechanisms of efficacy of the placebo. The authors followed a policy of blind empiricism in selecting their placebo groups for this meta-analysis and very likely accepted an unreliable definition of some placebos by simply accepting any group that a study "labeled a placebo group." Their definition of a placebo was simply based on any "intervention labeled as such in the report of a clinical trial" (Hröbjartsson & Gotzsche 2001). Hence, we have no assurance that the placebo groups in this study were characterized by any uniform criteria.

The above basic considerations of ignored mechanisms of placebo efficacy and lack of uniform criteria of definition of the placebo cast doubt on both the process by which the placebo groups in this study were constituted and on any conclusions about placebo efficacy drawn by the study.

References
Core belief in powerful effects of placebo interventions is in conflict with no evidence of important effects in a large systematic review

The five interesting, and at times polemical, comments on our review, "Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment" (Hróbjartsson & Gøtzsche 2001), did not demonstrate flaws in our review, so we see no reason for changing our conclusion that there is little evidence that placebos in general have powerful effects.

Broad and narrow concept of "placebo effect"

A general problem in placebo research is the vagueness of the central concept of "placebo effect." It is not a coincidence that such a concept does not appear in our paper. The phrase has been used to describe phenomena as different as patients' improvement after a placebo intervention, the effect of a placebo intervention, psychologically mediated effects in general, the effect of the patient-provider interaction, the effect of suggestion, the effect of expectancies, and the effect of patients' experience of meaning, etc. We think the notion is associated with too different (though overlapping) phenomena to serve as a conceptual tool for clear analyses.

All five comments discuss "the placebo effect." What we investigated was the effect of placebo interventions (as defined by the researchers conducting the randomized trials we reviewed), or what Greene et al. call "the narrow definition" of placebo effect. We could not show that patients receiving placebos were markedly better off than patients not receiving placebos. Our result is neutral to many of the above meanings of the term "placebo effect." It is therefore a misinterpretation of our work to claim that, for example, our results show lack of psychologically mediated effects on health or that the patient-doctor relation is not important.

Brody and Weisman focus on whether "the placebo effect is real," and Greene et al. find it implausible that placebos should have no effects "beyond natural history or regression to the mean." It is not correct, however, to conclude from our findings that there is no effect of placebo. Our focus was clinical, that is, whether placebos induce effects of a magnitude that is important to patients. We were unable to find such effects. We feel the question whether there is, or is not, an effect of