Correspondence



Is the Placebo Powerless?

To the Editor: On the basis of their meta-analysis, Hróbjartsson and Gøtzsche (May 24 issue)[1] doubt the power of the placebo. Such meta-analyses are inevitably restricted by the studies chosen and the sensitivity of their measures. For example, binary outcomes have less power to detect effects generally than do continuous outcomes, and both power and effect size for binary outcomes are very sensitive to base rates. The technique of meta-analysis was designed for trials addressing similar questions.[2,3] This was not at all the case with the studies analyzed by Hróbjartsson and Gøtzsche. The populations varied widely, influenced by the disorders and the active treatments used. The studies used 40 different outcome measures, some more reliable than others and some more likely to exhibit a response to placebo than others. This is the classic apples-and-oranges problem in meta-analysis. Furthermore, although pain, which was reduced by placebo across studies, has a subjective component, as do many medical symptoms, reports of pain are closely correlated with physiological stress.[4,5]

The placebo response in randomized clinical trials (as opposed to its clinical use in individual subjects) includes such statistical artifacts as regression to the mean, the expectations of both patients and evaluators, and drift in measurement of the response over time, as well as real effects such as spontaneous recovery, a tendency to seek treatment outside the study, and the response to additional attention and concern. These factors affect both placebo groups and no-treatment groups, even in the absence of a sugar pill or sham procedure. In short, this meta-analysis was closer to a comparison of two placebo groups than to an evaluation of the placebo effect. What this study shows is not that placebos do not improve anything, but rather that they do not improve everything.

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1. Hróbjartsson A, Gøtzsche PC. Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. N Engl J Med 2001;344:1594-602. [Erratum, N Engl J Med 2001;345:304.]
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To the Editor: In his 1955 article, Beecher was statistically naive to the extreme.[1] First, the 35.2 percent improvement reported by Beecher accounts only for patients who received placebo and had improvement. The figure does not account for patients who had worsening with placebo treatment. Gamblers would love to play under such rules, where losing hands do not count. Second, Beecher stated that he chose studies "at random," yet 7 of the 15 studies were his own.

In 1983, a colleague and I made a fresh estimate of the size of the before-and-after change with placebo treatment on the basis of a random sample of 30 randomized clinical trials identified by a Medline search.[2] The mean improvement per study was 9.9 percent. Then we used mathematical and empirical methods to estimate the size of the "improvements" we could expect from statistical regression. Regression helps explain why in groups of persons abnormal measures selected because they are abnormal improve on average when the measures are repeated.[3] For 15 objective laboratory measures, the expected improvement ranged from 2 to 37 percent. Our results show that the placebo may have no ef-

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fect, because the regression is large enough to account for the observed improvement after placebo treatment. In their marvelous study, Hróbjartsson and Gøtzsche have now shown directly that the placebo does have no effect. It is time to call a myth a myth.

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To the Editor: Hróbjartsson and Gøtzsche did not control for the potential therapeutic effects of clinical attention received by patients in the placebo and no-treatment groups. The clinician–patient relationship may have contributed to improvements observed in patients receiving placebo and in those receiving "no treatment." Hence, the absence of significant differences on the whole between placebo treatment and no treatment in these trials does not mean that the placebo effect is minimal or nonexistent. The authors acknowledge that their analysis did not assess the effects of the clinician–patient relationship, but they claim without argument that such effects "may be largely independent of any placebo intervention." This statement is surprising, since the clinician–patient relationship is widely considered to be one of the main factors contributing to placebo effects.[1] The authors' dismissal of the clinician–patient relationship as irrelevant to the placebo effect seriously undermines their skeptical conclusion about the clinical power of placebo interventions.

(The opinions expressed in this letter are those of the author and do not necessarily reflect the policy of the National Institutes of Health, the Public Health Service, or the Department of Health and Human Services.)

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1. Shapiro AK, Shapiro E. The powerful placebo: from ancient priest to modern physician. Baltimore: Johns Hopkins University Press, 1997.

To the Editor: A single, well-performed meta-analysis is insufficient to reject the traditional consensus about the placebo effect. In fact, other avenues of prospective research provide evidence that a placebo effect exists that is much more than regression to the mean or natural history. For example, multiple randomized, controlled trials designed to compare two different types of placebo (such as a saline injection vs. a sugar pill) suggest that in such diverse conditions as hypertension, varicose veins, and osteoarthritis, the outcomes with placebos that involve devices are significantly different from the outcomes with pill placebos.[1] If a placebo has no effect beyond natural history, changing the type of placebo should make no difference. Numerous experiments performed under laboratory conditions have demonstrated that the inhalation of placebo saline can have dramatic effects on asthma in both positive and negative directions, depending on the instruction given.[2] In addition, much of the data on basic mechanisms in the role of endogenous opioids and placebos indicates that placebo effects do, in fact, exist and that opioid receptors are implicated not only in analgesia but in respiratory responses.[3]

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To the Editor: The controls selected by Hróbjartsson and Gøtzsche did not constitute a do-nothing alternative.

We attempted to retrieve all the articles the authors cited that reported binary outcomes. We were successful in extracting data from 10 articles; 2 were not available to us,[1,2] and we were unable to extract the no-treatment data from 1.[3]

In most of the randomized, controlled trials, the no-treatment group still involved some form of treatment. Examples were contact with a psychiatrist, maintenance of interpersonal psychotherapy, weekly 60-minute small-group meetings, and additional pharmacotherapy. In some trials, patients were selected after a response to a specific treatment (e.g., only those who had a response to amitriptyline were enrolled in the trial by Klerman et al.,[4] and those with a response after placebo in the trial by Rabkin et al.).[5] Therefore, the hypothesis that there is no difference between placebo and no treatment was not actually tested, and no definitive conclusions can be drawn.

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To the Editor: The main reason we are skeptical about Hróbjartsson and Gøtzsche's condemnation of placebos in

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nontrial settings concerns expectations. A patient enrolled in a clinical trial with, say, one-to-one randomization knows that there is only a 50 percent chance of getting the putative active ingredient and, furthermore, that there is considerable doubt about the effectiveness of the active ingredient. This is very different from the use of placebos in nontrial settings, in which many patients may believe, 100 percent, that they are receiving a useful active substance. We hypothesize that the relation between doubt about the effectiveness of a treatment and its placebo effect (which we would define as the psychologically mediated effect of treatment) is nonlinear, with a huge reduction in the placebo effect once any substantial doubt is present.

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To the Editor: The importance of expectations was recently demonstrated by Amanzioa and colleagues,[1] who showed that hidden injections of analgesics are far less effective than open injections of the same substances. The investigator's expectations also contribute to the placebo response, as demonstrated by Gracely and colleagues.[2] Therefore, to obtain the full power of the placebo response as it occurs in clinical practice, study designs are needed that make the subject and the physician believe that the real drug is being administered. This cannot be accomplished by double-blind studies with informed consent, but it may be achieved with the balanced placebo design.[3] In this design, subjects are randomly assigned to one of four groups. The subjects in the first group are told they will receive a drug, and they do receive it; the subjects in the second group are told they will receive a drug, but instead they receive placebo; the subjects in the third group are told they will receive placebo and do receive it; and those in the fourth group are told they will receive placebo but instead receive a drug.

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To the Editor: If subjects do not believe they received the active treatment, no placebo effect is expected, which is what Hróbjartsson and Gøtzsche found. The correct analysis would compare subjects in the placebo group who believed they received the active treatment with subjects in the placebo group who believed they did not receive the active treatment. However, the patients' beliefs must be recorded before any effect can be noticed; those who have spontaneous improvement are more likely to believe that they received the active treatment (bias in favor of placebo).

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To the Editor: It is probably naive to attribute the placebo effect solely to receipt of the placebo itself.[1] Its effect may largely be a consequence of all the trappings associated with participating in a formal clinical trial,[2] such as the supplemental attention of enthusiastic and appreciative investigators. Accordingly, the placebo effect and the intertwined Hawthorne effect, in the most inclusive terms, are not totally confined to the placebo group but extend to no-treatment and active-treatment groups.[3]

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1. DiNubile MJ. Skepticism: a lost clinical art. Clin Infect Dis 2000;31:513-8.
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To the Editor: In his excellent editorial, Bailar[1] suggests that "it is not clear how one could study and compare the effects of placebo in research and nonresearch settings, since that would of course require a research study."

One approach is a study in which subjects are given placebos, which are identified as such but perhaps called "plakebos" or some similar name, and which are clearly identified on the package label as "chemically inert but shown to be effective in the symptomatic treatment of pain, anxiety, malaise, dysthymia," and so forth.

Furthermore, the label would state that the mechanism of help seems to be correlated with the belief that the pill will help. In other words, subjects would be told that although there is no known chemical basis for explaining why the pills work, they work best in those who believe they will be helpful.

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1. Bailar JC III. The powerful placebo and the Wizard of Oz. N Engl J Med 2001;344:1630-2.

The authors reply:

To the Editor: The interesting commentaries did not demonstrate flaws in our systematic review, so our conclusion that there is little evidence that placebo interventions in general have powerful effects remains unchanged.

Several commentators focus on the "placebo effect." The

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term has been used for overlapping but remarkably different phenomena — for example, the effect of placebo interventions, psychologically mediated effects, the effect of the patient–provider interaction, and the effect of expectations. The notion of a placebo effect does not appear in our report, and our result is neutral with respect to many of its meanings. We hope that our result is not misinterpreted as meaning that there is evidence of a lack of psychologically mediated effects.

Spiegel et al., Miller, Einarson et al., and DiNubile question the meaningfulness of a no-treatment control group. If our aim had been to study the effect of the patient–provider interaction, such control groups would have been problematic.[1] However, we studied the effect of placebo interventions — that is, whether patients fare better when they receive a placebo treatment. In this situation, a control group that does not receive the placebo intervention is crucial.

Kupers, Lilford and Braunholtz, and Shrier hypothesize that the informed-consent procedure reduces patients' expectations and the effects of placebos. They do not cite conflicting results of randomized trials investigating this question.[2,3] We assumed that investigators in the more recent studies we reviewed sought informed consent more often than those in the earlier studies. We therefore investigated whether the effect in earlier trials differed from that in more recent ones, but found no statistically significant difference.

Contrary to the assertion made by Spiegel et al., a broad approach to meta-analysis is often appropriate, in particular when there is no good a priori reason to exclude some conditions from consideration, as is the case with placebo and, for instance, homeopathy.[4]

Kaptchuk and Kupers cite other types of research (e.g., laboratory research), but their approach is not systematic and does not help answer the clinical question of whether patients are better off after receiving a placebo treatment.

Einarson et al. question the inclusion of trials in which both the placebo group and the control group received identical standard treatment. We found no difference between the results when the placebo intervention was the only treatment and the results when it was an add-on treatment. Einarson et al. attempted to retrieve the 32 articles that reported binary outcomes but were unable to obtain 2 articles and in some cases found it difficult to extract data. We retrieved the two articles by standard interlibrary loan, and data extraction sometimes required scrutiny of the trial reports or communication with the primary authors. Einarson et al. discuss only 10 of the 32 trials; this is not a recommended approach for meta-analysis.

To prove there is little, if any, effect of placebo interventions in all settings is impossible, even with a large number of heterogeneous trials. Despite our mostly negative findings, important effects of placebo interventions might exist — for example, in subgroups not identified in the review or in outcomes not included. However, the burden of proof now rests with those who claim there are important effects of placebo interventions. Such claims should be based on reliable evidence, preferably data from rigorously conducted, systematic reviews of randomized trials.

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High-Altitude Illness

To the Editor: Altitude sickness is common in the Himalayas, where thousands of people come for trekking every fall and spring. For those of us who offer health care in Nepal to travelers at high altitude (which Peter Hackett helped to start many years ago) the review by Hackett and Roach (July 12 issue)[1] was fascinating, but I do have a few comments.

More than overhydration, the great danger in the mountains is dehydration due to the general unavailability or poor quality of water or to the lack of thirst. Dehydration may simulate acute mountain sickness, as the authors suggest. It may also interfere with proper acclimatization[2] and aid in the pathogenesis of acute mountain sickness.[3] Hence, at our clinic we advise drinking adequate water (without going to extremes) so that the urine is clear. Epidemiologic studies have shown that respiratory infections may predispose persons to acute mountain sickness and not only to high-altitude pulmonary edema.[3,4] Therefore, persons with symptoms of a cold or influenza before a trek or a climb must be more cautious.

In the Himalayas, we caution people not to sleep more than 400 m above their sleeping altitude of the previous night, when this is logistically possible, although data regarding the effect of changes in sleeping altitude are lacking; 600 m may be too large a change. Finally, impaired cerebral autoregulation may contribute to high-altitude cerebral edema, as suggested, but my colleagues and I were amazed to find in a study we conducted that even healthy, well-adapted Sherpas had impaired cerebral autoregulation at 4300 m.[5]

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To the Editor: Hackett and Roach recommend that adults take acetazolamide at a dose of 125 mg twice a day to prevent high-altitude illness. They state that this low dose is as effective as larger doses, while implying that the minimal

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effective dose remains uncertain. Unfortunately the reference they cite[1] does not support this assumption. After a systematic review, Dumont et al.[1] concluded that 750 mg of acetazolamide was more effective than placebo, regardless of the rate of ascent (relative risk, 2.18; 95 percent confidence interval, 1.52 to 3.15), whereas a dose of 500 mg was not significantly more effective than placebo (relative risk, 1.22; 95 percent confidence interval, 0.93 to 1.59). Although it is likely that a dose of 750 mg would be associated with a higher incidence of paresthesia and polyuria than would the 250-mg dose suggested by Hackett and Roach, it does not seem reasonable to use a dose that is unlikely to provide any benefit and yet may have adverse effects.

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To the Editor: The use (and potential abuse) of dexamethasone at high altitude is becoming more commonplace. Although somewhat controversial, dexamethasone does not enhance the acclimatization process or reduce objective physiological abnormalities related to exposure to high altitudes but, rather, suppresses the symptoms of acute mountain sickness.[1] Severe rebound illness can occur when it is discontinued at high altitude.[2] For these reasons, dexamethasone should not be used immediately before or while ascending to a higher altitude, but should be reserved for treatment on descent or when descent to a lower altitude must be delayed.

With increasing frequency, modern high-altitude climbers favoring the "alpine-style" method of short, rapid ascents to high altitudes are using dexamethasone prophylactically immediately before their climbs, risking rebound disease in the event that they are unable to descend quickly. Most alpine-style climbers are able to avoid serious high-altitude illness by descending before the sequelae of hypoxemia incapacitate them. Others are increasingly pushing their limits from hours to days at very high altitudes, sustained by dexamethasone, which is a potentially dangerous strategy.

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To the Editor: Hackett and Roach refer to studies suggesting that a deficiency of nitric oxide may underlie the development of symptoms in vulnerable persons. I was surprised that they did not mention the therapeutic use of this gas in treating high-altitude pulmonary edema. Studies have found it to be beneficial at concentrations from 10 to 40 parts per million,[1,2] with improvement in clinical findings such as rales, as well as in findings on chest radiography.[1] Nitric oxide also markedly reduced the mean systolic pulmonary-artery pressure and improved oxygenation in susceptible mountaineers, although it worsened both in their colleagues who were resistant to high-altitude pulmonary edema.[2] In patients with high-altitude pulmonary edema, the effect on oxygenation of oxygen supplemented with nitric oxide significantly exceeds that of oxygen alone.[3] Since these effects occur rapidly, the administration of nitric oxide could be of critical value in severe cases of this illness.

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The authors reply:

To the Editor: We agree with Dr. Basnyat that dehydration in the mountains is a concern, but no compelling data confirm that dehydration has a role in acute mountain sickness. The report he cites demonstrated a correlation between lower water intake and acute mountain sickness, but causality could not be established; persons with acute mountain sickness are often nauseated and therefore have reduced fluid intake. The only well-controlled investigation found no effect of hydration status on the development of acute mountain sickness.[1] As for the rate of ascent, 600 m per day may indeed be too rapid for some, whereas for others, 400 m per day is agonizingly slow. Such is the problem with offering general guidelines.

We cited the article by Dumont et al. only to acknowledge the uncertainty regarding the lowest effective dose of acetazolamide. Unlike Dr. Ogilvie, we consider the conclusion by Dumont et al. invalid, for reasons that have already been described elsewhere.[2,3] In fact, 500 mg of acetazolamide per day is helpful during rapid ascent.[2,3] Only studies directly comparing different doses of acetazolamide will be able to establish the optimal dose; the meta-analysis of Dumont et al. does not.

Dr. White highlights the risk of dexamethasone abuse. Dexamethasone should not be used for routine prophylaxis, since it does not enhance acclimatization, as acetazolamide does. However, it is useful for those who have an intolerance to acetazolamide, preferably in the setting of rapid ascent to a high altitude with no further ascent until acclimatization has occurred. We agree that its use as a performance-enhancing agent at high altitude is dangerous. In addition, dexamethasone does not prevent high-altitude pulmonary edema, a deadly risk for those who push their limit of acclimatization.

In response to Dr. O'Brien: we did not mention nitric oxide as a therapeutic agent for high-altitude pulmonary edema because no clinical advantage over oxygen has yet been demonstrated, and its use is impractical in the field.

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Oxygen is remarkably effective for the rapid resolution of high-altitude pulmonary edema. Whether the finding of Anand et al.[4] that oxygen combined with nitric oxide is more effective than either alone for decreasing pulmonary vascular resistance will translate into a clinical benefit remains unknown. Perhaps the combination will prove useful for the occasional victim who does not have a prompt response to oxygen. Only a clinical trial can answer this question.

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Case 8-2001: Low Anion Gap in Lymphoplasmacytic Lymphoma

To the Editor: In his excellent discussion of Case 8-2001 (March 15 issue),[1] Dr. Wong did not mention that the low anion gap is another helpful clinical clue. On the day of admission, the patient had a relatively low anion gap of 5 mmol per liter, and the value on the third hospital day was 4 mmol per liter. Given such findings, the differential diagnosis is limited to three underlying mechanisms: a decrease in the levels of unmeasured anions (i.e., albumin); inaccuracies in the laboratory determinations of sodium or chloride that are related to the presence of hypertriglyceridemia, very high serum sodium values, hyperviscosity, or bromism; and an increase in unmeasured cations owing to the presence of cationic paraproteins (and occasionally extremely high levels of calcium, potassium, lithium, or magnesium). Since the serum albumin was reportedly normal and there was nothing to suggest circumstances that would lead to inaccurate laboratory results, the electrolyte levels on admission suggest the presence of a paraprotein due to a plasma-cell dyscrasia. Ultimately, of course, this did turn out to be the diagnosis. Murray et al.[2] called attention to this association in 1975.

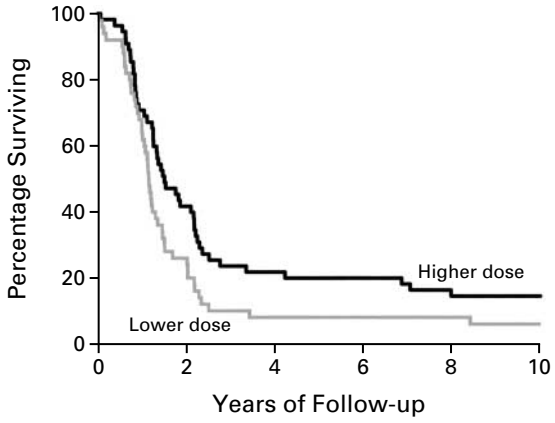
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Initial Chemotherapeutic Doses and Long-Term Survival in Limited Small-Cell Lung Cancer

To the Editor: We previously reported that in a multicenter, randomized trial that involved 105 patients with limited small-cell lung cancer, higher initial doses of cyclophosphamide and cisplatin improved overall survival.[1] The study was stopped early at the recommendation of an independent data-monitoring committee, and the median duration of follow-up at the time of publication was 33 months.[2] To evaluate whether these findings persisted over the long term, we reevaluated the patients after a median follow-up period of 11 years.

The updated overall survival rates for patients who received higher initial doses of cisplatin (100 mg per square meter of body-surface area) and cyclophosphamide (300 mg per square meter daily for four days) and for those who received lower initial doses (cisplatin, 80 mg per square meter; cyclophosphamide, 225 mg per square meter daily for four days) are shown in Figure 1. The two- and five-year survival rates were 42 percent and 26 percent, respectively, in the higher-dose group, and 20 percent and 8 percent, respectively, in the lower-dose group. The relative risk of death among those who received higher initial doses of chemotherapy, as compared with those who received lower doses, was 0.63 (95 percent confidence interval, 0.42 to 0.96). The results were similar when the analyses were stratified according to center.



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Higher dose	55	23	12	11	8	6
Lower dose	50	13	4	4	4	3

Figure 1. Overall Survival among Patients with Limited Small-Cell Lung Cancer, According to Treatment (Higher vs. Lower Initial Doses of Chemotherapy).
P=0.03 by the log-rank test for the comparison between the groups.

These results are consistent with previously published findings and demonstrate that moderate increases in the initial doses of drugs may lead to a significant improvement in

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long-term survival among patients with limited small-cell lung cancer.

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