Is the Placebo Powerless?

To the Editor: On the basis of their meta-analysis, Hróbjartsson and Gøtzsche (May 24 issue) 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. 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 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.

David Spiegel, M.D.
Helena Kraemer, Ph.D.
Robert W. Carlson, M.D.
Stanford University School of Medicine
Stanford, CA 94305
dspiegel@stanford.edu


To the Editor: In his 1955 article, Beecher was statistically naive to the extreme. 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. 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. For 15 objective laboratory measures, the expected improvement ranged from 2 to 37 percent. Our results show that the placebo may have no ef-
fect, because the regression is large enough to account for the observed improvement after placebo treatment. In their marvelous study, Hróbjartsson and Gotzsche have now shown directly that the placebo does have no effect. It is time to call a myth a myth.

CLEMENT J. MCDONALD, M.D.
Regenstrief Institute
Indianapolis, IN 46202-2872
cjm@regenstrief.org


To the Editor: Hróbjartsson and Gotzsche 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.)

FRANKLIN G. MILLER, PH.D.
National Institutes of Health
Bethesda, MD 20892-1156
fmiller@nih.gov


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

TED J. KAPTCHUK
Harvard Medical School
Boston, MA 02115
tkaptchuk@caregroup.harvard.edu


To the Editor: The controls selected by Hróbjartsson and Gotzsche 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,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 pharacotherapy. 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.

THOMAS E. EDINARSON, PH.D.
MICHEL HEMELS, M.S.C.
University of Toronto
Toronto, ON M5S 2S2, Canada
t.cinarson@utoronto.ca

PIETER STOLK
Utrecht Institute for Pharmaceutical Sciences
3584 CA Utrecht, the Netherlands


To the Editor: The main reason we are skeptical about Hróbjartsson and Gotzsche’s condemnation of placebos in
To the Editor: The importance of expectations was recently demonstrated by Amanzio 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.

RON KUPERS, PH.D.
Positron-Emission Tomography Center
DK-8000 Aarhus, Denmark
ron@pet.auh.dk


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).

IAN SHRIER, M.D., PH.D.
Sir Mortimer B. Davis Jewish General Hospital
Montreal, QC H3T 1E2, Canada

To the Editor: It is probably naïve to attribute the placebo effect solely to receipt of the placebo itself. 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

MARK J. DiNUBILE, M.D.
505 Bartram Rd.
Moorestown, NJ 08057
dinubi@aol.com


To the Editor: In his excellent editorial, Bailar1 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 “placebos” 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.

MICHAEL BELDOCH, PH.D.
1130 Park Ave.
New York, NY 10128
mbeldoch@ mindspring.com


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
flicting results of randomized trials investigating this ques-
tion 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 problem-
atic. However, we studied the effect of placebo interven-
tions — that is, whether patients fare better when they re-
ceive a placebo treatment. In this situation, a control group
that does not receive the placebo intervention is crucial.

Einarson et al. discuss only 10 of the 32 trials; this is not a rec-
ommended approach for meta-analysis. We retrieved the two articles by standard interlibrary loan,
that the informed-consent procedure reduces patients’ ex-
pectations and the effects of placebos. They do not cite con-
trary 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 con-
ditions from consideration, as is the case with placebo and,
for instance, homeopathy.

Kaptchuk and Kupers cite other types of research (e.g.,
laboratory research), but their approach is not systematic
and does not answer the clinical question of whether
Kupers, Lilford and Braunholtz, and Shrier hypothesize
that the informed-consent procedure reduces patients’ ex-
pectations and the effects of placebos. However, we studied the effect of placebo interven-
tions — that is, whether patients fare better when they re-
ceive a placebo treatment. In this situation, a control group
that does not receive the placebo intervention is crucial.

Kaptchuk and Kupers cite other types of research (e.g.,
laboratory research), but their approach is not systematic
and does not 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 be-
tween 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 ar-
ticles 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. Ein-
arson et al. discuss only 10 of the 32 trials; this is not a rec-
ommended approach for meta-analysis.

To prove there is little, if any, effect of placebo interven-
tions in all settings is impossible, even with a large number
of heterogeneous trials. Despite our mostly negative find-
ings, important effects of placebo interventions might ex-
ist — 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 re-
liable evidence, preferably data from rigorously conducted,
 systematic reviews of randomized trials.

1. Hróbjartsson A. The uncontrollable placebo effect. Eur J Clin Pharma-
of the effect of informed consent on the analgesic activity of placebo and
informed consent influence therapeutic outcome? A clinical trial of the
1986;293:363-4.
4. Gotzsche PC. Why we need a broad perspective on meta-analysis: it may

High-Altitude Illness

To the Editor: Altitude sickness is common in the Him-
layas, 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) was fascinating, but I do have a few comments.

More than overhydration, the great danger in the moun-
tains 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 and aid in
the pathogenesis of acute mountain sickness. 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 per-
sons to acute mountain sickness and not only to high-alti-
tude pulmonary edema. Therefore, persons with symp-
toms 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 re-
garding 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 ed-
ema, 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.

BUDHA BASNYAT, M.D.
Nepal International Clinic
Katmandu, Nepal
nic@naxal.wlink.com.np

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

107-14.
2. West JB. High life; a history of high altitude physiology and medicine.
3. Basnyat B, Lemaster J, Litch JA. Everest or Bust: a cross sectional, ep-
idemiologic study of acute mountain sickness at 4243 meters in the Hi-
malayas, Aviat Space Environ Med 1999;70:867-73.
4. Murdoch DR. Symptoms of infection and altitude illness among hikers
in the Mount Everest region of Nepal. Aviat Space Environ Med 1995;66:
148-51.
5. Jansen GFA, Krins A, Basnyat B, Bosch A, Odoom JA. Cerebral auto-
regulation in subjects adapted and not adapted to high altitude. Stroke

To the Editor: Hackett and Roach recommend that adults
take acetazolamide at a dose of 125 mg twice a day to pre-
vent high-altitude illness. They state that this low dose is
effective as larger doses, while implying that the minimal
effective dose remains uncertain. Unfortunately the refer-
dence they cite does not support this assumption. After a sys-
tematic review, Dumont et al. 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.

R.I. OGILVIE, M.D.
Toronto Western Hospital
Toronto, ON MST 288, Canada
ri.ogilvie@utoronto.ca

To the Editor: The use (and potential abuse) of dexamet-
asone at high altitude is becoming more commonplace. Al-
though somewhat controversial, dexamethasone does not
enhance the acclimatization process or reduce objective phys-
iological 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 discon-
tinued 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 climb-
ers 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 al-
pine-style climbers are able to avoid serious high-altitude
illness by descending before the sequelae of hypoxemia in-
capitate them. Others are increasingly pushing their lim-
its from hours to days at very high altitudes, sustained by
dexamethasone, which is a potentially dangerous strategy.

ANDREW P. WHITE, M.D.
Yale University School of Medicine
New Haven, CT 06510
andrew.white@yale.edu


To the Editor: Hackett and Roach refer to studies sug-
gest that a deficiency of nitric oxide may underlie the
development of symptoms in vulnerable persons. I was sur-
pised 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 pul-
monary-artery pressure and improved oxygenation in sus-
ceptible 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 ni-
tric oxide significantly exceeds that of oxygen alone.3 Since
these effects occur rapidly, the administration of nitric ox-
ide could be of critical value in severe cases of this illness.

BRIAN O'BRIEN, M.MED.SC., F.C.A.R.C.S.I.
Beaumont Hospital
Dublin 9, Ireland
drobin@hotmail.com

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 sick-
ness. 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 sick-
ness 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 in-
deed 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 acknowl-
edge the uncertainty regarding the lowest effective dose of
acetazolamide. Unlike Dr. Ogilvie, we consider the conclu-
sion by Dumont et al. invalid, for reasons that have already
been described elsewhere.2,3 In fact, 500 mg of acetazolo-
mide 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 Du-
mont 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-enhanc-
ing agent at high altitude is dangerous. In addition, dex-
amethasone does not prevent high-altitude pulmonary
edema, a deadly risk for those who push their limit of ac-
climatization.

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.

3. Anand BS, Prasad BA, Chugh SS, et al. Effects of nitric oxide and oxy-
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.

PETER H. HACKETT, M.D.
International Society for Mountain Medicine
Ridgway, CO 81432
hackett@ssmmed.org

ROBERT C. ROACH, PH.D.
New Mexico Resonance
Albuquerque, NM 87108


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.

STEPHEN J. GLUCKMAN, M.D.
University of Pennsylvania School of Medicine
Philadelphia, PA 10104
gluckman@mail.med.upenn.edu


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.

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 long-term survival.

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.

<table>
<thead>
<tr>
<th>NO. AT RISK</th>
<th>HIGHER DOSE</th>
<th>LOWER DOSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIGHER DOSE</td>
<td>55</td>
<td>23</td>
</tr>
<tr>
<td>LOWER DOSE</td>
<td>50</td>
<td>13</td>
</tr>
</tbody>
</table>

[Graph not shown in text]

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

RODRIGO ARRIGADAR, M.D.
JEAN-PIERRE PIGNON, M.D., PH.D.
THIERRY LE CHEVALIER, M.D.
Institut Gustave-Roussy
94805 Villejuif CEDEX, France
gocchi@ctcinet.fcl

doses and survival in patients with limited small-cell lung cancer.

Correspondence Copyright © 2001 Massachusetts Medical Society.