

Trial methodology and patient characteristics did not influence the size of placebo effects on pain

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Abstract

Objective: To determine whether trial-design, patient-type, or placebo-type factors influence the size of the placebo analgesic effect in clinical trials.

Study Design and Setting: Trials that measured pain outcomes in Hróbjartsson and Gøtzsche's meta-analysis were retrieved and coded for eight factors potentially predictive of placebo effect size. Random effects meta-regression was used to explore the predictive power of each factor on placebo effect size. The factors investigated aspects of trial design (nonstandardized co-analgesia, co-intervention), patients (pain type, patient group, residual pain score), and placebo (placebo type, indistinguishability, structural equivalence). The meta-analysis undertaken in the original study was also repeated to confirm the results.

Results: The pooled effect of placebo was 3.2 points on a 100-point scale (95% confidence interval [CI] = 1.6–4.7). None of the selected factors influenced the size of placebo effect: the effect of all factors was close to zero, all CIs spanned 0, and *P*-values ranged from 0.13 to 0.90.

Conclusion: This study confirms the findings of previous researchers that, at present, the evidence for large placebo analgesic effects in clinical trials is lacking. Importantly, this analysis also establishes that larger placebo effects are not associated with particular aspects of the trial methodology, patient, or placebo type. © 2008 Elsevier Inc. All rights reserved.

Keywords: Placebo; Analgesia; Meta-regression; Pain; Trial design; Clinical trial

1. Introduction

In the 1950s, a review by Beecher was responsible for persuading the scientific community that placebo effects were powerful enough to produce satisfactory relief in a large proportion of patients with various medical conditions [1]. Recently, Hróbjartsson and Gøtzsche argued that Beecher had overestimated the size of the placebo effect because his estimates were based on within-group improvements reported in placebo groups [2,3]. Within-group improvements reflect not only the placebo effect but also factors such as the natural course of the condition and regression to the mean. Hróbjartsson and Gøtzsche pointed out that the size of placebo effects is more accurately estimated by subtracting improvements seen in a no-treatment group from the improvement seen in a placebo group.

This reasoning underpinned Hróbjartsson and Gøtzsche's reviews of the effects of placebo [2,3]. They systematically

reviewed randomized trials that included both placebo and no-treatment conditions. Meta-analysis of this clinically heterogeneous set of trials revealed statistically significant effects on pain of approximately 6 points on a 100-point scale. We suspect, few clinicians would consider effects of this magnitude to be of clinical significance. Additionally, there was some indication that the effect may have been due to a small study effect, such as reporting bias [3].

Despite the striking evidence provided by the Hróbjartsson and Gøtzsche reviews that placebos have only modest effects, their findings have often been ignored in recent research [4–7]. This may be in part due to criticisms directed at the methods used in the reviews, such as pooling studies on a heterogeneous group of medical conditions [6–8] and including trials in which co-interventions were allowed in the no-treatment group [9]. In line with these criticisms, we were concerned that placebo effects were potentially masked by some aspect of the trial methodology or patient type. Our aim was to define some of these potentially confounding factors and test whether they influenced placebo effect size. For the purposes of this article, we have

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considered placebo effects to be those therapeutic effects resulting from the treatment ritual. We acknowledge that this definition does not take into account the totality of the effect of interactions between patients and providers [10].

2. Methods

We independently reanalyzed the studies identified by Hróbjartsson and Gøtzsche who reported on pain outcomes. Subsequently we conducted a series of meta-regressions to evaluate whether characteristics of trial methodology or patient type were predictive of placebo effect size.

2.1. Data extraction

The studies included in the “pain” comparison of Hróbjartsson and Gøtzsche’s updated review [3] were collected, data were extracted, and the studies were coded for eight preselected trial-level features considered potentially predictive of placebo effect size. Data extraction and coding were completed independently by two authors, and inconsistencies were resolved by consensus or by a third author.

Means and standard deviations of pain scores were extracted from the first postintervention time-point. Most pain data were reported on 0–10 or 0–100 scales; where necessary they were converted to a 0–100 scale. To reduce the impact of one source of heterogeneity, we decided a priori to analyze only pain scores reported on continuous scales. The size of the placebo effect was estimated from the between-group differences in mean outcomes or, where outcomes scores were not reported, between-group differences in mean change scores of the placebo and no-treatment groups [11].

Prior to data extraction, we selected eight characteristics that potentially influence the magnitude of the placebo effect. Selection of these features was based on opinions expressed in the literature and consensus among the authors, and are outlined below. The features assess aspects of the trial design (co-analgesia, co-interventions), aspects of the patient (pain type, patient group, residual pain score), and aspects of the placebo (placebo type, indistinguishability, equivalence).

2.1.1. Nonstandardized co-analgesia

Administration of analgesics to subjects on an “as-needed” basis could reduce the apparent size of the placebo effect. Our rationale was that if the placebo had an analgesic effect subjects in the no-treatment group might use relatively more co-analgesia, and that this could reduce the difference in pain scores between the placebo and no-treatment groups.

2.1.2. Co-intervention

In some trials, an intervention other than the placebo was applied to both placebo and no-treatment groups. This

feature was included to determine if the analgesic effect of the co-intervention overwhelmed the placebo.

2.1.3. Pain type

Trials were coded according to whether the intervention was for “acute” or “chronic” pain. Chronic pain was defined as pain that had persisted for more than 3 months in all subjects. All studies that investigated pain from surgical or other medical procedures were coded as “acute.”

2.1.4. Patient group

To test whether different classes of pain conditions are intrinsically more or less responsive to placebo interventions, trials were coded according to pain condition. The categories were surgical, procedural, headache, musculoskeletal, low back pain, and other.

2.1.5. Residual pain score

Postintervention pain scores in the no-treatment group were recorded for all studies. This feature was used to determine if “floor effects” attenuated estimates of effects of placebo.

2.1.6. Placebo type

Placebo interventions were classified as physical, pharmacological, or psychological [3].

2.1.7. Placebo indistinguishability

This feature was considered to reflect the adequacy of the placebo intervention. A placebo intervention was considered indistinguishable if “an objective observer could not identify differences [between the placebo and active interventions]” [12]. All trials that investigated psychological interventions were coded as “no” for this feature.

2.1.8. Placebo equivalence

A second measure of placebo adequacy also involved comparison of placebo and active interventions. The interventions were considered equivalent if six criteria were met [12]: equivalent number of sessions, length of sessions, format (group or individual), level of therapist training, individualization (the degree to which the intervention was tailored to the individual), and relevance (the appropriateness of the intervention with regard to the condition).

2.2. Data analysis

Pooled estimates of effects of placebo were obtained using a random effects model. As all pain data were scaled on a common 0–100 scale, the pooled effects of placebo were expressed using this metric.

Random effects meta-regression was used to explore effects of continuous and dummy-coded dichotomous predictors on the magnitude of the placebo effect. Categorical predictors were analyzed with a mixed-effects model. There was one continuous predictor (residual pain score),

five dichotomous predictors (nonstandardized co-analgesia, co-intervention, placebo indistinguishability, placebo equivalence, and pain type), and two categorical predictors (placebo type, patient group). As the number of predictors was more than a small proportion of the number of trials (eight predictors and 44 trials) we investigated the effect of each predictor in a separate meta-regression. The analysis was conducted using MetaWin v2.1 and Comprehensive Meta-Analysis v2.2 software.

3. Results

Point estimates of the effects of placebo from individual trials ranged from -12 to 18 points on a 100-point scale, and the distribution of effects was approximately normal (Fig. 1A). Visual inspection of funnel plots did not suggest small sample bias (Fig. 1B).

The pooled estimate was that placebo reduced pain, on average, by 3.2 points on a 100-point scale (95% confidence interval [CI] = 1.6–4.7).

There was evidence of moderate statistical heterogeneity ($I^2 = 39.3\%$; $Q = 70.93$, $df = 43$, $P = 0.005$). That is, between-study variation exceeded that which could plausibly be attributed to sampling error in individual trials). Consequently we conducted a series of meta-regressions to explore the source of variability of estimates.

Estimates of the effect of each of the predictors are given in Table 1. All predictors had near-zero effects, and the 95% CI ruled out effects of greater than 6 points on the 100-point scale.

The results of the meta-regression indicate that none of the selected variables predict the size of the placebo effect. This is to say there is no evidence that the presence or absence of nonstandardized analgesia or co-intervention influences placebo effect size. There is no evidence that patients are more or less likely to report a placebo analgesic effect if their pain is acute or chronic, or results from surgery, a procedural intervention, headache, musculoskeletal pathology, or from some other cause. Placebo effect size is not predicted by absolute pain level, as measured by the pain score in the control group at the follow-up stage. Finally, there is no evidence that the size of the placebo effect is influenced by whether the placebo is pharmaceutical, physical, or psychological or by the degree to which it mimics the active treatment.

4. Discussion

Our analysis confirms the conclusions of Hróbjartsson and Gøtzsche that, at least in the context of clinical trials, placebo interventions appear to have little effect on pain. The results of the meta-regression analysis found that none of eight trial-level factors describing characteristics of the placebo, trial design, and trial participants predicted the

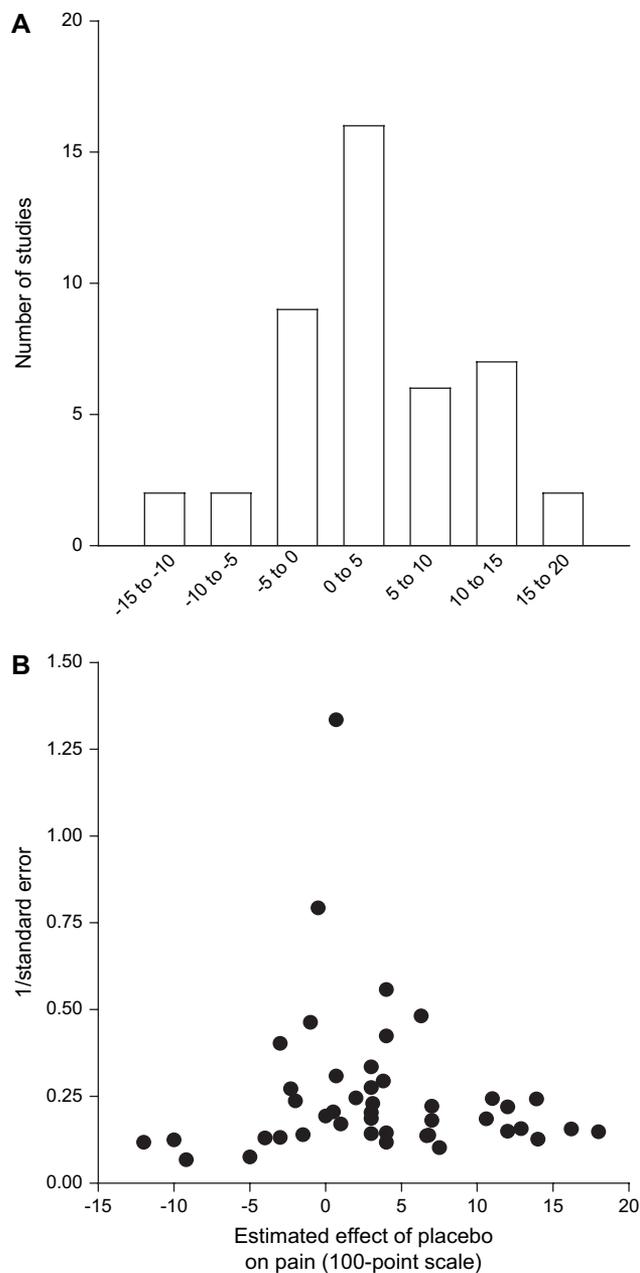


Fig. 1. Distributions of effects of placebo. A) Distribution of estimates of effects of placebo. B) Funnel plot showing relationship between estimates of effect and the inverse of the standard error of the estimate.

size of placebo effects. Our results also suggest that some of the criticisms of Hróbjartsson and Gøtzsche's review are not valid. For example, the result of Hróbjartsson and Gøtzsche's review was questioned by several authors [5–8] and attributed to pooling a heterogeneous group of conditions and outcome measures. We reviewed only the studies that specifically measured pain as an outcome and found a similar result to Hróbjartsson and Gøtzsche. We also found no evidence that placebo effects depended on the type of pain condition being treated. To address concerns raised by Einarson et al. [9] and Wampold et al.

Table 1
“Effects” of predictors on estimates of effect of placebo

	Effect	95% CI	P
Dichotomous predictors			
Nonstandardized co-analgesia	2.1	−0.9 to 5.2	0.17
Co-intervention	1.7	−1.8 to 5.2	0.34
Placebo indistinguishability	2.5	−0.7 to 5.8	0.13
Placebo equivalence	0.2	−3.5 to 4.0	0.90
Pain type	1.2	−1.9 to 4.4	0.18
Continuous predictor			
Residual pain score (0–100 scale)	0.0007	−0.0042 to 0.0056	0.77
Categorical predictor			
Placebo type (three levels ^a)			0.65
Patient group (five levels ^b)			0.72

Note: The effects are meta-regression coefficients. Coefficients of dichotomous variables can be interpreted as effects of predictors. They show, for example, that trials with nonstandardized co-analgesia report, on average, that placebo reduces pain by 2.1 points less than trials with standardized co-analgesia. The continuous predictor indicates that placebo effects increased, on average, by 0.0007 points for every point of residual pain in the no-treatment group. Effects are not given for categorical predictors.

^a Physical, pharmacological, or psychological.

^b Surgical, procedural, headache, musculoskeletal, low back pain, and other.

[13] we examined whether placebo effect size was predicted by the use of a co-intervention and by indistinguishability of the placebo and active treatment conditions and found no evidence to support this conclusion. Finally, only continuous outcomes were extracted for our analysis, avoiding concerns about the lower sensitivity to detect changes of dichotomous outcomes [5].

The list of trial-level factors entered into our meta-regression is not exhaustive, and it may be argued that important predictors have been missed. One such predictor is the expectation of the therapeutic benefit, regarded as one of the crucial mechanisms underlying placebo effects [14]. Although we were unable to obtain direct measures of expectancy from the included trials, we did include two measures of placebo adequacy that could influence expectancy, namely indistinguishability and equivalence. We acknowledge that this does not provide an absolute measure of expectation, rather a measure of the relationship between the real and placebo interventions.

There is evidence that placebo effects can be maximized by the use of suggestions of powerful analgesia [15–18]. Although this approach is frequently used in studies investigating the placebo effect per se, or placebo effect trials [19], the focus of a placebo group in clinical trials is usually not to maximize placebo’s efficacy but to mimic the index intervention without invoking its theorized “active” constituent. Therefore, it is possible that placebo effects in clinical trials could be greater if placebo groups were designed to manipulate expectancy rather than to resemble the active treatment. Vase et al. reviewed this evidence and compared the placebo effect in clinical analgesic trials (which tend to use comparable placebos) with trials investigating placebo analgesic mechanisms (which allegedly use maximized

placebos) and found that placebo effects were significantly higher in trials of placebo mechanisms [15]. Unfortunately serious errors were made in the extraction, handling, and analysis of Vase’s data, and a recent reanalysis [20], after correcting for errors, found that the mean difference between trials of placebo mechanisms and clinical analgesic trials was five times less than that reported in the original analysis.

To make a distinction between these two approaches to the implementation of placebo groups, we recommend the use of the terms “comparable placebo,” where expectancy is matched to that of the index intervention, and “maximized placebo,” where the greatest possible expectation of benefit is attached to the placebo condition. A similar terminology is used by Hróbjartsson to characterize study groups in clinical trials [19].

Our study showed that placebo effects in clinical trials are small and are not associated with an obvious aspect of trial design or patient characteristics. This evidence suggests that both placebo and no-treatment groups may represent feasible strategies to control for “undesirable effects” in clinical trials, including placebo effects. Nevertheless, because placebo groups have the potential to control for other forms of biases in clinical trials [21], they are still a helpful tool when an active comparator of proven efficacy is not available.

5. Conclusion

In the context of clinical trials and along with other researchers, we found that placebo interventions produce little more reduction in pain than no treatment. Importantly we found no evidence that placebo effects were masked by some aspect of the trial methodology, placebo, or patient type. At present, the evidence for large placebo analgesic effects in clinical trials is still lacking.

References

- [1] Beecher H. The powerful placebo. *JAMA* 1955;159:1602–6.
- [2] Hróbjartsson A, Gotzsche P. Is placebo powerless? *N Engl J Med* 2001;344:1594–602.
- [3] Hróbjartsson A, Gotzsche P. Is placebo powerless? Update of a systematic review with 52 new randomized trials comparing placebo with no treatment. *J Intern Med* 2004;256:91–100.
- [4] Wager T, Rilling J, Smith E, Sokolik A, Casey K, Davidson R, et al. Placebo-induced changes in fMRI in the anticipation and experience of pain. *Science* 2004;303:1162–7.
- [5] Spiegel D. Placebos in practice: doctors use them, they work in some conditions, but we don’t know how they work. *BMJ* 2004;329:927–8.
- [6] Stewart-Williams S, Podd J. The placebo effect: dissolving the expectancy versus conditioning debate. *Psychol Bull* 2004;130:324–40.
- [7] Evans D. Placebo. Mind over matter in modern medicine. 2nd edition. London: Harper Collins Publishers; 2004.
- [8] Spiegel D, Kraemer H, Carlson R. Is the placebo powerless?. [Letter]. *N Engl J Med* 2001;345:1276.
- [9] Einarson TE, Hemels M, Stolk P. Is the placebo powerless?. [Letter]. *N Engl J Med* 2001;345:1277.

- [10] Hróbjartsson A. What are the main methodological problems in the estimation of placebo effects? *J Clin Epidemiol* 2002;55:430–5.
- [11] Green S, Deeks J, Savio F. Meta-analysis of continuous data: does the end justify the mean? In: *BMC Abstracts: 9th International Cochrane Colloquium: 2001; Lyon, France; 2001*.
- [12] Baskin T, Tierney C, Minami T, Wampold B. Establishing specificity in psychotherapy: a meta-analysis of structural equivalence of placebo controls. *J Consult Clin Psychol* 2003;71:973–9.
- [13] Wampold B, Minami T, Tierney S, Baskin T, Bhati K. The placebo is powerful: estimating placebo effects in medicine and psychotherapy from randomized clinical trials. *J Clin Psychol* 2005;61:835–54.
- [14] Benedetti F, Arduino C, Costa S, Vighetti S, Tarenzi L, Rainero I, et al. Loss of expectation-related mechanisms in Alzheimer's disease makes analgesic therapies less effective. *Pain* 2006;121:133–44.
- [15] Vase L, Riley J, Price D. A comparison of placebo effects in clinical analgesic trials versus studies of placebo analgesia. *Pain* 2002;99:443–52.
- [16] de Pascalis V, Chiaradia C, Carotenuto E. The contribution of suggestibility and expectation to placebo analgesia phenomenon in an experimental setting. *Pain* 2002;96:393–402.
- [17] Price D, Milling L, Kirsch I, Duff A, Montgomery G, Nicholls S. An analysis of factors that contribute to the magnitude of placebo analgesia in an experimental paradigm. *Pain* 1999;83:147–56.
- [18] Pollo A, Amanzio M, Arslanian A, Casadio C, Maggi G, Benedetti F. Response expectancies in placebo analgesia and their clinical relevance. *Pain* 2001;93:77–84.
- [19] Hróbjartsson A. The uncontrollable placebo effect. *Eur J Clin Pharmacol* 1996;50:345–8.
- [20] Hróbjartsson A, Gøtzsche PC. Unsubstantiated claims of large effects of placebo on pain: serious errors in meta-analysis of placebo analgesia mechanism studies. *J Clin Epidemiol* 2006;59:336–8.
- [21] Jüni P, Altman G, Egger M. Assessing the quality of controlled clinical trials. *BMJ* 2001;323:42–6.