Journal of Clinical Epidemiology 68 (2015) 442–451

Journal of Clinical Epidemiology

A systematic review found no consistent difference in effect between more and less intensive placebo interventions

Margrit Fässler[a,*,1], Karin Meissner[a,1], Jos Kleijnen[b], Asbjørn Hróbjartsson[c], Klaus Linde[a]

[a]*Institute of General Practice, Klinikum rechts der Isar, Technische Universität München, Orleansstrasse 47, 81667 Munich, Germany*
[b]*School for Public Health and Primary Care (CAPHRI), Maastricht University, P.O. Box 616, 6200 MD Maastricht, The Netherlands*
[c]*Nordic Cochrane Centre, Rigshospitalet, 7811, Blegdamsvej 9, 2100 Copenhagen, Denmark*

Accepted 24 November 2014; Published online 17 December 2014

Abstract

Objectives: It has been suggested that some placebo interventions might be associated with larger clinical effects than others. In a systematic review, we investigated whether there is evidence from direct comparisons in randomized clinical trials including two or more placebo groups supporting this hypothesis.

Study Design and Setting: Eligible trials were identified through electronic database searches and citation tracking up to February 2013. Placebo interventions in a trial were categorized into a more intense and a less intense intervention based on complexity, invasiveness, or route of administration and time needed for application.

Results: Twelve studies with 1,059 patients receiving placebo met the eligibility criteria. Studies were highly heterogeneous regarding patients, interventions, outcomes, and risk of bias. Seven studies did not find any significant differences between the more intense and the less intense placebo intervention, four studies found differences for single outcomes, and one study consistently reported significantly larger effects of the more intense placebo. An explorative meta-analysis yielded a standardized mean difference −0.22 (95% confidence interval: −0.46, 0.02; $P = 0.07$; $I^2 = 68\%$).

Conclusion: In the studies included in this review, more intense placebos were not consistently associated with larger effects than less intense placebos.

Keywords: Placebos; Placebo effect; Randomized controlled trial; Systematic review; Therapy; Treatment outcome

1. Introduction

When evaluating the efficacy of medical treatments, placebo controls are an important tool in randomized controlled trials. They have several functions such as separating specific from nonspecific effects and as reducing biases by means of blinding participants or investigators. Placebo controls are thought to be essential to evaluate whether a medical intervention has pharmacologic or physical activity that benefits patients and to confirm a postulated mechanism of action of a therapy. However, the response to placebo is not constant. Based on the assumption that placebo effects are triggered by the psychosocial context of the therapy [1], it seems plausible that the effects depend on many factors such as the prevailing condition or individual characteristics, the type of placebo intervention used, and the information given to participants. There is some evidence that the response varies depending on the type of placebo intervention used (eg, Kaptchuk et al. [2]), how such interventions are provided (eg, in an enthusiastic or a neutral manner; eg, di Blasi et al. [3]), and how informed consent is obtained (eg, Bergmann et al. [4]).

Systematic variations in placebo responses due to the type of placebo used would have important implications for the interpretation of clinical trials. If, for instance, in chronic pain conditions, some complex placebo procedures were systematically associated with larger placebo response rates than, for example, the prescription of a

Funding: This review was funded by the German Ministry of Education and Research (BMBF) (01KG0924).

Competing interests: All the authors declare that they have no conflicts of interest to disclose. M.F., K.M., and K.L. reported grants from Bundesministerium für Bildung und Forschung (01KG0924) (German Ministry of Education and Research), during the conduct of the study. J.K. and A.H. reported personal fees from the same grants for reimbursement of travel costs and allowances during the conduct of the study. J.K. reported various grants from pharmaceutical companies outside the submitted work.

[1] These two authors contributed equally to this work.

* Corresponding author. Tel.: +41 44 634 4081; fax: +41 44 634 8389.
E-mail address: faessler@ethik.uzh.ch (M. Fässler).

http://dx.doi.org/10.1016/j.jclinepi.2014.11.018
0895-4356/

What is new?

Key findings

- We found only 12 randomized controlled trials with two or more groups receiving placebos, which differed by route of administration or other important aspects. The available studies provide only weak evidence of differences between the effects of distinctive placebo interventions.

What this adds to what was known?

- This study provides direct comparisons of different types of placebos, whereas so far we only had evidence from indirect comparisons.

What is the implication and what should change now?

- Further carefully designed studies are desirable.

placebo pill, trials that compare oral drugs with placebo drug would have a higher a priori likelihood to find a significant difference than trials that compare more complex interventions with the corresponding placebo. This would also imply that without a direct comparison of the complex intervention and the drug, it could happen that the complex intervention would be considered a placebo due to not finding an effect over the sham control while still being more effective than the drug (shown to be superior to placebo). These considerations have been named ''efficacy paradox'' [5]. The results of three-armed trials of acupuncture (eg, Haake et al. [6]) and a meta-analysis of acupuncture for migraine prophylaxis (Linde et al. [7]) lend some support to this idea.

The most reliable way to investigate whether one type of placebo intervention is associated with larger clinical effects than another would be in randomized trials including both. However, such trials are rare and dispersed over a variety of conditions. Until now, only one narrative review of a few studies exists. It suggested that sham acupuncture and other complex interventions might be associated with larger effects than placebo pills [8]. We aimed to investigate whether there is evidence from randomized controlled trials including two or more different placebo control groups that some placebo or sham interventions are more effective than others.

2. Methods

We performed a systematic review with explorative meta-analyses. Basic methods for searching and selecting studies, data extraction, quality assessment, categorizing placebo interventions, and summarizing of results were predefined in a review protocol. Methods were refined during the review process (adding search methods, further specification or selection and categorization criteria, planning details of summarizing study results).

2.1. Search strategies

We searched MEDLINE, EMBASE, the Cochrane Controlled Trials Register (CENTRAL), PsychInfo, Google Scholar, and HighWire from inception to February 2013. For database searches, we used a combination of key words and text words including terms such as ''placebo,'' ''sham,'' or ''mock'' and terms related to different treatments such as drug therapy, psychological treatments (eg, behavior therapy), physical treatments (eg, radiotherapy), treatments with medical devices (eg, biofeedback), or spiritual therapies. Besides these, we searched using several combinations of search terms for different routes of administration for pharmacologic placebos (placebo pills, injections, inhalations, and so forth). These searches were combined with validated filters for randomized controlled trials [9]. The strategy was inductive and iterative using search terms found in potentially relevant publications. The search strategy for MEDLINE is shown in Appendix at www.jclinepi.com. We also tried to identify relevant studies by contacting experts and reviewing articles on related topics.

2.2. Selection criteria

At least two reviewers assessed the eligibility of the studies. To be included, studies had to meet the following criteria: (1) allocation to groups: explicitly randomized; (2) participants: subjects with any condition and a treatment or to prevent a disease or adverse event; (3) intervention/comparison groups: at least two different placebo interventions or control groups that could be interpreted as placebo controls in a broad sense such as sham treatment or attention control missing the specific component of experimental treatment (eg, a placebo pill and sham biofeedback or a placebo pill and sham acupuncture) and which differed by the route of administration or other important aspects; (4) outcomes: measurement and reporting of at least one clinical outcome (eg, response, symptom severity adverse events).

The comparison of a subcutaneous vs. intravenous placebo group was not considered because we judged these placebos to be too similar. Both types of injections penetrate the skin, and information to the patient about side effects includes similar information such as risk of infection or bleeding at the site of injection. No treatment groups and usual care groups were not considered placebo interventions. Studies exclusively measuring outcomes without direct relevance to a patient (eg, biochemical outcomes without direct relation to the severity of the disease) were not included. We excluded such studies, as the link from a biochemical parameter to clinical relevance is often inconsistent, unclear, or controversial. We decided to focus