Journal of Clinical Epidemiology 87 (2017) 35–46

Journal of Clinical Epidemiology

ORIGINAL ARTICLES

Active placebo control groups of pharmacological interventions were rarely used but merited serious consideration: a methodological overview

Jakob Solgaard Jensen[a,*], Andreas Ørsted Bielefeldt[a], Asbjørn Hróbjartsson[a,b]

[a]*The Nordic Cochrane Centre, Rigshospitalet Department 7811, Blegdamsvej 9, 2100 Copenhagen Ø, Denmark*

[b]*Center for Evidence-Based Medicine, University of Southern Denmark/Odense University Hospital, Sdr. Boulevard 29, indgang 50 (Videncentret), Odense C 5000, Denmark*

Accepted 3 March 2017; Published online 22 March 2017

Abstract

Objectives: Active placebos are control interventions that mimic the side effects of the experimental interventions in randomized trials and are sometimes used to reduce the risk of unblinding. We wanted to assess how often randomized clinical drug trials use active placebo control groups; to provide a catalog, and a characterization, of such trials; and to analyze methodological arguments for and against the use of active placebo.

Study Design and Setting: An overview consisting of three thematically linked substudies. In an observational substudy, we assessed the prevalence of active placebo groups based on a random sample of 200 PubMed indexed placebo-controlled randomized drug trials published in October 2013. In a systematic review, we identified and characterized trials with active placebo control groups irrespective of publication time. In a third substudy, we reviewed publications with substantial methodological comments on active placebo groups (searches in PubMed, The Cochrane Library, Google Scholar, and HighWirePress).

Results: The prevalence of trials with active placebo groups published in 2013 was 1 out of 200 (95% confidence interval: 0–2), 0.5% (0–1%). We identified and characterized 89 randomized trials (published 1961–2014) using active placebos, for example, antihistamines, anticholinergic drugs, and sedatives. Such trials typically involved a crossover design, the experimental intervention had noticeable side effects, and the outcomes were patient-reported. The use of active placebos was clustered in specific research settings and did not appear to reflect consistently the side effect profile of the experimental intervention, for example, selective serotonin reuptake inhibitors were compared with active placebos in pain trials but not in depression trials. We identified and analyzed 25 methods publications with substantial comments. The main argument for active placebo was to reduce risk of unblinding; the main argument against was the risk of unintended therapeutic effect.

Conclusion: Pharmacological active placebo control interventions are rarely used in randomized clinical trials, but they constitute a methodological tool which merits serious consideration. We suggest that active placebos are used more often in trials of drugs with noticeable side effects, especially in situations where the expected therapeutic effects are modest and the risk of bias due to unblinding is high.

Keywords: Active placebo; Methodological overview; Randomised clinical trials; Blinding; Placebo

1. Introduction

Blinding is often used in randomized trials to reduce the risk of bias. Blinding controls for several types of bias, for example, participants' and investigator's expectations, response bias, and observer bias [1,2]. The standard method used in drug trials to induce blinding is matching, that is, to design experimental and control interventions that externally appear indistinguishable, for example, tablets, capsules, or inhalers that have the same size, texture, feel, smell, appearance, and taste [3]. Such matching often involves a placebo control intervention.

However, even perfect matching of the physical appearance of experimental/control drug interventions cannot control for differences in side effects [4,5]. A trial of a drug with marked side effects, for example, lithium which induces tremor [6], has an increased risk of bias due to unblinding. Patients may become unblinded when experiencing side effects, but also outcome assessors and

Conflicts of interest: None.

* Corresponding author. Tel.: 004540738077.

E-mail address: jakobsolgaarden@gmail.com (J.S. Jensen).

http://dx.doi.org/10.1016/j.jclinepi.2017.03.001

0895-4356/

What is new?

Key findings

- From a random sample, 1 out of 200 randomised clinical placebo controlled trials used active placebo control interventions.
- Trials that used active placebo control interventions had patient-reported outcomes, experimental intervention with frequent and noticeable side effects and a tendency for a crossover design.
- The most frequently used active placebos were diphenhydramine, anticholinergic agents, benzodiazepines and benztropine.
- The use of active placebos was clustered in specific research settings, and did not appear to reflect consistently the side effect profile of the experimental intervention, e.g., selective serotonin reuptake inhibitors were compared with active placebos in pain trials but not in depression trials.
- The main argument in favour of active placebo control groups was the reduced risk of unblinding.
- The main argument against the use of active placebo control groups concerned the risk of active placebos having unintended therapeutic effects.

What this adds to what was known?

- We assessed the proportion of trials using active placebos, provided a description and catalogue of such trials, and conducted a systematic overview of published arguments for and against the use of active placebo control groups.
- Our study thus provides a coherent framework for a methodological reflection of the pros and cons of using active placebos which could be of help to readers of trial reports or researchers planning a placebo controlled drug trial.

What is the implication and what should change now?

- An active placebo control intervention is a methodological tool which merits serious consideration for researchers planning a randomised trial.
- The core role of active placebos could be in trials that investigate the effect of drugs with noticeable side effects, especially in situations where trials with standard placebo control groups have found only modest effects, and where there remains a concern that loss of blinding has caused bias.

treatment providers may deduce from patients' reports or physiological responses which intervention the patient has received [7]. Investigators know the expected side effects of an intervention, and their beliefs and expectations may influence outcome measurements [8–10].

A possible solution to the methodological predicament of risk of unblinding due to side effects in placebo-controlled trials is to use active placebo control groups. Active placebos are control interventions that mimic some of the physiological but nontherapeutic effects of the experimental intervention. For example, atropine has been used as placebo to mimic the sedative and anticholinergic effects of the tricyclic antidepressives [11,12].

Lasagna and Meier [13] discussed active placebos as early as 1958, and they have sporadically been used in drug trials, but it is unclear under which circumstances and why investigators choose to use or not use them. Thus, we decided to provide an overview of the use of pharmacological active placebo control groups in randomized clinical trials. Our main aims were (1) to assess the prevalence of active placebos in contemporary randomized clinical drug trials, (2) to provide a catalog of published drug trials using active placebos and characterize such trials, and (3) to review and analyze published texts providing methodological arguments for and against the use of active placebo control groups.

2. Methods

We conducted an overview consisting of three thematically linked substudies: an observational study of the frequency of use of pharmacological active placebo control groups, a systematic review of randomized trials using pharmacological active placebo control groups, and a review of publications arguing for or against use of active placebo control groups.

2.1. Terminology

We defined an active drug placebo as a pharmacological control intervention that reproduces or mimics side effects of the experimental drug (but with no known or suspected beneficial effect on the outcome studied).

2.2. Observational study of the frequency of use of active placebo

We searched PubMed for articles indexed as randomized controlled trials and with publication date in October 2013, producing a database of 2,772 articles. From this database, we selected iteratively random samples of randomized clinical trial (a total of 396), until we had identified 200 randomized clinical placebo-controlled drug trials.

The full-text articles were read by two authors (J.S.J. and A.Ø.B.), and any use of active placebo was noted. In addition, the same two authors extracted data concerning