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[Methodology Protocol]

Active placebo versus standard placebo control interventions in pharmacological randomised trials

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (methodology). The objectives are as follows:

To estimate differences in effects between pharmacological active placebo interventions and standard placebo interventions in randomised trials.

BACKGROUND

Placebo control interventions are used in randomised clinical trials to blind participants and healthcare providers, making them unaware of the allocated treatment. A trial in which these people are aware of a participant's treatment allocation may potentially be biased. For example, patients may report what they think will please the doctors (i.e. response bias) (Hróbjartsson 2011a), or experience or interpret symptoms differently (i.e. placebo effect) (Hróbjartsson 2002), or outcome assessors may rate one of the interventions more favourably (i.e. observer bias) (Schulz 2002; Hróbjartsson 2011a). The use of a placebo control intervention to induce and maintain blinding reduces the risk of bias (Schulz 2002; Hróbjartsson 2011a).

Placebos enable blinding by mimicking the experience of receiving an experimental intervention without containing any supposed therapeutic components. Placebos are often associated with pharmacological trials where they are typically designed to be indistinguishable in appearance, smell, taste and texture from the drug under investigation.

However, some experimental drug interventions may have instantaneous and perceptible psychotropic or adverse effects with a risk of patient unblinding. Examples of such drugs and their adverse effects are. selective serotonin reuptake inhibitors inducing nausea, insomnia and nervousness (Greenberg 1994); tricyclic antidepressants inducing anticholinergic effects, such as mouth dryness (Moncrieff 2004); methylphenidate inducing euphoria and nausea (Storebø 2015); and lithium inducing tremor (Marini 1976). Inadequate matching between active drugs and standard placebo controls by external characteristics is not uncommon and poses a potential risk for unblinding (Bello 2016). Similarly, this risk of unblinding is also likely to be an issue when placebo controls do not match internal characteristics such as psychotropic or adverse effects.

To address the potential issue of unblinding due to adverse effects, some drug trials have used a so-called active placebo instead of standard placebo as their control intervention (Jensen 2017).

Description of the methods being investigated

Pharmacological active placebos are designed to imitate the external characteristics and also the internal sensations of receiving the treatment, by mimicking some of its psychotropic or adverse effects. One example is atropine, which can imitate the anticholinergic effects of tricyclic antidepressants (Thomson 1982).

Some non-pharmacological placebos can also be regarded as active placebos, closely mimicking the experience of receiving active treatment. For example, a device intervention such as transcutaneous electrical nerve stimulation (TENS) may be compared to a sham TENS, which will provide subtherapeutic levels of stimulation just above the minimal sensory threshold (Tucker 2015). Surgical placebos can be considered a more invasive form of active placebo with adverse reactions from the surgery itself and have their own ethical challenges (Wartolowska 2014). Psychological placebos, on the other hand, are different from the other types of nonpharmacological placebo in that they do not match the intervention (Hróbjartsson 2011b). For our Cochrane Review, we will only consider pharmacological active placebos.

How these methods might work

Active placebos aim to more closely simulate the experience of receiving the experimental intervention. This reduces the perceptible differences between the experimental and control treatments and will ideally reduce the risk of patients and healthcare providers identifying the allocated treatment. Active placebos may thereby reduce the risk of bias due to unblinding and prevent overestimation of treatment benefits (Jensen 2017).

Thus, active placebos can, in theory, more effectively control for placebo effects and certain biases in trials. However, it is not entirely clear what could cause the effects of active placebos to differ from those of standard placebos. One possible explanation may concern expectations. For example, physical placebos are associated with higher effects than standard pharmacological placebos (Hróbjartsson 2010). One could therefore hypothesise that the more extensive or theatrical an intervention is, be it active placebo or surgical placebo, the higher are the expectations of receiving an effective treatment, which in turn could lead to a greater treatment response (Meissner 2011; Rief 2011). Hence, active placebos may increase the expectation of receiving the actual treatment through experiencing of adverse effects, thus increasing the placebo effect.

On the other hand, active placebos also carry a risk of having unintended therapeutic effects on the outcome of interest, thereby potentially underestimating the true effect of the intervention (Jensen 2017).

Why it is important to do this review

The history of active placebos goes back to the 1950s and the early development of the randomised trial (Lasagna 1955; Lasagna 1958). In recent methodology literature, this part of trial design has received little attention (Salamone 2000; Edward 2005; Wartolowska 2014), with few studies focusing on use and impact of active placebos (Moncrieff 2003; Moncrieff 2004; Jensen 2017). A recent review by Jensen et al. aimed to record all drug trials using active placebos, including trials comparing experimental drug to active placebo (Jensen 2017). They noted that active placebos were rarely and inconsistently used. For example, active placebos were used in trials of selective serotonin reuptake inhibitors for pain, but not for depression.

The use of active placebos, therefore, does not seem always to be based on rational and transparent choices. This highlights a likely need to develop guidelines for use of active placebos in trials, and to answer the central empirical question: do active placebos, on average, reduce the risk of bias due to unblinding; and if so, under what circumstances?

OBJECTIVES

To estimate differences in effects between pharmacological active placebo interventions and standard placebo interventions in randomised trials.

METHODS

Criteria for considering studies for this review

Types of studies

We will include all randomised clinical and preclinical trials that allocate participants to standard placebo intervention and to active placebo intervention.

We define 'randomised' to mean any trial denoted explicitly as such, or reporting a design which can be assumed to have a random allocation schedule, e.g. Latin square design.

We define a 'clinical trial' to mean any trial investigating the effects of a healthcare intervention on patients or on participants at risk of disease. We define a 'preclinical trial' to mean any trial investigating the effects of a healthcare intervention on healthy participants. By 'healthcare intervention', we mean that the intervention is or could potentially be used for the treatment or prevention of disease.

We will include trials with a parallel or crossover design, but not split-body or cluster randomisation.

Types of data

The data for this review will consist of data from trial publications, including trial characteristics, information on the standard and active placebo used and outcome results such as patient-reported continuous outcomes and observer-reported continuous outcomes.

Types of methods

We will include trials with a randomised head-to-head comparison of pharmacological active placebo versus standard placebo. We will not consider trials having only comparisons of experimental drug versus active placebo (which have been recorded in Jensen 2017) or experimental drug versus standard placebo.

We define 'active placebo' as any intervention labelled as such, or any intervention stated to imitate the instantaneous and perceptible psychotropic or adverse effects of the experimental intervention (e.g. anticholinergic effects of tricyclic antidepressants, or tremor from lithium), but without any known or suspected benefit on the outcomes under investigation. The active placebo may also be labelled as, for example, 'active control' or 'active control treatment'. We will only consider trials where the active placebo is designated a priori as such. We will exclude trials reinterpreting an intervention designed to be experimental as an active placebo, for example when the trial authors reflect on their results in the discussion section of their trial report.

We define 'standard placebo' as any intervention labelled as such, or any intervention designed to only mimic the external sensory properties of the experimental intervention, such as appearance, smell, taste and texture, but not designed to imitate its psychotropic or adverse effects. The standard placebo may also be labelled as, for example, 'inert placebo', 'inactive placebo', 'true placebo' or 'sham'.

We will include trials both with and without a study group treated with an experimental drug, i.e. both three (or more) and two-group trials.

Types of outcome measures

We will not restrict the study selection based on outcome measures.

The outcomes of interest for our review are listed below.

Primary outcomes

- The standardised mean difference (SMD) for patient-reported outcomes of benefit (e.g. visual analogue scale (VAS) for pain, symptom score)
  - at the earliest post-treatment time point

Secondary outcomes

- SMD for patient-reported outcomes of benefit
  - at the latest follow-up time point
- SMD for blinded observer-reported outcomes of benefit (e.g. rating scale)
  - at the earliest post-treatment time point and
  - at the latest follow-up time point
- SMD for any type of outcomes of harm (e.g. adverse reaction assessment)
  - at the earliest post-treatment time point and
  - at the latest follow-up time point
- Odds ratio (OR) for any type of outcomes of harm (e.g. adverse reactions)
  - at the earliest post-treatment time point and
  - at the latest follow-up time point
- Difference in attrition rates
  - at the latest follow-up time point
- Difference in co-intervention rates
  - at the latest follow-up time point
- Difference in mean co-intervention use
  - at the latest follow-up time point

Search methods for identification of studies

We will use the following sources to screen for eligible trial publications:

1. the 89 randomised trials included in Jensen 2017, which is a systematic review aimed at identifying trials with pharmacological active placebo groups that had been reported before 15 January 2015
2. update of the database search done for Jensen 2017 from January 2015 onwards
3. more specific database searches and searching other sources

We expect that relevant studies may be difficult to identify in standard database searches, due to differing and non-standardised ways of reporting active placebos. Our search will mainly focus on points 1 and 3 above, because most relevant studies are likely to have been found by Jensen 2017 or be found by searching sources other than the standard databases.

Updated database search

For the updated electronic search from Jensen 2017, we will search PubMed and Cochrane Central Register of Controlled Trials (CENTRAL) for potentially relevant trial publications added in or since 2015. We will use the search strategy developed by Jensen 2017 (see Appendix 1).

Specific database search and searching other resources

We will perform a more specific search in Google Scholar and Ovid Embase (including Embase Classic) aimed at finding randomised trials comparing active and standard placebos, with no time restrictions (see Appendix 1).

We will screen reference lists of relevant publications for potentially eligible studies and use Web of Science to search for potentially eligible citations to the relevant publications (Horsley 2011).

We will perform searches in trial registries (e.g. ClinicalTrials.gov, WHO ICTRP) and other databases (e.g. ProQuest) and contact relevant experts and authors for other potentially relevant trial publications.

Data collection and analysis

Selection of studies

For the above sources, one review author (DL) will screen titles and abstracts and perform obvious exclusions. For Google Scholar, one review author (DL) will screen text excerpts and, if needed, the full text of the first 100 hits of each search term and perform obvious exclusions.

Then, two review authors (DL and a second review author) will screen relevant publications in full for eligibility. We will resolve any disagreements by discussion.

Data extraction and management

Two review authors (DL and a second review author) will extract data from eligible studies. The data are classified as: basic data, outcomes, covariates. We will resolve any disagreements by discussion.

Basic data

For basic data, we plan to extract publication and first author information, trial characteristics (clinical or preclinical, clinical area, country, trial design, information on funding and conflicts of interest, type of participants or condition, interventions and comparators), information on trial conduct (duration of treatment and follow-up, description of randomisation, blinding and co-interventions), as well as participant flow numbers (number of participants screened, enrolled and randomised) (see Appendix 2 for more details).

Outcomes

For all outcome results reported, we plan to extract the following data: basic outcome information (e.g. outcome type: continuous; domain and instrument: pain on VAS scale; directionality: lower is better), time for registration (e.g. two weeks post-treatment).

For continuous outcomes, we plan to extract the summary data from the active placebo and standard placebo groups which are needed for a calculation of the standardised mean difference (SMD): the mean, standard deviation (SD) (or another measure of variability, e.g. standard error (SE) or confidence interval (CI)) and number of patients (N). For dichotomous outcomes, we plan to extract the summary data from each group needed for a calculation of the OR: number of patients registered as having the event and total number of patients assessed.

If summary data are not available, but only effect estimates (e.g. mean difference, SMD, OR), we will extract these instead along with measures of variability (e.g. CI, P value).

For each outcome, we will prefer the most complete analysis based on available patients as they are randomised. If multiple publications report on the same trial, we will use data from all the sources. In case of discrepancies, we will attempt to contact the study authors.

Selection of review outcomes in individual trials

Two review authors will independently select appropriate primary and secondary outcomes from each trial and will resolve any disagreement by discussion. The preferred order is:

1. continuous outcomes, otherwise dichotomous outcomes (for patient-reported and observer-reported outcomes)
2. primary outcomes, if noted, otherwise the clinically most relevant outcomes
3. absolute values, otherwise change scores
4. for patient-reported outcomes:
   a. symptom-specific outcomes (e.g. pain), otherwise global outcomes (e.g. quality of life score)
   b. private (e.g. pain), otherwise potentially observable (e.g. emesis)
5. for observer-reported outcomes:
   a. subjective interactive (e.g. rating scales with patient contact, health-care provider decision outcomes), otherwise subjective pure observational, otherwise objective outcomes (e.g. non-repeatable measurements such as blood samples)
6. for outcomes of harm:
   a. patient-reported outcomes, otherwise observer-reported outcomes
   b. then same principles as above, except we select both a continuous and a dichotomous outcome of harm

Covariates

For the active placebo in each trial, we will grade the adequacy of the active placebo on a ranking scale from 1 to 5, where we will consider the quality, intensity and rapidness of the psychotropic effects and the similarity to the experimental treatment, as a measure of the likelihood to cause unblinding compared to standard placebo. We will base grading primarily on information from the trial publication, but also using relevant references and an informal probing of the literature. Two review authors will assess the adequacy and disagreements will be resolved by discussion.

Based on the same principles, we will also grade the risk of unintended therapeutic effects from the active placebo on a ranking scale from 1 to 5.

Assessment of risk of bias in included studies

We will assess the risk of bias in the included trials using the following domains from the 2011 'Risk of bias' tool (Higgins 2011): selection bias, attrition bias, reporting bias and other bias. We will not assess those related to blinding (performance bias and detection bias) since these domains are the subjects of the investigation in this review.

Unit of analysis issues

For crossover trials, we will attempt to use outcome results from all crossover periods using reported or estimated correlation coefficients. Alternatively, we will use data from the first period before crossover, if available.

Dealing with missing data

If data are partly or completely missing and not available for our analyses, we will attempt to contact study authors (Young 2011) or will impute the missing values using estimates from other studies (e.g. same scales in similar trials).

Data synthesis

Data conversion

For continuous outcomes, if the necessary summary data for each intervention group are available (mean, SD, and number of participants), we will calculate an estimate of the SMD and its standard error directly based on these numbers. If the above summary data are not reported directly, we will attempt to estimate them using other measures, e.g. standard error, CIs, test statistics, P values.

For dichotomous outcomes, if the necessary summary data for each intervention group are available, we will calculate the OR based on a standard 2x2 table. If the dichotomous outcome has been selected for our review outcomes because of the unavailability of continuous outcomes, we will convert the OR to a SMD (Hasselblad 1995; Chinn 2000).

If summary data for each intervention group are not available for the given outcome of interest, but rather an estimate is available (e.g. mean difference or SMD, along with a measure of variability), we will use these in our data analysis.

We will convert directions of outcomes, such that SMD < 0 and OR < 1 indicate greater benefit of active placebo compared to standard placebo.

Data analysis

We will use the inverse-variance method to perform random-effects meta-analyses for primary and secondary outcomes. We will stratify for type of trial, presenting clinical and preclinical trials separately. To explore heterogeneity, we will calculate I^2, τ^2 and prediction intervals.

For continuous primary and secondary outcomes, we will use the SMD and corresponding standard error from each trial, calculated or estimated as described above. If this is not possible due to missing data, the trial will be omitted from the given meta-analysis and the results from such trials will be summarized qualitatively. Two review authors (DL and a second review author) will decide whether or not a trial will be included in the meta-analysis.

For dichotomous secondary outcomes (e.g. attrition, co-interventions), we will perform a meta-analysis using OR.

Summarising the evidence

Based on the main and additional analyses, we will summarise the evidence qualitatively to answer the review's objective. We will reflect on the quality of evidence informally based on the same components as in the GRADE assessment, e.g. risk of bias, inconsistency, publication bias (Guyatt 2011).

Subgroup analysis and investigation of heterogeneity

To explore potential heterogeneity, we plan to perform the following metaregression analysis for our primary and secondary outcomes with the two covariates noted previously as variables:

- adequacy of the active placebo, on a ranking scale from 1 to 5
- risk of unintended therapeutic effects, on a ranking scale from 1 to 5

Sensitivity analysis

To study the robustness of our results, we plan to perform the following sensitivity analyses for our primary and secondary outcomes:

- continuous outcome data only, excluding dichotomous outcome data that have been converted to SMD
- inclusion of excluded, but nearly eligible trials

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APPENDICES

Appendix 1. Search strategy

Screening trials included in Jensen 2017 study

After correspondence to Jensen 2017 we retrieved the list of 89 trials using an active placebo.

Updated systematic search

We will base the updated search on the strategy from Jensen 2017, performed in PubMed and Cochrane Central Register of Controlled Trials (CENTRAL) from 2015 onwards:

"active placebo" OR "active placebos" OR "active control treatment" OR "active control" OR "sham diphenhydramine" OR "diphenhydramine placebo" OR "sham atropine" OR "atropine placebo" OR "sham benztropine" OR "sham benzodiazepine" OR "histamine placebo" OR "benztropine placebo" OR "benzodiazepine placebo"

Focused electronic search

Our search strategy is in part informed by Jensen 2017. We have the following draft for a search strategy for Ovid EMBASE:

#	Search term
1	active placebo*.af.
2	active control*.af.
3	(inert or inactive or standard or sham or true placebo* or lactose or saline).af.
4	exp Placebos/ or exp PLACEBO EFFECT/
5	2 and (3 or 4)
6	(diphenhydramine or atropine or benztropine or benzodiazepine* or midazolam or diazepam or lorazepam or histamine).af.
7	(inert placebo* or inactive placebo* or standard placebo* or true placebo*).af.
8	6 and 7
9	(sham diphenhydramine or diphenhydramine placebo* or sham atropine or atropine placebo* or sham benztropine or benztropine placebo* or sham benzodiazepine or benzodiazepine placebo*

(Continued)

	or sham diazepam or diazepam placebo* or sham histamine or histamine placebo* or sham midazolam or midazolam placebo* or sham lorazepam or lorazepam placebo*).af.
10	1 or 5 or 8 or 9
11	((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or randomised.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (exp animals/ not humans.sh.)
12	((double-blind*.ab.) not (exp animals/ not humans.sh.))
13	10 and (11 or 12)

For full-text search in Google Scholar, we plan to perform a search on the search strings (#1 and #3), #5, #8 and #9 separately, and without the subject headings. We plan to screen the first 100 search results for each block.

Appendix 2. Data extraction

Basic data

- Publication information
  - Corresponding author
  - Contact information
  - Country of first author
- Trial characteristics
  - Study IDs and other identifiers
  - Clinical or pre-clinical trial
  - Clinical area (e.g. by journal topic or author's affiliated department)
  - Country or countries of recruitment
  - Trial design, e.g. parallel design
  - Information on funding and conflicts of interest (e.g. non-industry-funded, and reports no conflicts of interest)
  - Type of participants and their conditions
  - Trial setting
  - Types of interventions and comparators
    - ☐ Description of active and standard placebo (e.g. design and mode of action)
- Trial conduct
  - Duration of treatment and duration of follow-up
  - Description of randomisation procedures
    - ☐ Including random allocation or quasi-random allocation
  - Description of blinding procedures
    - ☐ Including blinding status on key trials persons, tests of blinding success and reports of unblinding
  - Description of co-interventions
- Trial results other than for specific outcome measures
  - Participant flow
    - ☐ Including number of participants randomised to each study intervention, attrition for each study arm and reasons for attrition

HISTORY

Protocol first published: Issue 7, 2020

CONTRIBUTIONS OF AUTHORS

AH conceived the idea for the systematic review. DL and AH primarily wrote the protocol, and CH and AP contributed. All authors read and approved the final protocol version.

DECLARATIONS OF INTEREST

DL has no known financial or non-financial conflicts of interest.
CH has no known financial or non-financial conflicts of interest.
AP has no known financial or non-financial conflicts of interest.
AH has no known financial or non-financial conflicts of interest.

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- Nordic Cochrane Centre, Denmark

  Funds 1.5 year of DL's PhD employment

External sources

- No sources of support supplied