Effects of Placebos Without Deception compared with no treatment: protocol for a systematic review and meta-analysis

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Background

Use of placebos in clinical practice is widespread, 1 and may be a cost-effective option for ailments such as mild pain and depression. However recommending or administering placebo interventions is often considered unethical because doctors must allegedly deceive patients by concealing the nature of the placebo therapy. 2, 3 However, a recent trial suggests ‘placebos’ without deception may produce clinically significant therapeutic benefit. While several other studies have investigated non-deceptive placebos, 4-10 a systematic review of these studies has not been conducted. 11

Description of the condition

Evidence suggests that placebos are most effective for stress-related conditions, 12 pain, depression, anxiety, and nausea. 13

Description of the intervention

We will include studies of placebo interventions (such as sugar pills, saline injections, and sham procedures) delivered ‘openly’. That is, where patients are told that the intervention is a placebo. Placebo interventions are likely to be lactose pills, saline injections, and sham procedures.

How the intervention might work

Studies suggest that placebos work by inducing positive expectations and also because of classical conditioning. It is anticipated that open label placebos will not induce the same level of conscious expectations in a patient as a deceptive placebo because the patient will expect to receive what they take to be an inert intervention. However open label placebos have often been combined with positive suggestions
(such as “we don’t know how placebos work, but we have found that they help many people with your condition” 14).

Open placebos with an expectation of therapeutic benefit could improve healthcare outcomes via a range of downstream mechanisms:

- **Inducing the relaxation response.** Attention from empathetic and positive healthcare practitioners could reduce stress. Stress-related conditions have been shown to be treatable by stress-reduction strategies such as mindfulness, relaxation. Reducing stress also has positive knock-on effects on health by reducing harmful stress related behaviours such as smoking and over- or under-eating.

- **Activate the dopamine reward and endogenous opioid systems in the brain.** Clinical studies have shown that where pain relief or anti-anxiety medication was administered covertly (where the patient did not know they were receiving treatment) compared with open (where the patient knew they were receiving treatment and expected a positive outcome) enhance care across conditions, such as pain, anxiety, and Parkinson's disease. The effects of influencing patients’ expectations on physiological outcomes has been most extensively documented in the field of pain research where an expectation of pain relief has been found to activate neurological systems involved in regulating pain. Conversely, negative expectations have been shown to adversely affect health, most notably by increasing pain.

- **Social support.** Social support is a well established determinant of health. Not only can social networks provide support in the form of care and advice, but social networks have also been shown to influence the neuroendocrine response. For similar reasons, lack of social networks can have a negative impact on health. Since encounters with a healthcare practitioner is a social event, we can expect such encounters to mitigate negative effects of lack of social networks, and to enhance the benefits of social networks.

- **A combination of the above mechanisms.** These mechanisms can all work independently, but are more likely to be combined and interact in various different and will have variable effects depending on the individual and the condition.

**Why it is important to do this review**

Surveys around the world suggest 17%-80% of doctors have prescribed ‘placebos’ such as saline injections in routine practice. Yet ‘placebo’ use during routine care is often considered unethical for several alleged reasons, including:

1. ‘placebos’ need to be delivered deceptively (disguised as though they were ‘real’ treatments) to be effective. Since deception requires breech of trust and violates patient autonomy, it is arguably unethical;

2. ‘placebos’ are allegedly ineffective.

Both reasons rest on empirical claims that require further analysis. There have been several investigations of ‘placebo’ effects. While earlier estimates were undoubtedly exaggerated, even skeptics admit that for some conditions such as pain and depression, ‘placebos’ are likely to be effective.

Yet whether ‘placebos’ need to be delivered deceptively in order to be effective requires further investigation. Several studies suggest that non-deceptive ‘placebos’ can be effective, but a systematic review is required to provide more definitive evidence.
A 2010 recent Cochrane Review of placebo effects for all clinical conditions included some of the studies that will be included in this review. However there are three relevant differences between this review and the Cochrane review. First, the Cochrane review is not up to date (relevant studies have been conducted since 14, 49). Second, no subgroup analysis addressing our specific question was included. Third and most importantly, data about how the open label placebos were delivered (for example the verbal instructions accompanying the pills) were not extracted or reported in the Cochrane Review, and due to the nature of the Cochrane Review will not be reported in future updates of the review. Information about how the open label placebos were delivered is essential for drawing out any ethical implications of the effects of open label placebos.

Objectives - primary

To assess the effects open label placebos.

Objectives - secondary

To assess how open label placebos are delivered (for example whether they were accompanied by verbal instructions that induced positive expectations).

Methods

Criteria for considering studies for this review

Types of studies

We will include trials in which participants either received placebos without deception or no treatment. We will include all trials that meet our eligibility criteria, but do a sub-group analysis of trials that used random allocation (see below). If there are trials involving three groups (no treatment, placebos without deception, and placebos with deception), we will look for a dose-response. We will exclude trials comparing placebos with and without deception that do not have a no treatment group because they cannot tell us whether placebos delivered without deception have effects, and thus will not answer the study question.

Types of participants

We will include both patients diagnosed with a particular medical condition (such as pain, depression, or irritable bowel syndrome) and also members of the general population (for example someone’s response to ‘placebo’ alcohol delivered without deception). The reason we will examine this broad range of patients is that we are interested in the general effects of non-deceptive placebos.

Types of interventions

We will compare any intervention that is delivered as an open label placebo. That is, the patient must be told they are receiving a placebo. We will compare non-deceptive placebos with no treatment. No treatment will include people on a waiting list or those simply left untreated.
Types of outcome measures

Primary outcomes
Our primary outcome measures will be patients' physical and psychological health status for specific clinical conditions (such as pain, anxiety, or depression). We will choose the primary outcome for the main clinical condition (as reported by study authors). If the primary outcome is unclear we will choose the one that is most relevant to patients, practitioners, and decision-makers, and a rationale will be provided. For example, if a study of the effect of manipulating empathy for pain, anxiety, and depression measured effects in more than one way for each condition, we will choose the main outcome for the main clinical condition. In cases where the main condition was not reported. We will not include outcome measures that are meaningless to patients, practitioners, and decision makers.

Secondary outcomes
We will report the following data if available:
1. Any instructions given to the patient alongside the open label placebo.
2. Quality of life
3. Harms
4. Placebo responsiveness

Timing of outcome assessment
Where outcomes were collected at more than one time point, we will choose the time point reported as primary by study authors. Where study authors did not state the primary time point we will choose the one most relevant to patients and provide a rationale. Longer term follow up (months rather than weeks) is more likely to benefit patients.

Main outcomes for 'Summary of findings' table
In our Summary of Findings table will include no more than seven outcomes per table (including harms). We will not include duplicate outcomes (the same outcome using different measures). We will report findings for all selected outcomes, even if they were not reported or we did not find data for them.

We will also include a separate table detailing the instructions provided by the practitioners to inform the participants that they received a placebo, and any other information about the intervention (for example length of consultation).

Search methods for identification of studies
Searching for relevant studies in this area is challenging because of the absence of a common terminology for interventions in which manipulation of practitioner empathy and communication of positive expectations is varied. Eligible studies can be found in areas ranging from placebo research, patient-practitioner communication, and psychological variables. This makes a specific search strategy difficult. Our search strategy was based on the one used by Di Blasi and Mistiaen with the exception that we focused exclusively on expectations and empathy whereas those authors included studies of all context effect manipulation.
The PubMed search strategy is given in Appendix 1 and been adapted for other databases. The search strategy will consist of nine concepts, relating to different components of standard search strategies. These have been derived from:

- standard PICO components (Participants, Intervention, Comparison and Outcome)
- patients
- the practitioner
- communication
- suggestion
- patient-practitioner communication
- empathy
- expectations
- placebo and placebo effects

### Electronic searches

We will search the following electronic databases from their start date through to April 2015:

- CINAHL
- Controlled-trials.com
- EMBASE
- LILACS
- OpenGREY
- PROQUEST Dissertations
- PsycINFO
- PubMed
- Sociological Abstracts
- The Cochrane Central Register of Controlled Trials (CENTRAL, The Cochrane Library)
- including Consumers and Communication Review Group Specialised Register
- Web of Sciences

Searches will not be restricted in terms of the language. The results from all searches were combined into a Reference Manager database and duplicate records will be removed.

### Searching other resources

We will search proceedings of placebo-specific conferences, and contact experts in the field and authors of included studies for advice about other studies. We will also search online trial registers (ClinicalTrials.gov, International Standard Randomised Controlled Trial Number (ISRCTN)).

### Data collection and analysis

#### Selection of studies

Two authors will independently screen all titles and abstracts identified from searches to determine which meet the inclusion criteria. We will retrieve in full text
any papers identified as potentially relevant by at least one author. Two review authors will independently screen full text articles for inclusion or exclusion, with discrepancies resolved by discussion and by consulting a third author if necessary to reach consensus. All potentially-relevant papers excluded from the review at this stage will be listed as excluded studies, with reasons provided in the ‘Characteristics of excluded studies’ table. We will also provide citation details and any available information about ongoing studies, and collate and report details of duplicate publications, so that each study (rather than each report) is the unit of interest in the review. We will report the screening and selection process in an adapted PRISMA flow chart.52

Data extraction and management

Two review authors will extract data independently from included studies. Any discrepancies will be resolved by discussion until consensus is reached, or through consultation with a third author where necessary. We will develop and pilot a data extraction form using the Cochrane Consumers and Communication Review Group Data Extraction Template (available at: http://cccrg.cochrane.org/author-resources). Data to be extracted will include the following items: Details of the study (study design, types of participants, description of intervention and intervention components, study design, description of comparison group, completeness of outcome data, outcome measures, country, funding source). See Appendix X (sample data extraction form for studies listed in Table 1) for details. All extracted data will be entered into RevMan (RevMan 2012) by one review author, and will be checked for accuracy against the data extraction sheets by a second review author working independently.

Assessment of risk of bias in included studies

We will assess and report on the methodological risk of bias of included studies in accordance with the Cochrane Handbook 53, which recommends the explicit reporting of the following individual elements for RCTs: random sequence generation; allocation sequence concealment; blinding (participants, personnel); blinding (outcome assessment); completeness of outcome data, selective outcome reporting; and other sources of bias [please specify]. We will consider blinding separately for different outcomes where appropriate (for example, blinding may have the potential to differently affect subjective versus objective outcome measures). We will judge each item as being at high, low or unclear risk of bias as set out in the criteria provided by Higgins (2008) 53 and provide a quote from the study report and a justification for our judgement for each item in the risk of bias table.

Studies will be deemed to be at the highest risk of bias if they are scored as at high or unclear risk of bias for either the sequence generation or allocation concealment domains [or other domains of the tool; please adapt], based on growing empirical evidence that these factors are particularly important potential sources of bias. 53

In all cases, two authors will independently assess the risk of bias of included studies, with any disagreements resolved by discussion to reach consensus. We will contact study authors for additional information about the included studies, or for clarification of the study methods as required. We will incorporate the results of the risk of bias assessment into the review through standard tables, and systematic narrative description and commentary about each of the elements, leading to an
overall assessment the risk of bias of included studies and a judgment about the internal validity of the review’s results.

For cluster-RCTs we will also assess and report the risk of bias associated with an additional domain: selective recruitment of cluster participants.

We will also report whether the interventions and control treatments were described in sufficient detail to replicate, investigate most relevant causal factors, and report these factors.

Data synthesis

Our review is designed to be heterogeneous in terms of outcome measures because empathy and expectations are likely to be effective across inter-related outcomes (see 'How the intervention might work', above). We also anticipate heterogeneity in terms of study participants, and intervention components/modalities. We nonetheless plan to pool results in a meta-analysis (using a random effects model), but will also conduct subgroup analyses which will include more heterogeneous groups of studies.

In addition, an aim of this review is to identify intervention features that may be responsible for the outcomes. A result of the review is therefore likely to be a list of relevant intervention characteristics that are likely to be responsible for the treatment outcomes. These can be used as a basis for planning future studies and also for post-hoc subgroup analyses. As noted above, we will include in meta-analysis all randomized trials irrespective of risk of bias in sequence generation, but will conduct sensitivity analyses, excluding those at unclear or high risk of bias.

Measures of treatment effect

For dichotomous outcomes, we will analyse data based on the number of events and the number of people assessed in the intervention and comparison groups. We will use these to calculate the risk ratio (RR) and 95% confidence interval (CI). For continuous measures, we will analyse data based on the mean, standard deviation (SD) and number of people assessed for both the intervention and comparison groups to calculate mean difference (MD) and 95% CI. If the MD is reported without individual group data, we will use this to report the study results. If more than one study measures the same outcome using different tools, we will calculate the standardised mean difference (SMD) and 95% CI using the inverse variance method in Review Manager 5.

To assess clinical relevance, we will compare the effects of open placebos with common treatments for the conditions being assessed.

Unit of analysis issues

If cluster-RCTs are included we will check for unit-of-analysis errors. If errors are found, and sufficient information is available, we will re-analyse the data using the appropriate unit of analysis, by taking account of the intracluster correlation (ICC). We will obtain estimates of the ICC by contacting authors of included studies, or impute them using estimates from external sources. If it not possible to obtain sufficient information to reanalyse the data we will report effect estimates and annotate ‘unit-of-analysis error.'
Dealing with missing data

We will attempt to contact study authors to obtain missing data (participant, outcome, or summary data). For participant data, we will, where possible, conduct analysis on an intention-to-treat basis; otherwise data will be analysed as reported. We will report on the levels of loss to follow-up and assess this as a source of potential bias.

For missing outcome or summary data we will impute missing data where possible and report any assumptions in the review. We will investigate, through sensitivity analyses, the effects of any imputed data on pooled effect estimates.

Assessment of heterogeneity

We anticipate heterogeneity in terms of intervention modalities, conditions, outcome measures, patients, and effects.

Where studies are considered similar enough (based on consideration of populations, interventions, or other factors) to allow pooling of data using meta-analysis, we will assess the degree of heterogeneity by visual inspection of forest plots and by examining the Chi² test for heterogeneity. Heterogeneity will be quantified using the I² statistic. An I² value of 50% or more will be considered to represent substantial levels of heterogeneity, but this value will be interpreted in light of the size and direction of effects and the strength of the evidence for heterogeneity, based on the P value from the Chi² test. 

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Where we detect substantial clinical, methodological or statistical heterogeneity across included studies we will not report pooled results from meta-analysis but will instead use a narrative approach to data synthesis. In this event we will attempt to explore possible clinical or methodological reasons for this variation by grouping studies that are similar in terms of populations, intervention features, methodological features, or other factors; please specify and adapt] to explore differences in intervention effects.

When too few trials are included in a meta-analysis, the Chi² test has little power to detect heterogeneity. Therefore a non-significant result should not necessarily be interpreted as evidence of no heterogeneity and will be interpreted with care.

Assessment of reporting (publication) biases

We will assess reporting bias qualitatively based on the characteristics of the included studies (eg if only small studies that indicate positive findings are identified for inclusion), and if information that we obtain from contacting experts and authors or studies suggests that there are relevant unpublished studies.

If we identify sufficient studies (at least 10) for inclusion in the review we will construct a funnel plot to investigate small study effects, which may indicate the presence of publication bias. We will formally test for funnel plot asymmetry, with the choice of test made based on advice in Higgins (2008), and bearing in mind that there may be several reasons for funnel plot asymmetry when interpreting the results.'
Subgroup analysis and investigation of heterogeneity

We anticipate heterogeneity in terms of intervention modalities, conditions, outcome measures, patients, and effects. We will therefore conduct rigorous subgroup analyses. To investigate whether specific subgroups of trials reported effects of empathy/expectation induction we will compare the following subgroups, with tests of interaction:

1. Randomized versus non-randomized trials.
2. Trials where a specific modality (pills, injections, sham interventions) were used will be analysed separately.
3. If three or more trials investigate the same ailment (such as pain, depression, or anxiety) we will analyse these separately.
4. Trials where allocation sequence was at a high risk of bias compared with trials in which allocation sequence was at a low risk of bias.
5. Subjective (patient-reported) versus objective (practitioner reported) outcomes will be analysed separately.
6. In cases where data about patients’ placebo responsiveness was measured we will do a subgroup analysis of the effects of the intervention in patients who are placebo responsive and those who are not.
7. If there are three or more trials in a given country, we will do a sub-group analysis of trials from that country.
8. In the subset of trials where intervention components were described in sufficient detail we will explore which components most strongly influence patient outcomes.
9. We will do a subgroup analysis of trials conducted in clinical as opposed to laboratory settings.

Sensitivity analysis

We anticipate performing separate sensitivity analyses

• excluding studies with high risk on a certain domain of risk of bias
• including exclusively trials deemed to be at a low or unclear risk of bias across
• excluding studies whose results cannot be confirmed in subsequent publications
• Characteristics of participants: excluding studies where where a majority but not all people in a study meet our pre-specified age range.
• Study design: excluding studies where the outcome assessment was not blinded or not clearly reported as being blinded.
• Continuous data: excluding studies where assumptions about standard deviations had to be made because they were missing.
• Cluster-randomized trials: excluding trials that had not been adjusted for clustering?
• Cross-over trials: sensitivity analyses using various values for within-subject correlation coefficients were imputed (but not reported in the study reports?
• Relationship between anxiety and other ailments (the stress hypothesis): We will also explore interactions between the effect of the intervention on anxiety and other ailments to test the stress hypothesis.

‘Summary of findings’ table
We will prepare a ‘Summary of findings’ table to present the results of meta-analysis, based on the methods described in chapter 11 of the Cochrane Handbook for Systematic Reviews of Interventions (Schünemann Available from www.cochrane-handbook.org). We will present the results of meta-analysis for the major comparisons of the review, for each of the major primary outcomes, including potential harms, as outlined in the ‘Types of outcome measures’ section. We will provide a source and rationale for each assumed risk cited in the table(s), and will use the GRADE system to rank the quality of the evidence using the GRADEprofiler (GRADEpro) software (Schünemann 2011). If meta-analysis is not possible, we will present results in a narrative ‘Summary of findings’ table format, such as that used by Chan 2011.

Assessing the quality of the evidence (alternative heading to ‘Summary of findings’ table)

We will assess and report the quality of the evidence, using the GRADE system to assess the quality of the evidence for each outcome on each of the following domains: study limitations, consistency, imprecision, indirectness and publication bias. Two authors will independently assess the quality of the evidence as implemented and described in the GRADEprofiler (GRADEpro) software (Schünemann 2011).

### Table 1. Examples of the intervention

<table>
<thead>
<tr>
<th>Study</th>
<th>Modality</th>
<th>Main outcomes</th>
<th>Main findings</th>
<th>Randomized?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaptchuk 2010&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Placebo pills</td>
<td>IBS Global Improvement Scales</td>
<td>Open label placebos outperform untreated groups</td>
<td>Yes</td>
</tr>
<tr>
<td>Kelley 2012&lt;sup&gt;49&lt;/sup&gt;</td>
<td>Placebo pills</td>
<td>Depression (HAM-D-17)</td>
<td>Open label placebos outperform untreated groups</td>
<td></td>
</tr>
<tr>
<td>Sandler 2008&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Placebo pills</td>
<td>ADHD</td>
<td>Open label placebos outperform untreated groups</td>
<td>Yes</td>
</tr>
<tr>
<td>Aulas 2003&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Placebo pills</td>
<td>Depression</td>
<td>Open label placebos outperform untreated groups</td>
<td>No (before/after study)</td>
</tr>
<tr>
<td>Park 1965</td>
<td>Placebo</td>
<td>Anxiety</td>
<td>Open label placebos outperform untreated groups</td>
<td>No (before/after study)</td>
</tr>
</tbody>
</table>
pills placebos outperform untreated groups study)

References


Appendix 1. Search Strategy

#1) placebo* and (told or nondecept* or "non decept**" or nonconceal* or "non conceal**" or nonblind* or "non blind**" or "without deception" or "without conceal**" or "without blind**"):ti (Word variations have been searched)

#2) placebo* near (told or nondecept* or "non decept**" or nonconceal* or "non conceal**" or nonblind* or "non blind**" or "without deception" or "without conceal**" or "without blind**"):ti,ab,kw (Word variations have been searched)

#3) "open placebo**" or "open label placebo**":ti,ab,kw (Word variations have been searched)

#4) #1 or #2 or #3