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Effects of placebos without deception compared with no treatment: a systematic review and meta-analysis

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Abstract

Objective

To investigate the clinical efficacy of open-label placebos compared with no treatment in a systematic review and meta-analysis.

Methods

We searched the Cochrane Injuries Group's Specialised Register, The Cochrane Central Register of Controlled Trials (CENTRAL), Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations (OvidSP), EMBASE (OvidSP), and clinical trials registers and screened reference lists. The search was run on April 27th 2015. We included all randomised controlled trials of any medical condition with open-label placebo and no-treatment groups. Authors independently assessed records and extracted data. We excluded non-randomised trials and non-clinical studies. Risk of bias was assessed using Cochrane criteria. We used random-effects model for meta-analysis.

Results

We screened 348 publications, assessed 24 articles for eligibility and identified 5 trials (260 participants) that met inclusion criteria. The clinical conditions were: irritable bowel syndrome (IBS), depression, allergic rhinitis, back pain and attention deficit hyperactivity disorder (ADHD). The risk of bias was moderate. We found a positive effect for non-deceptive placebos (standardized mean difference 0.88, 95% CI 0.62 to 1.14, $P < 0.00001$, $I^2 = 1\%$).

Conclusions

Open-label placebos appear to have positive clinical effects compared to no treatment. Caution is warranted when interpreting these results due the limited number of trials identified, lack of assessor blinding, and the fact that positive messages were included alongside open label placebos. Larger definitive trials are now warranted to explore the potential patient benefit of open-label placebos, to investigate the relative contributions of positive suggestions, and ethical implications.

Registration number
Protocol registered on PROSPERO (CRD42015023347).

Key words: suggestion, placebo, non-deceptive, expectation, ethics

Introduction

Surveys from around the world estimate that 17%-97% of doctors have prescribed placebos—such as dummy pills—in routine practice.[1,2] While early estimates of placebo effects were exaggerated,[3,4] it is widely acknowledged that placebos are able to offer some benefit to patients suffering from conditions such as pain and depression.[5–7] However, prescribing placebos is considered unethical because it has been presumed that it was necessary to deceive the patient by asserting the presence, or potential presence, of an active ingredient in order to achieve clinical efficacy.[8,9] Yet several studies suggest that non-deceptive or 'open-label' placebos (which are delivered to patients who are told that the treatments are placebos) are effective. This could remove the ethical objection to placebo use in clinical practice.[10–13] For example, a large study of 80 participants with irritable bowel syndrome (IBS) by Kaptchuk and colleagues randomized participants to either open-label placebo pills or no-treatment controls.[11] The study demonstrated significant global improvement for IBS symptoms at both 11 and 21 days (study endpoint) amongst the placebo group compared to no treatment.

Despite this growing literature, a systematic review of open-label placebos has not been conducted, which makes it problematic to draw definitive conclusions about the effects of non-deceptive placebos.[14] A 2010 Cochrane Review of placebo treatments (both deceptive and open label) for all clinical conditions included some open label placebo studies [5] but did not assess the efficacy of non-deceptive placebos alone. Furthermore, studies of non-deceptive placebos compared with a no treatment arm have since been published,[11,15] which highlights the need for this systematic review.

The aim of this study was to assess the effect of placebos, delivered non-deceptively, compared to no treatment, for adults or children patients with any clinically diagnosed disease and for any clinical outcome.

Methods

Eligibility criteria

Studies were eligible for this review if they included participants with any diagnosed medical condition such as pain, depression or irritable bowel syndrome. We included only studies which included a comparison of an open label placebo intervention (such as sugar pills, saline injections, and sham procedures) with a 'no treatment' condition. No treatment conditions included patients receiving other interventions, so long as this was identical between open-label placebo and no treatment groups. Studies must have clinical outcomes reported and we took the primary clinical outcome identified by each study. If none was described the authors identified the most relevant clinical outcome and justified this decision (Table 1).

We only included randomised trials. We excluded non-clinical studies, for example those involving healthy volunteers. We did not have any age, time or language restrictions.

Information sources and search

Searches, using the strategy listed in Appendix 1, commenced from the start date of the database through to 27th April 2015. We searched using, EMBASE [OvidSP] (1974 to 2015 April 24), Medline & Medline In-process [OvidSP] (1946-present), The Cochrane Central Register of Controlled Trials [CENTRAL, The Cochrane Library, Wiley] (Issue 3 of 12, March 2015). In addition, we searched for proceedings of placebo-specific conferences and contacted experts in the field and authors of included studies for advice about other studies. We also searched the online clinical trial registers ClinicalTrials.gov and International Standard Randomised Controlled Trial Number (ISRCTN). All returned records were combined into a Reference Manager (Endnote) database, with duplicate records removed.

Two authors independently screened all titles, abstracts, and full records for inclusion, with discrepancies resolved by discussion with a third author. Two authors extracted data independently from the included studies with discrepancies resolved by discussion or by consultation with third author. Data extraction was carried out by adapting the Cochrane Consumers and Communication Review Group Data Extraction Template (available at: http://cccrg.cochrane.org/author-resources). The following items were extracted: study design; types of participants; description of intervention and intervention components; description of comparison group; completeness of outcome data; outcome measures; country; and funding source.

Reporting outcomes

Primary outcomes, as specified by study authors, were reported (Table 1). When not stated, the most clinically relevant outcome was selected and a rationale provided. All other outcomes for the studies are presented (Table 2). A separated table detailing instructions given to inform participants that they received a placebo is included (Table 3).

Risk of bias in individual studies

We have assessed and reported on the methodological risk of bias of included studies in accordance with the Cochrane Handbook,[16] which recommended explicit reporting of the following individual elements for randomized control trials: random sequence generation; allocation sequence concealment; blinding (participants, personnel, outcome assessment); completeness of outcome data, selective outcome reporting; and other sources of bias. We judged each item as being at high, low or unclear risk of bias as set out in the criteria provided by the Cochrane Collaboration,[16] and provide a quote from the study report and a justification for our judgment for each item in the risk of bias table (supplementary Table 1).

Studies were deemed to be at the highest risk of bias if they scored as high or unclear risk of bias for either of the random sequence generation or allocation concealment domains, based on growing empirical evidence that these factors are particularly important potential sources of bias.[16] Two authors independently assessed the risk of bias of included studies, with any disagreements resolved by discussion to reach consensus, again involving a third author where required. We contacted study authors for additional information about included studies, or to clarify study methods where required.

We have also reported details of the interventions and verbal instructions that accompanied the open-label placebos (Table 3).

We commented on reporting bias qualitatively based on the characteristics of the included studies, but have not identified sufficient studies to produce a reliable funnel plot to identify and quantify publication bias.

Missing data

We contacted study authors to obtain missing and incomplete data. Studies with missing outcome or summary data were identified, and we have reported this in the narrative description of the results.

Meta-analysis

Meta-analysis was carried out using Review Manager (RevMan) Version 5.3. (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014). Only studies with continuous measures were identified. The standardized mean difference (SMD), standard deviation (SD) and 95% confidence interval (CI) were calculated.

We anticipated heterogeneity in terms of intervention modalities, conditions, outcome measures, patients, and effect sizes. For this reason a random effects model was used for the meta-analysis.

The degree of heterogeneity was assessed by visual inspection of forest plots and using the chi-square test for heterogeneity. Heterogeneity was further quantified by using the I^2 statistic. We considered an I^2 value of 50% or more as representing a substantial level of heterogeneity.[16]

Protocol amendments

There was an insufficient number of trials included to conduct the planned subgroup analyses.

We deviated from the protocol by including only clinical studies, for three reasons. Firstly, the clinical and non-clinical studies were qualitatively different, undermining the rationale for inclusion within the same systematic review. The latter mostly investigated the effects of decaffeinated coffee on healthy volunteers.[17–20] Secondly, the non-clinical studies lack clinical relevance by definition and are therefore not pertinent for a general medical audience. Finally, only the included studies are relevant to the question of how open-label placebos might be relevant to clinical practice.[21]

The protocol was also amended such that 'no additional treatment' control groups were considered equivalent to 'no treatment' controls. [21;22] This was justified as it may be unethical to withhold known beneficial treatment in a trial where the only intervention is a placebo. The effect of open label placebos can still be fairly assessed so long as the addition of placebo is the only difference between the control and intervention groups. Furthermore, identifying a strict 'no treatment' group is particularly difficult in a clinical trial, where enrolling and observing participants may result in the well-documented Hawthorne effects and hence could be considered an intervention themselves (explored in further in the discussion). Worthy of note is that this definition of a 'no treatment' control group is consistent with the 2010 Cochrane Review which examined placebos against no treatment.[5]

Results

After removing duplicates we screened 348 trials, assessed 24 articles for eligibility, and identified 5 trials (260 patients) that met our inclusion criteria (Figure 1).[11,13,15,22,23] The risk of bias for each study and domain is shown in Figure 2. Given that we are specifically assessing only open-label studies, bias for participant blinding of is necessarily high. Thus, excluding the high risk of participant blinding, overall low risk of bias was assessed in 47% of domains, with 33% at unclear risk and 20% at high risk. We suggest that overall this implies there is a moderate risk of bias from all studies. All of these were eligible for meta-analysis (Figure 3). We found a positive effect of non-deceptive placebos SMD) 0.88, 95% CI 0.62 to 1.14, $p < 0.00001$, $I^2 = 1\%$). The conditions treated in these trials were: depression,[15] attention deficit hyperactivity disorder (ADHD),[13] irritable bowel syndrome (IBS),[11] allergic rhinitis,[22] and chronic lower back pain.[23] One study reported harms,[13] and found a non-significant reduction in side-effects within the open-label placebo group compared with the treatment and control groups.

Narrative summary of results

Kaptchuk 2010.[11] This parallel two-group trial randomized 80 patients to receive either open-label placebo pills presented as in table 1 or no treatment. Investigators then measured the effect of the treatment on the IBS Global Improvement Scale (IBS-GIS, stated primary outcome). Open label placebo produced significantly higher mean global improvement scores (IBS-GIS) at both 11-day midpoint and at 21-day endpoint (table 2).

Kelley 2012.[15] This pilot two-group parallel trial randomized 20 patients diagnosed with non-psychotic Major Depressive Disorder (MDD) to either open-label placebo (2 pills/day) or waitlist control. At baseline and after 2 weeks investigators used the 17-item Hamilton Scale for Depression (HAM-D-17, explicit primary outcome) to measure depressive symptoms. There was a positive, but not statistically significant, difference between the open-label placebo and waitlist control groups (table 2).

Sandler 2008.[13] This pilot parallel crossover trial of 26 children randomized participants with attention deficit hyperactivity disorder (ADHD) who were receiving stimulant therapy to one of two arms: (1) 100% dose for the first week, 50% dose for the second week, then 50% dose + open-label placebo for the third week, or (2) 100% dose for the first week, 50% dose + open-label placebo for the second week, then 50% dose for the third week The authors reported four primary outcomes, and e deemed the Clinical Global

Impressions (CGI) to be the most clinically relevant because it included the other measures and was therefore the most comprehensive. Physicians completed the CGI after interviewing parent and child. There was an important and statistically significant benefit of open-label placebos (Table 2).

Carvalho 2016.[23] This 2-group parallel trial of 83 patients with at least 3 months of chronic lower back pain. Participants were randomized to receive 2 placebo tablets, taken twice daily, or treatment as usual, for 3 weeks. All participants were again primed towards placebo for 10-15 minutes at the mid-point review. Primary outcomes were mean weekly retrospective pain assessments (0-10) and the Roland-Morris Disability Questionnaire (RMDQ) assessed at 3 weeks; we took RMDQ to be the most relevant clinical outcome for the meta-analysis (Table 1). The open-label placebo demonstrated a statistically significant benefit over treatment as usual (table 2)

Schaefer 2016.[22] This 2-group randomised controlled trial of 25 participants with physician-diagnosed allergic rhinitis compared open-label placebo pills against treatment as usual for two weeks. Participants completed a symptom severity questionnaire and a subjective wellbeing checklist (SF-12). At randomization, open-label placebo patients had a non-significantly greater symptom severity than the treatment as usual group. The two-week trial had no significant effect on the subjective experiences of 11 individual physical symptoms, however there was a significant improvement in subjective wellbeing ($p = 0.009$). The reduction in overall symptom severity was significantly greater amongst the open-label placebo group, compared with the treatment as usual group (table 2).

Risk of bias

As shown in Figure 2, overall, the studies had a moderate risk of bias. Participants in the studies were, by definition, unblinded, and all but one of the studies used unblinded outcome assessors.[15] None of the studies were at a high risk of bias for incomplete outcome reporting or selective reporting. Three of the studies were at an unclear risk of bias for incomplete outcome data.[11,15,23] Two of the studies was at a high risk of 'other' bias. These were because data in Sandler et al., were not presented for the teacher-reported outcome measure, although this was commented on in the text,[13] and Schaefer et al., had a trend toward higher symptom severity within the placebo-treated group and did not describe participants at baseline with respect to their allergic triggers (see Supplementary Table 1).

Discussion

Summary of evidence

We found that open-label placebos have a statistically significant, medium-sized effect across the 5 randomised trials that were included. To our knowledge, this is the first systematic review to evaluate the effect of open-label placebos. However, the results of this meta-analysis should be interpreted with caution because of the small number of studies, the small sample sizes of the included studies, the moderate risk of bias identified and the heterogeneity of sample populations (children and adults), clinical conditions, and reporting methods.

Comparison with existing evidence

Systematic reviews of placebos in general show a small but statistically significant benefit of placebos.[5,24] The effect size estimate for open-label placebos in the current systematic review and meta-analysis is larger than previous estimates for deceptively delivered placebos, [5] suggesting the possibility that open-label placebos may have effects that are equal to, or perhaps even larger than, deceptive placebos. This could be because most of the open label placebos included positive messages together with the placebos (see below), or it could be that the effects of 'standard' placebos are an underestimate because they are delivered in conditions of doubt.[25]

However, the evidence for the efficacy of placebos delivered in blinded conditions is much more robust. Moreover, given that conscious expectancy is presumably less powerful when placebos are delivered openly, it is often suggested that open-label placebos are likely to be less effective than placebos delivered deceptively. Despite this, we are aware of only four studies that compare the physiological outcomes of

open-label and deceptively delivered placebos,[17–20] and none reported a significant difference between the open-label.

Strengths and weaknesses

To our knowledge, this is the first systematic review and meta-analysis of open-label placebos. It provides evidence to suggest that open-label placebos provide symptom relief to patients suffering from IBS, depression, allergic rhinitis, chronic lower back pain and ADHD. The key limitation was size: there were 5 studies (260 patients) eligible for inclusion. This made it difficult to assess the risk of publication bias. Two of the five included studies were carried out by the same author, suggesting the need for independent replication within this field.

Furthermore, 4 in 5 of the studies included interventions with explicit positive suggestions alongside the open-label placebo,[11,13, 22, 23] making the effects of non-deceptive placebos difficult to distinguish from benefits of positive framing. [26] The only study lacked any positive framing and instruction sets [15] and this study also showed the smallest effect size. The inclusion of positive suggestions alongside the open label placebos may explain why open label placebos appear to have a greater effect than 'standard' placebos delivered in blind conditions. [5] Reporting bias in the individual studies might have arisen due to inherent lack of blinding for the participants and caregivers within the included studies. In only one of the included studies were outcomes assessed by blinded observers,[15] however non-deceptive placebos remained statistically significant in this study alone. Hawthorne effects may also have influenced unblinded participants. In being studied participants may be more likely to report efficacy.[27] The John Henry effect could have exacerbated this bias. Patients in the control groups could have been incentivised to demonstrate efficacy when observed given the perception they are 'competing' with the treatment group, therefore greater efficacy is reported amongst unblinded control groups.[28,29] At the same time, the dose-response evidence (see below) suggests that open label placebo effects cannot be reduced to bias alone.

A limitation of our methodology is that in some cases the authors had to judge the most clinically relevant outcome of a study, we address this by providing a rationale in table 1 and have reported on all outcomes separately (Table 2). Finally, while statistical heterogeneity was low due to the consistently positive effect, the studies varied in terms of participants (children/adults), conditions (IBS, depression, allergic rhinitis, back pain and ADHD), control interventions (no treatment versus waiting list versus treatment as usual) and outcome measures. The quality of the placebos and fidelity of the consultations in which the open label placebos were delivered is also another potential source of bias that we could not assess due to lack of reporting.

How open-label placebos might work

The mechanisms by which open-label placebos remain to be confirmed, with classical conditioning being the most strongly supported by evidence.[30] A recent clinical study of open-label placebos showed that prolonged conditioning (4 versus 1 day) demonstrated greater benefit in the treatment of pain.[31] This dose-response data is evidence of causation.[32] In addition, conscious expectancy is a relevant mechanism here, as we have shown that open-label placebos are often accompanied by a suggestion that the placebo is effective. It is known that the expectation of pain relief has been found to modulate the central regulation of pain through, in particular, the dopamine reward system and the endogenous opioid system.[30] There is also a growing body of evidence that in addition to what practitioners say, the way in which they deliver these messages (for example with more or less empathy) can also affect health outcomes.[33–35]

'Embodied cognition' is a relatively new theory that beginning to help explain how open label placebos might work but is currently at the speculative stage. According to this theory,[36] our physical interaction with the world influences or even determines our cognitions .[37] For example, the sound of the dentist's drill might trigger a specific bodily sensation.[38] Hence sensory signals could evoke different reactions including those involved in positive and negative healing experiences.[38,39] Embodied cognition is related to conditioning because it operates at a sub-conscious level and is automatic. However it also

differs in important respects. For one, it does not require a specific conditioning procedure (such as the learned pairing of a bell ringing with food). Relatedly, the cognitions arise directly from bodily experiences that are not mediated by the brain. Some healthcare settings in which open label placebos are delivered could induce the body to react in a way that subsequently leads to cognitions, which, in turn, induce the brain to produce endogenous substances such as analgesic endorphins. Further work is warranted to investigate the role of embodied condition in explaining how open label placebos work.
In the real-world setting of healthcare, these putative placebo mechanisms are likely to operate in unison. The positive reinforcement of previous efficacy, the healthcare environment and positive framing. Therefore it is reasonable to assume that these proposed mechanisms are combined, to differing degrees depending on the individual and their disease, to demonstrate efficacy.

Conclusions and implications

Open-label placebos may have a medium sized effect that may help reduce symptoms in patients with some medical conditions. Since placebos may not require deception, this study also suggests that ethical restrictions to using placebos in clinical practice need to be revisited, [40] although replacement of more effective treatment with placebos (open-label or not) would remain unethical. Moreover the limited number of studies in this review, the moderate risk of bias and lack of blinding suggests caution in drawing any definitive clinical conclusions from our results. Furthermore, the delivery of open-label placebo was often (4 in 5 studies) accompanied by positive suggestions and further research is required to investigate what the relative contribution of suggestions are. Independent replication with a large high quality randomized trial is now warranted, together with evaluation of clinician and patient attitudes towards open label placebo use.

Table 1. Description of included studies

Study	Country	Condition	No. Participants	Mean age, years	Male Sex, %	Intervention	Control treatment	Intervention timing	No. Primary outcomes	Primary outcome measure used for meta-analysis	Rationale for choice of primary outcome measure
Kaptchuk 2010	United States	IBS	80	47	30	Open label placebo pills with positive suggestion.	No treatment	21 days	1	IBS Global improvement	(only one primary outcome)
Kelley 2012	United States	Major Depressive Disorder	20	38.8	30	Open label placebo pills	Waitlist	14 days	1	17-item Hamilton Scale for Depression	(only one primary outcome)
Sandler 2008	United States	ADHD	26	not stated (range 7-15)	73	Open label placebo pills described as a 'dose extender'	50% of baseline medication (mirrored by placebo group)	7 days	4	7 CGI (7-point clinical global impression)	Because it takes parent, teacher, and side-effect rating as well as clinician impression into account.
Carvalho 2016	Portugal	Chronic lower back pain	83	44	28.9	Open label placebo pills with positive suggestion.	Treatment as usual	21 days	2	Roland–Morris Disability Questionnaire	Validated disability questionnaire which relates to the extent of functional impairment in everyday life
Schaefer 2016	Germany	Allergic Rhinitis	25	26	16%	Open label placebo pills	Treatment as usual	14 days	2	Composite allergic rhinitis symptom	Clinically relevant disease outcome,

	severity (1-7)	only with data reported in the paper.

Table 2 Summary of outcomes all outcomes with reported data

Outcome	No studies (patients)	Effect size (SMD, 95% CI, p-value if reported)	Heterogeneity (I^2)
All studies	5 (260) (12, 14, 16, 32, 33)	SMD 0.88, 95% CI 0.62 to 1.14, p < 0.00001	1%
IBS symptoms (IBS Global Improvement Scale)	1(80) (12)	0.78, 95% CI 0.32 to 1.24, p = 0.0008	n/a
IBS symptoms (IBS-SSS)	1(80) (12)	0.53, 95% CI 0.08 to 0.97, p = 0.02	n/a
IBS relief (IBS-AR)	1(80) (12)	ODDS RATIO: 2.74, 95% CI 1.10 to 6.79, p = 0.03	n/a
IBS quality of life (IBS-QoL)	1(80) (12)	0.39, 95% CI -0.05 to 0.84, p = 0.08	n/a
ADHD symptoms – parent reported (Parent-reported ADHD Scale)	1(26) (14)	0.70, 95% CI 0.13 to 1.26, p = 0.02	n/a
ADHD symptoms – clinician reported (Clinical Global Impression Scale)	1(26) (14)	1.37 (95% CI 0.76 to 1.98, p < 0.0001	n/a
Stimulant side effects (parent-reported)	1(26) (14)	0.21, 95% CI -0.33 to 0.76, p = 0.44	n/a
Depression symptoms (17-Item Hamilton Depression Scale)	1(20) (16)	0.51, 95% CI -0.38 to 1.41, p = 0.26	n/a
Depression symptoms (Quick Inventory of Depressive Symptoms (QIDS))	1(20) (16)	0.72, 95% CI -0.20 to 1.63, p = 0.12	n/a
Depression symptoms (Symptoms of Depression Questionnaire (SDQ))	1(20) (16)	0.14, 95% CI -0.74 to 1.02, p = 0.76	n/a
Pain (Improvement) minimum weekly mean at endpoint	1(83) (33)	0.62, 95% CI 0.17 to 1.06, p = 0.006	n/a
Pain (Improvement) usual weekly mean at endpoint	1(83) (33)	0.52, 95% CI 0.08 to 0.96, p = 0.02	n/a
Pain (Improvement) maximum weekly mean at endpoint	1(83) (33)	0.45, 95% CI 0.01 to 0.89, p = 0.05	n/a
Pain (Improvement) composite weekly mean at endpoint	1(83) (33)	0.75, 95% CI 0.30 to 1.20, p = 0.001	n/a
Disability (Roland-Morris Disability Questionnaire - RQD), adapted in Portuguese.	1(83) (33)	0.74, 95% CI 0.29 to 1.18, p < 0.001	n/a
Chronic back pain 'bothersomeness' (improvement)	1(83) (33)	0.26, 95% CI -0.18 to 0.69, p = 0.25	n/a
Change (reduction) in allergic rhinitis symptom severity	1 (25) (32)	1.15. 95% CI 0.29 to 2.01, p = 0.009	n/a

Table 3. Detailed description of interventions

Study	Open label placebo	Verbal instructions (if included)
Kaptchuk 2010	"Placebo pills were blue and maroon gelatin capsules filled with Avicel, a common inert excipient for pharmaceuticals"	"The provider clearly explained that the placebo pill was an inactive (i.e., ''inert'') substance like a sugar pill that contained no medication and then explained in an approximately fifteen minute a priori script the following ''four discussion points:'' 1) the placebo effect is powerful, 2) the body can automatically respond to taking placebo pills like Pavlov's dogs who salivated when they heard a bell, 3) a positive attitude helps but is not necessary, and 4) taking the pills faithfully is critical."
Kelley 2012	"Blue capsules containing microcrystalline cellulose."	"Patients were instructed to take two placebo pills, twice daily."
Sandler 2008	"a visually distinctive placebo capsule"	"This little capsule is a placebo. Placebos have been used a lot in treating people. It is called 'Dose Extender'. As you can see, it's different from Adderall. *(Describe its features)*. Dose Extender is something new. It has no drug in it. I can promise you that it won't hurt you at all. It has no real side effects. But it may help you to help yourself. It may work well with your Adderall, kind of like a booster to the dose of Adderall. That's why it's called a Dose Extender. I won't be surprised when I hear from you and your parents and your teachers that you're able to control your ADHD better. For the next 4 weeks, every time you take your Adderall, you will also take your Dose Extender. This

		will really give them a chance to work well together. Okay? Do you have any questions about Dose Extender?"
Carvalho 2016	"A typical prescribed medicine bottle of placebo pills with a label clearly marked "placebo pills" and "take 2 pills twice a day." The placebo pills were Swedish Orange gelatin capsules filled with microcrystalline cellulose, a common inert excipient for pharmaceuticals"	"The PI explained that the placebo pill was an inactive substance, like a flour pill, that contained no active medication in it. After informed consent, all participants were asked if they had heard of the "placebo effect" and explained in an approximately 15-minute a priori script, adopted from an earlier OLP study,18 the following "4 discussion points": (1) the placebo effect can be powerful, (2) the body automatically can respond to taking placebo pills like Pavlov dogs who salivated when they heard a bell, (3) a positive attitude can be helpful but is not necessary, and (4) taking the pills faithfully for the 21 days is critical. All participants were also shown a video clip (1 minute 25 seconds) of a television news report, in which participants in an OLP trial of irritable bowel syndrome were interviewed (excerpted from: http://www.nbcnews.com/video/nightly-news/40787382#40787382)"
Schaefer 2016	"The placebo group received a white tube containing 28 placebo pills. The tube was labeled with the logo of the local university and the following information: 'placebo pills (28), take one in the morning and one before night for 14 days'."	"We explained that placebos are inactive substances and that they contain no medications. Participants were further told that although placebos contain no medication, placebo effects may still be powerful. The effect was explained to them by pointing out that the body may automatically respond to taking placebo pills, like Pavlov's dogs that salivated when they heard the bell. In addition, they were told that a positive attitude may be helpful for the placebo effect, but is not necessary. Last, they were told that those participants who were in the placebo group needed to take the placebos faithfully."

Figure 1. PRISMA flowchart

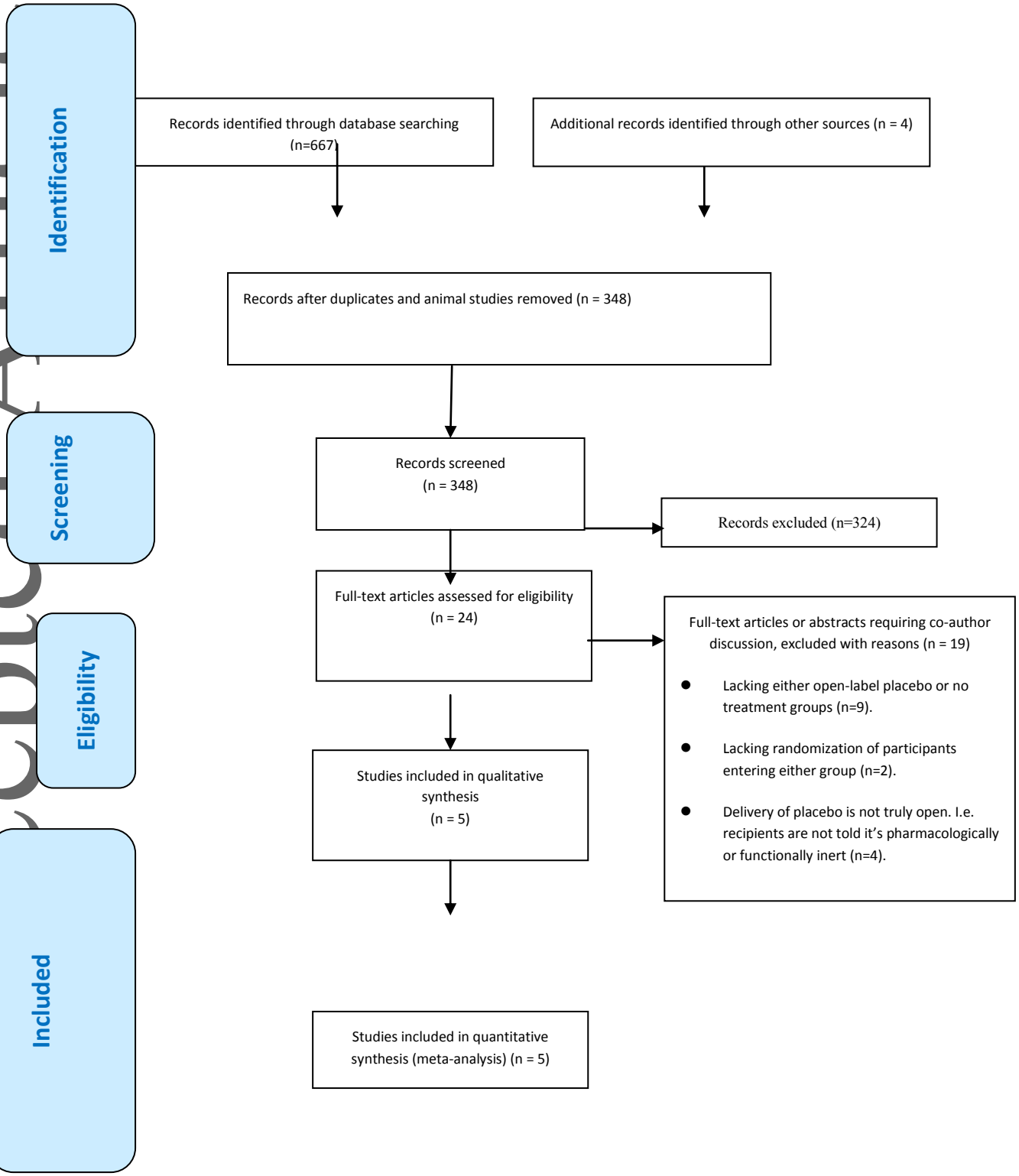


Figure 2. Risk bias of included studies

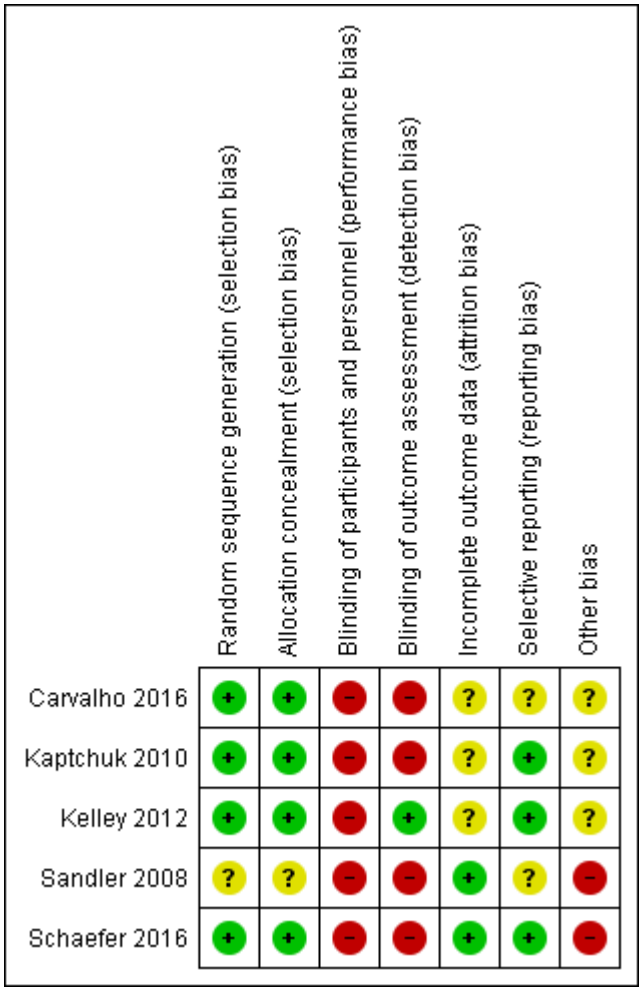
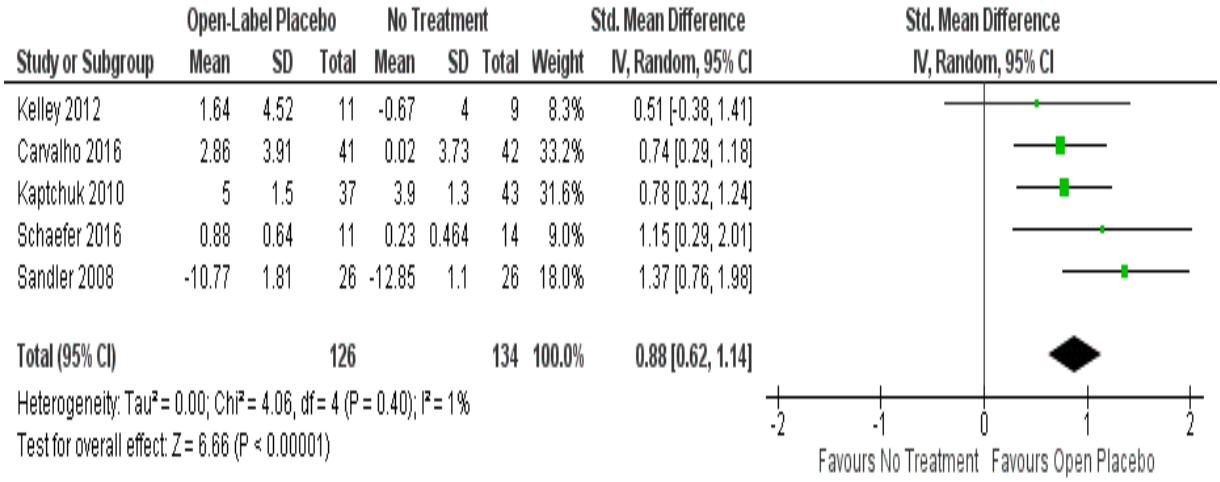


Figure 3. Forest plot for main outcome



Dissemination

This protocol has been registered on PROSPERO(2015:CRD42015023347), and was also published. (31)

Authors' Contributions

JH drafted the protocol, devised the study, assisted with search strategy, assisted with data extraction and analysis, drafted the results and discussion sections, and conducted some of the data analysis. GP and JC revised the protocol, assisted with study design, carried out most of the data collection and analysis, and contributed to writing protocol and manuscript. NR designed and conducted the search strategy and provided input on the wording of the manuscript. JK provided input on the protocol, statistical analysis plan, and overall structure of the manuscript, and helped revise the manuscript. FM provided input on the drafting of the protocol, rationale for the study, and helped write the manuscript. IO provided expertise in the statistical analysis and revised the manuscript. MH provided expertise on the mechanisms for open-label placebos, drafted the section on embodied cognition, and helped revise the manuscript.

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Competing Interests Statement

The authors declare no competing interests.

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