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

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Word count: 5521 (excluding abstract, title page, and references)

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ABSTRACT

Aim

Our aim was to address the clinical efficacy of open-label placebos compared with no treatment by systematic review, and meta-analysis where possible.

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. We ran the most recent search on April 27 2015. All randomised controlled trials of any medical condition, which had both open-label placebo and no-treatment or treatment as usual groups were included. Two authors independently applied the selection criteria and extracted data. The risk of bias of included studies was assessed using the Cochrane criteria. We used random-effects model for meta-analysis.

Results

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

Conclusions

Open-label placebos appear to have favorable clinical outcomes, compared to no treatment or no additional treatment. Caution is warranted when interpreting the results due to the limitations including the small number of trials and lack of blinding. Larger definitive trials are now warranted to explore the potential patient benefit of open-label placebos.

Registration number

This protocol has been registered on PROSPERO (2015:CRD42015023347).

KEY WORDS

1. Suggestion
2. Placebo
3. Non-deceptive
4. Expectation
5. Ethics

INTRODUCTION

Rationale

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 are effective, which could remove the ethical objection to placebo use in clinical practice.(10-14) 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. (12) 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. Yet despite a 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.(15) 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, (12, 16) which highlights the need for this systematic review.

How open-label placebos might work

The mechanisms of action for open-label placebos are currently speculative,(17) with classical conditioning being the most likely candidate. A recent study of open-label placebos for treating pain showed that patients who had been conditioned for longer (four days) experienced benefits compared with patients conditions for shorter (one day) durations.(18) If patients have been conditioned by previous visits to the doctor—or by having taken a pill—to recover, then the act of receiving an open-label placebo pill could generate a positive response. One clinical study even suggests that the immune system can be conditioned.(19) Conscious expectancy may also play a role since open-label placebos are usually accompanied by a suggestion that the placebo is effective. Trials suggest that positive expectation can relieve pain, lower anxiety and reduce the symptoms of Parkinson's disease.[17] The expectation of pain relief has been found to activate neurological systems involved in regulating pain, such as the dopamine reward system and the endogenous opioid system.(20) Daily consumption of open-label placebos may act as a daily positive autosuggestion that generates positive expectations. Related to classical conditioning, 'embodied cognition' is a theory that human cognition can be shaped by aspects of the body (such as the motor and perceptual systems, and the body's interactions with the environment) that are beyond the brain alone. (21) Embodied cognition is different from conditioning in that it focuses on how bodily experiences can unconsciously influence a person's cognition, resulting in changes in thinking, behavior, and even physiology even without previous conditioning. Hence sensory signals could evoke different reactions including those involved in positive and negative healing experiences.(22, 23) For instance, the sound of the dentist's drill might trigger a specific bodily sensation.(22) If open-label placebos are delivered in the context of a healthcare setting that usually delivers a relevant stimulus, this could enhance the bodily reaction that influences healing. There are also 'indirect' mechanisms of open-label placebos, such as the effects of contact with therapist.(24, 25) These mechanisms are likely to operate together, producing variable effects depending on the individual and the condition.

Aims

The aim of this study was to assess the effect of placebos delivered non-deceptively compared to no treatment.

METHODS

Eligibility criteria

We included only randomised controlled studies of placebo interventions (such as sugar pills, saline injections, and sham procedures) delivered 'openly' where there was also a 'no treatment' condition. Participants given open-label placebos must have been told they are receiving a placebo whereas 'no treatment' could include people on a waiting list, treatment as usual, or those simply left untreated. We included only studies of participants with a particular medical condition (such as pain, depression or irritable bowel syndrome). 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.

Study selection

Study selection and data extraction

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 of 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,(26) 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,(26) 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.(26) 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).

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.

Assessment of heterogeneity

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.(26)

Risk of bias across studies

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.

Subgroup & Sensitivity Analysis

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

'Summary of findings' table

Our 'Summary of findings' table (Table 2) presents the results of the meta-analysis for the major comparisons of the review, for each of the major primary outcomes.(26)

Protocol amendments

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. (27-30) 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.(31)

The protocol was also amended such that 'no additional treatment' control groups were considered equivalent to 'no treatment' controls. 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

Summary of evidence

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).(12, 14, 16, 32, 33) The overall risk of bias was moderate (Figure 2). 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,(16) attention deficit hyperactivity disorder (ADHD),(14) irritable bowel syndrome (IBS), (12) allergic rhinitis, (32) and chronic lower back pain. (33) One study reported harms,(14) 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.(12) This parallel two-group trial randomized 80 patients (70% female, mean age 47±18) to receive either open-label placebo pills presented as "placebo pills made of an inert substance, like sugar pills, that have been shown in clinical studies to produce significant improvement in IBS symptoms through mind-body self-healing processes" 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 (±SD) global improvement scores (IBS-GIS) at both 11-day midpoint (5.2±1.0 vs. 4.0±1.1) and at 21-day endpoint (5.0±1.5 vs. 3.9±1.3). At the 21 day endpoint the SMD was 0.78 (95% CI 0.32 to 1.24, P=0.0008).

Kelley 2012.(16) This pilot two-group parallel trial randomized 20 patients (70% female, mean age 38.8±4.9) 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 (SMD 0.51, 95% CI -0.38 to 1.41, P=0.26).

Sandler 2008.(14) This pilot parallel crossover trial of 26 children (27% female, 7-15 years old) 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. For this review the 50% dose arm is considered the 'no treatment' group, with the 50% dose + open-label placebo arm serving as the 'non-deceptive placebo' group. Both groups therefore receive identical medication, with addition of placebo 'treatment' in the intervention group. This was deemed an appropriate amendment to the protocol,(31) as it would have been ethically unjustifiable to withhold treatment in the control group. The authors reported four primary outcomes: the IOWA Conners rating scale (separately for parents and teachers), the Clinical Global Impressions (CGI) scale, and the Pittsburgh side effects rating scale (PSERS), all after three weeks. Data were not reported for the teacher-rated IOWA Conners rating scale, and we failed to obtain these data even after contacting the authors via email three times. We deemed 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, and reviewing parent and teacher IOWA and PSERS scales. There was an important and statistically significant benefit of open-label placebos 1.37 (95% CI 0.76 to 1.98, P<0.0001).

Carvalho 2016. (33) This 2-group parallel trial of 83 patients with at least 3 months of chronic lower back pain, unprecipitated by a number of chronic health conditions as per the exclusion criteria. A 15 minute discussion including news clips describing advantages of placebos preceded treatment. 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. All participants remained on their usual analgesia. Primary outcomes were mean weekly retrospective pain assessments (0-10) and the Roland-Morris Disability Questionnaire (RMDQ) assessed at 3 weeks, which addresses more functional consequences of pain. Mean 'bothersomeness' was a secondary outcome. We took RMDQ to be the most relevant clinical outcome for the meta-analysis. In isolation, RMDQ showed a significantly greater effect by open-label placebo compared to treatment as usual (SMD 0.74, 95% CI 0.29 to 1.18, P<0.001).

Schaefer 2016. (32) 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 were recruited via flyers and social media, and were all on usual medication (unspecified). Once recruited, participants completed a symptom severity questionnaire (scoring 1-7) and a subjective wellbeing checklist (SF-12). At randomisation open-label placebo patients (n=11) had a non-significantly greater symptom severity than the treatment as usual (n=14) group (mean and SD 3.55 ± 0.73, compared to 3.11 ± 0.66, respectively, P>0.1). Following the two-week trial no significant reduction was observed in any single symptom severity or wellbeing. The reduction in overall symptom severity was significantly greater amongst the open-label placebo group, compared with the treatment as usual group (SMD 1.15, 95% CI 0.29 to 2.01, P=0.009).

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.(16) 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.(12, 16, 33)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,(14) 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 3 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, 34) 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, suggesting the possibility that open-label placebos may have effects that are equal to, or perhaps even larger than, deceptive placebos.

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,(27-30) and none reported a significant difference between the open-label.

Strengths and weaknesses [STATISTICAL HETEROGENEITY LOW]

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 additional independent replication within this field.

Furthermore, some of the interventions included explicit positive suggestions alongside the open-label placebo,(12, 14, 33) making the effects of non-deceptive placebos difficult to distinguish from benefits of positive framing.(35) Reporting bias in the individual studies might have arisen due to inherent lack of blinding for the participants and caregivers within the included studies. However, in one of the included studies outcomes were assessed by blinded observers,(16) and non-deceptive placebos were statistically significant in this study alone. Another limitation 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.

Conclusions and implications

Open-label placebos may have a medium sized effect that may help reduce symptoms in patients with some medical outcomes. Our results also point towards a way to overcome the ethical barrier to using placebos in clinical practice,(36) although replacement of known effective treatment with placebos (open label or not) would remain unethical. Moreover the limited number of studies and moderate risk of bias suggest caution in drawing any definitive clinical conclusions. 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 severity (1-7)	Clinically relevant disease outcome, only with data reported in the paper.

12

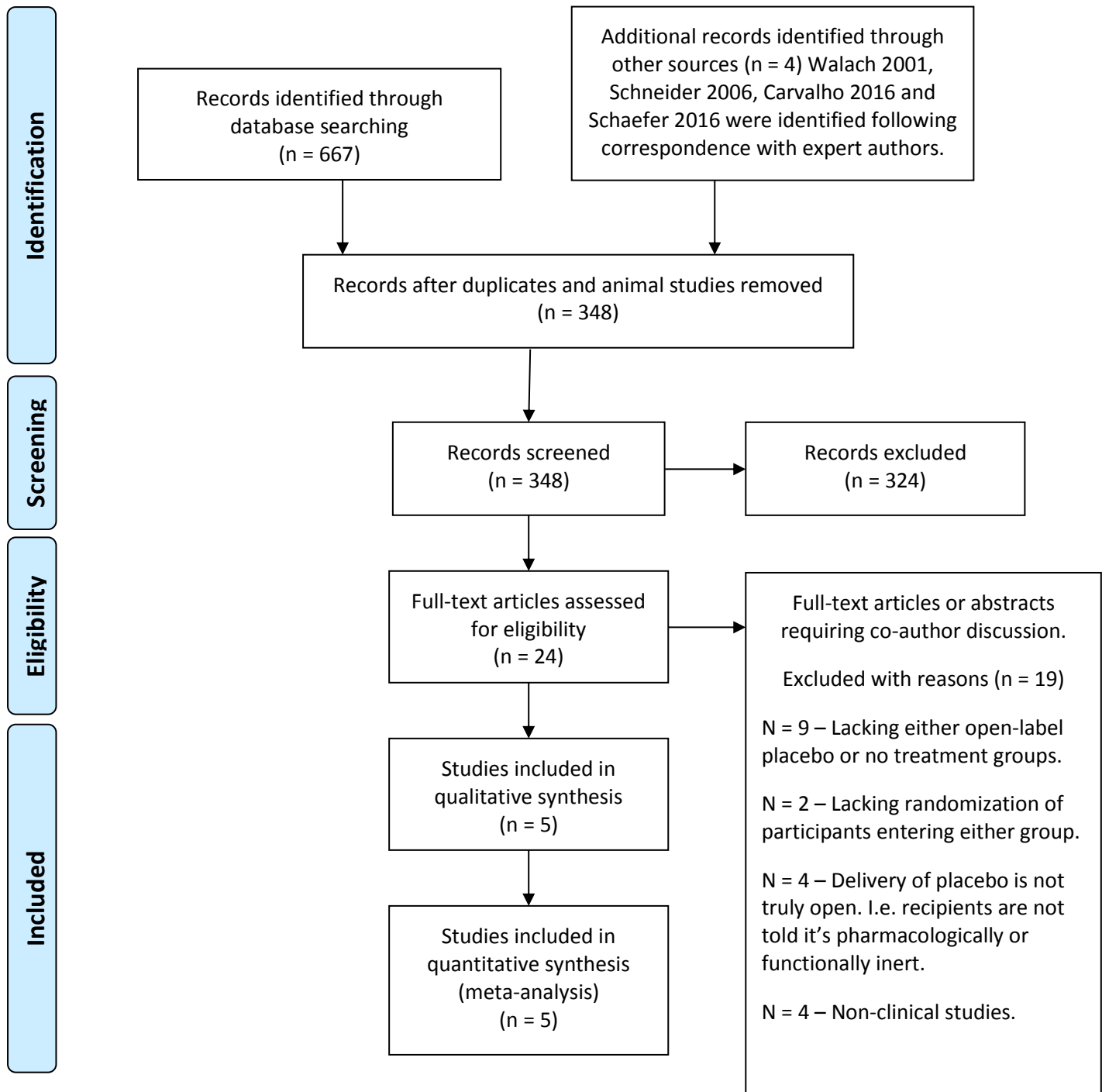**Table 2. Summary of outcomes all outcomes with reported data**

Outcome	No studies (patients)	Effect size (SMD, 95% CI, *P*-value if reported)	Heterogeneity (I²)
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

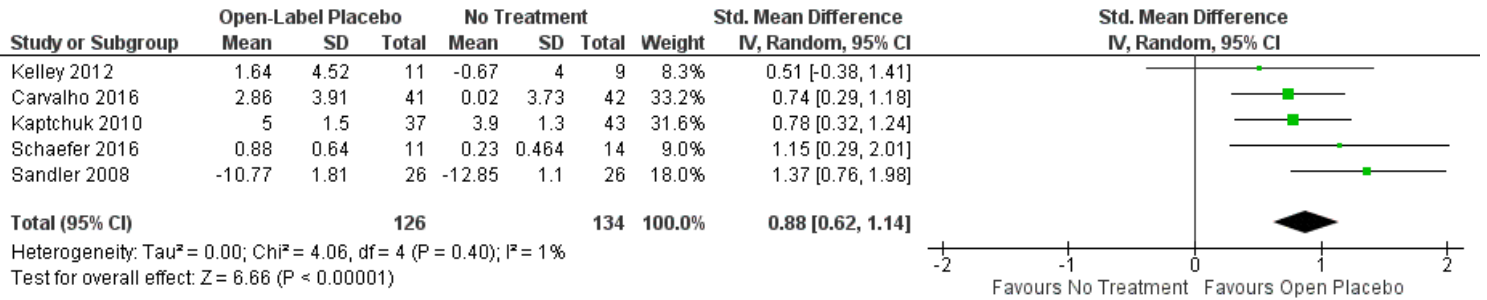|		that those participants who were in the placebo group needed to take the placebos faithfully."

Figure 1. PRISMA flowchart

Figure 2. Risk of bias in included studies

Figure 3. Forest plot for main outcome

Study or Subgroup	Open-Label Placebo Mean	SD	Total	No Treatment Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Kelley 2012	1.64	4.52	11	-0.67	4	9	8.3%	0.51 [-0.38, 1.41]
Carvalho 2016	2.86	3.91	41	0.02	3.73	42	33.2%	0.74 [0.29, 1.18]
Kaptchuk 2010	5	1.5	37	3.9	1.3	43	31.6%	0.78 [0.32, 1.24]
Schaefer 2016	0.88	0.64	11	0.23	0.464	14	9.0%	1.15 [0.29, 2.01]
Sandler 2008	-10.77	1.81	26	-12.85	1.1	26	18.0%	1.37 [0.76, 1.98]
Total (95% CI)			126			134	100.0%	0.88 [0.62, 1.14]

Heterogeneity: Tau² = 0.00; Chi² = 4.06, df = 4 (P = 0.40); I² = 1%
Test for overall effect: Z = 6.66 (P < 0.00001)

Std. Mean Difference
IV, Random, 95% CI

Favours No Treatment   Favours Open Placebo

17

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.

Competing Interests Statement

The authors declare no competing interests.

References

1.   Fassler M, Meissner K, Schneider A, Linde K. Frequency and circumstances of placebo use in clinical practice--a systematic review of empirical studies. BMC medicine. 2010;8:15. PubMed PMID: 20178561. Pubmed Central PMCID: 2837612. Epub 2010/02/25. eng.

2.   Howick J, Bishop FL, Heneghan C, Wolstenholme J, Stevens S, Hobbs FDR, et al. Placebo Use in the United Kingdom: Results from a National Survey of Primary Care Practitioners. Plos One. 2013 Mar 20;8(3). PubMed PMID: WOS:000317562600014. English.

3.   Beecher HK. The powerful placebo. J Am Med Assoc. 1955 Dec 24;159(17):1602-6. PubMed PMID: 13271123.

4.   Kienle GS, Kiene H. The powerful placebo effect: fact or fiction? J Clin Epidemiol. 1997 Dec;50(12):1311-8. PubMed PMID: 9449934.

5.   Hróbjartsson A, Gøtzsche P. Placebo interventions for all clinical conditions. Cochrane database of systematic reviews. 2010 (1):CD003974. PubMed PMID: 20091554. Epub 2010/01/22. eng.

6.   Hróbjartsson A, Gøtzsche P. Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. N Engl J Med. 2001 May 24;344(21):1594-602. PubMed PMID: 11372012.

7.   Hróbjartsson A, Gøtzsche P. Is the placebo powerless? Update of a systematic review with 52 new randomized trials comparing placebo with no treatment. J Intern Med. 2004 Aug;256(2):91-100. PubMed PMID: 15257721.

8.   GMC. Good Medical Practice (2006). The duties of a doctor registered with the General Medical Council. London: GMC; 2006.

9.   Bostick NA, Sade R, Levine MA, Stewart DM, Jr. Placebo use in clinical practice: report of the American Medical Association Council on Ethical and Judicial Affairs. J Clin Ethics. 2008 Spring;19(1):58-61. PubMed PMID: 18552054. Epub 2008/06/17. eng.

10.   Aulas JJ, Rosner I. [Efficacy of a non blind placebo prescription]. L'Encephale. 2003 Jan-Feb;29(1):68-71. PubMed PMID: 12640329. Epub 2003/03/18. Effets de la prescription d'un placebo "annonce". fre.

11.   Dahan R, Caulin C, Figea L, Kanis JA, Caulin F, Segrestaa JM. Does informed consent influence therapeutic outcome? A clinical trial of the hypnotic activity of placebo in patients admitted to hospital. British Medical Journal. 1986 Aug 9;293(6543):363-4. PubMed PMID: 3089521. Pubmed Central PMCID: 1341050. Epub 1986/08/09. eng.

12.   Kaptchuk TJ, Friedlander E, Kelley JM, Sanchez MN, Kokkotou E, Singer JP, et al. Placebos without deception: a randomized controlled trial in irritable bowel syndrome. PLoS One. 2010;5(12):e15591. PubMed PMID: 21203519. Pubmed Central PMCID: 3008733. Epub 2011/01/05. eng.

13.   Park LC, Covi L. Nonblind Placebo Trial: an Exploration of Neurotic Patients' Responses to Placebo When Its Inert Content Is Disclosed. Arch Gen Psychiatry. 1965 Apr;12:36-45. PubMed PMID: 14258363.

14.   Sandler AD, Bodfish JW. Open-label use of placebos in the treatment of ADHD: a pilot study. Child Care Health Dev. 2008 Jan;34(1):104-10. PubMed PMID: 18171451. Epub 2008/01/04. eng.

15.   Chalmers I. The lethal consequences of failing to make full use of all relevant evidence about the effects of medical treatments: the importance of systematic reviews. In: Rothwell PM, editor. Treating individuals: from randomised trials to personalized medicine. London: The Lancet; 2007.

16.   Kelley JM, Kaptchuk T, Cusin C, Lipkin S, Fava M. Open-label placebo for major depressive disorder: A pilot randomized controlled trial. Psychother Psychosom. 2012;81:312-14.

17.   Thomas AS, Aristotle M, Rowan JP. Commentary on Aristotle's Metaphysics. Notre Dame, Ind. ; [Great Britain]: Dumb Ox; 1995. xxxi, 839 p. p.

18.   Schafer SM, Colloca L, Wager TD. Conditioned placebo analgesia persists when subjects know they are receiving a placebo. J Pain. 2015 May;16(5):412-20. PubMed PMID: 25617812. Pubmed Central PMCID: 4424173.

19.   Goebel MU, Trebst AE, Steiner J, Xie YF, Exton MS, Frede S, et al. Behavioral conditioning of immunosuppression is possible in humans. FASEB J. 2002 Dec;16(14):1869-73. PubMed PMID: 12468450.

20.   Price DD, Finniss DG, Benedetti F. A comprehensive review of the placebo effect: recent advances and current thought. Annu Rev Psychol. 2008;59:565-90. PubMed PMID: 17550344. Epub 2007/06/07. eng.

21.   Kemmerer D, Miller L, Macpherson MK, Huber J, Tranel D. An investigation of semantic similarity judgments about action and non-action verbs in Parkinson's disease: implications for the Embodied Cognition Framework. Frontiers in human neuroscience. 2013;7:146. PubMed PMID: 23616759. Pubmed Central PMCID: 3629304.

22.   Thompson JJ, Ritenbaugh C, Nichter M. Reconsidering the Placebo Response from a Broad Anthropological Perspective. Cult Med Psychiat. 2009 Mar;33(1):112-52. PubMed PMID: WOS:000262806400006. English.

23.   Fuchs T, Schlimme JE. Embodiment and psychopathology: a phenomenological perspective. Curr Opin Psychiatry. 2009 Nov;22(6):570-5. PubMed PMID: 19730373.

24.   Friedman R, Sedler M, Myers P, Benson H. Behavioral medicine, complementary medicine and integrated care. Economic implications. Prim Care. 1997 Dec;24(4):949-62. PubMed PMID: 9386264.

25.   Caspi O, Bootzin RR. Evaluating how placebos produce change - Logical and causal traps and understanding cognitive explanatory mechanisms. Evaluation & the Health Professions. 2002 Dec;25(4):436-64. PubMed PMID: WOS:000179094200007. English.

26.   Higgins JJ, Green S. The Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 [updated March 2011] ed. Chichester: The Cochrane Collaboration; 2011.

27.   Walach H, Schmidt S, Bihr YM, Wiesch S. The Effects of a Caffeine Placebo and Experimenter Expectation on Blood Pressure, Heart Rate, Well-Being, and Cognitive Performance. Eur Psychol. 2001;6(1):15-25. PubMed PMID: WOS:000208276000002. English.

28.   Walach H, Schmidt S, Dirhold T, Nosch S. The effects of a caffeine placebo and suggestion on blood pressure, heart rate, well-being and cognitive performance. Int J Psychophysiol. 2002 Mar;43(3):247-60. PubMed PMID: 11850090.

29.   Urroz P. Effect of acupuncture and instruction on post-exercise recovery: A balanced-placebo controlled trial. Sydney, Australia: University of Western Sydney; 2014.

30.   Schneider R, Gruner M, Heiland A, Keller M, Kujanova Z, Peper M, et al. Effects of expectation and caffeine on arousal, well-being, and reaction time. International journal of behavioral medicine. 2006;13(4):330-9. PubMed PMID: 17228991.

31.   Petkovic G, Charlesworth JE, Kelley J, Miller F, Roberts N, Howick J. Effects of placebos without deception compared with no treatment: protocol for a systematic review and meta-analysis. BMJ Open. 2015;5(11):e009428. PubMed PMID: 26610763.

32.   Schaefer M, Harke R, Denke C. Open-Label Placebos Improve Symptoms in Allergic Rhinitis: A Randomized Controlled Trial. Psychother Psychosom. 2016;85(6):373-4. PubMed PMID: 27744433.

33.   Carvalho C, Caetano JM, Cunha L, Rebouta P, Kaptchuk TJ, Kirsch I. Open-label placebo treatment in chronic low back pain: a randomized controlled trial. Pain. 2016 Dec;157(12):2766-72. PubMed PMID: 27755279. Pubmed Central PMCID: 5113234.

34.   Zhang W, Robertson J, Jones AC, Dieppe PA, Doherty M. The placebo effect and its determinants in osteoarthritis: meta-analysis of randomised controlled trials. Ann Rheum Dis. 2008 Dec;67(12):1716-23. PubMed PMID: 18541604.

35.   Di Blasi Z, Harkness E, Ernst E, Georgiou A, Kleijnen J. Influence of context effects on health outcomes: a systematic review. Lancet. 2001 Mar 10;357(9258):757-62. PubMed PMID: 11253970. Epub 2001/03/20. eng.

36.   Foddy B. A duty to deceive: placebos in clinical practice. The American journal of bioethics : AJOB. 2009 Dec;9(12):4-12. PubMed PMID: 20013484. Epub 2009/12/17. eng.