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REVIEW ARTICLE

Imperfect placebos are common in low back pain trials: a systematic review of the literature

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Abstract The placebo is an important tool to blind patients to treatment allocation and therefore minimise some sources of bias in clinical trials. However, placebos that are improperly designed or implemented may introduce bias into trials. The purpose of this systematic review was to evaluate the adequacy of placebo interventions used in low back pain trials. Electronic databases were searched systematically for randomised placebo-controlled trials of conservative interventions for low back pain. Trial selection and data extraction were performed by two reviewers independently. A total of 126 trials using over 25 different placebo interventions were included. The strategy most commonly used to enhance blinding was the provision of structurally equivalent placebos. Adequacy of blinding was assessed in only 13% of trials. In 20% of trials the placebo intervention was a potentially genuine treatment. Most trials that assessed patients' expectations showed that the placebo generated lower expectations than the experimental intervention. Taken together, these results demonstrate that imperfect placebos are common in low back pain trials; a result suggesting that many trials provide potentially biased estimates of treatment efficacy. This finding has implications for the interpretation of published trials and the design of future trials. Implementation of strategies to facilitate blinding and balance expectations in randomised groups need a higher priority in low back pain research.

Keywords Systematic review · Low back pain · Trial methodology · Blinding · Expectation

Introduction

Placebo-controlled trials are designed to control for incidental factors such as natural recovery, regression to mean and placebo effects. In theory, this permits the specific (non-incidental) effects of treatment to be determined. To control for placebo effects, participants must be kept unaware of their group assignment, that is, they must be blinded. If a placebo-controlled trial fails to achieve acceptable blinding, it is possible that the estimates of treatment effects will be biased due to imbalances in the magnitude of placebo effects between groups. Blinding also contributes to the prevention of other sources of bias in trials such as measurement bias, treatment non-compliance and loss to follow-up [79, 125].

Ideally, blinding is achieved by using placebos that are indistinguishable from the experimental intervention. While this is relatively easy to achieve in pharmaceutical trials, it is more difficult in trials of complex interventions such as exercise or psychological interventions [66, 113]. This is because in trials investigating complex interventions, indistinguishability is often achieved at the expense of having placebos that are not inert.

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There is a controversy surrounding the use of term "inert" to describe non-pharmaceutical placebos [18, 34], but much of this debate seems to be merely semantic. For example, Rosenthal and Frank [119] have expanded the inert nature of placebos to psychotherapy by defining placebo as "an activity regarded as therapeutically inert from the standpoint of the theory of the therapy being studied" (p. 299). Semantics apart, trialists should avoid the use of non-inert placebos in trials because they may cause the underestimation of treatment effects. Rather than use placebos that are not inert, the alternative is to instead choose placebos that are clearly inert but distinguishable from the experimental intervention. An example is the use of sham electrotherapy in trials of spinal manipulation or exercise. Theoretically, this could be equally problematic because the dissimilar nature of the interventions may not generate placebo effects of similar magnitude in the experimental and control groups [80, 81].

A systematic review of the literature was conducted to ascertain the adequacy of placebo interventions implemented in clinical trials. We chose to review the trials investigating the efficacy of interventions for low back pain because low back pain represents a common and costly health condition for which a wide range of treatment options are currently available [91].

Methods

Search strategy

A systematic search was conducted from the earliest record to November 2006 in MEDLINE, CINAHL, PsychInfo, Cochrane Central Register of Controlled Trials and EMBASE using the strategy recommended by the Cochrane Back Review Group [140]. Results were combined with the terms "placebo", "sham", "attention-control" and "minimal intervention".

Inclusion and exclusion criteria

Eligible studies were randomised placebo-controlled trials evaluating the efficacy of conservative (non-surgical) interventions for non-specific low back pain or sciatica in which outcomes had been reported in terms of pain, disability, quality of life, sick leave, global perceived effect or recurrence. Non-English studies were included when a translation was available. Studies in which participants presented with cauda equina syndrome, infection, neoplasm, fracture, inflammatory disease, pregnancy or spinal surgery in the past 12 months were excluded, as were primary prevention studies.

Data extraction and analysis

Two independent reviewers used a standard form to extract data. Disagreements were resolved by discussion and consensus. Trial quality was assessed using the PEDro scale, an 11-item checklist in which higher scores represent higher quality and 10 is the maximum possible score [100] (the full scale can be viewed at http://www.pedro.fhs.usyd.edu.au/scale_item.html). In this review, trials were included in the analysis regardless of the result of their quality ratings. The reviewers extracted information on the substances or procedures used in placebo groups, whether the assessment of blinding or the evaluation of patients' expectations was reported, and the results of these assessments. Additionally, trials were coded according to the use of the following specific strategies, which have the potential to facilitate blinding in trials [9, 38].

Indistinguishable placebo

The most obvious way of blinding patients to allocation is to provide one group with a placebo intervention that is indistinguishable from the experimental intervention. We examined descriptions of placebo interventions in trial reports to judge whether patients would be able to differentiate them from the experimental intervention. Placebos that replicate side effects of pharmaceutical interventions are known as "active placebos". However, in this study a pharmaceutical placebo did not have to replicate side-effects to be considered indistinguishable. For those interventions delivered by procedures that break the skin, such as acupuncture and injections, the placebo was considered indistinguishable only when skin penetration was also involved. In accordance to Baskin and colleagues [9], placebos of psychological interventions were never considered indistinguishable.

Inert placebo

In this review, placebo interventions were coded as not inert if they involved a treatment used in current clinical practice. (Note that having inert placebos does not, on its own, secure blinding).

Structurally equivalent placebo

One strategy used to promote comparability of intervention and placebo groups is to ensure the structural equivalence of the experimental and placebo interventions. Structural equivalence is particularly important when indistinguishability is not feasible. The structural equivalence of each of the placebo interventions was evaluated by considering a list of criteria adapted from the psychotherapy literature

[9]. To qualify as being structurally equivalent in this review, the placebo intervention had to match the experimental intervention in the following criteria: number of sessions, length of sessions, format (group or individual), level of therapist training, individualisation (the degree to which the intervention was tailored to the patient), and relevance of the intervention with regard to the condition (e.g. lying prone was not considered to be a relevant placebo for low back pain [61]).

Sample consisting of naïve subjects

Patients were considered "naïve" if the trial reported that they had not been exposed to the active form of the intervention employed in the placebo group. This strategy contributes to blinding because a non-naïve sample would be more likely to know the sensation of true treatment and therefore correctly guess their allocation. To code trials for this feature, their inclusion and exclusion criteria were examined. For example, in a trial in which the placebo consists of inactive transcutaneous electrical nerve stimulation (TENS), patients were considered naïve if an exclusion criterion was previous treatment with TENS.

Results

Electronic searches identified 1,002 studies. Of these, 126 were eligible and included in the analysis (Fig. 1). Because nine of the trials had a third group consisting of a different intervention, 135 comparisons against placebo were available. For simplicity, each comparison was treated as an individual trial. Trials reported on the following categories of interventions: acupuncture (10 trials) [25, 42, 73, 74, 85, 95, 99, 104, 106, 128], back school (2 trials) [11, 28], behavioural (7 trials) [10, 21, 62, 111, 130, 132, 133], electrotherapy (20 trials) [8, 15, 25, 27, 37, 49–51, 54, 57, 63, 69, 76, 77, 89, 94, 107, 122, 137, 143], exercise (10 trials) [29, 37, 43, 48, 50, 59, 67, 116, 131, 136], heatwrap therapy (2 trials) [109, 110], insoles (1 trial) [127], magnets (1 trial) [33], massage (1 trial) [116], neuroreflexotherapy (1 trial) [93], pharmaceutical (65 trials) [1–7, 12–14, 17, 19, 20, 22–24, 26, 30–32, 35, 36, 39–41, 45–47, 52, 53, 55, 56, 58, 60, 64, 71, 72, 75, 82–84, 86–88, 90, 92, 97, 101–103, 108, 112, 114, 115, 118, 120, 123, 124, 134, 135, 138, 139, 141, 142, 145], spinal manipulative therapy (12 trials) [11, 29, 48, 54, 61, 65, 68, 72, 78, 96, 121, 146] and traction (3 trials) [16, 117, 129]. Trial characteristics are presented in Table 1.

The quality of the included trials was mostly moderate (range 1–10, median 7 points). Six trials scored 3 points or less on the PEDro scale [48, 50, 121, 131, 132, 136] and two pharmaceutical trials scored the maximum of 10 points [41, 108]. Over 25 different substances or procedures were used as placebo interventions. The placebo tablet/capsule was the most frequent (28%), followed by sham electrotherapy (20%). Pharmaceutical trials were highly consistent in their choices of placebo, whereas exercise and spinal manipulative therapy trials had the largest diversity of placebos.

Only 17 trials (13%) provided information on success of blinding. Of these, 2 failed to achieve acceptable blinding, represented by a significantly greater number of participants in the placebo group correctly guessing their group allocation. Patients' expectations were assessed in 14 trials (10%), and in 8 of those higher expectations were observed in the experimental group. The methods used to assess expectations included single questions about expectations for pain relief or for treatment efficacy, modified expectation scales, structured credibility scales, and questions on preferences for future treatment. The latter was considered to be a measure of expectations because it is often one of the items included in credibility scales. The time at which expectation was measured differed greatly across trials, ranging from baseline [104] to 6 months after enrolment [85].

Provision of structural equivalence was the strategy most frequently used to facilitate blinding (87% of trials). Indistinguishable placebo interventions were used in 58% of trials. Placebos that were clearly inert were used in 79% of trials. Of the remaining trials (those whose placebo was not clearly inert) most, but not all, were trials with indistinguishable placebos; suggesting that indistinguishability was achieved at the expense of potentially causing specific treatment effects. Few trials (18%) explicitly included only naïve subjects. The proportion of trials with placebos that were indistinguishable, inert, structurally equivalent and used naïve subjects varied with the type of intervention. Figure 2 describes these proportions among groups of interventions tested in ten or more trials. A post hoc analysis excluding low-quality trials (trials scoring 3 points or lower on the PEDro scale) provided results almost identical to those described in Fig. 2.

Discussion

This review reveals that imperfect placebos are common in low back pain trials, a finding that has implications for the design of future trials and also for the interpretation of published trials evaluating treatment of low back pain. Two common problems were identified in the design of trials: the use of placebos that are potentially not inert (as indicated by contemporary treatment) and the uncertain success of blinding.

It may be argued that our search strategy may have inflated the proportion of trials with non-inert placebos,

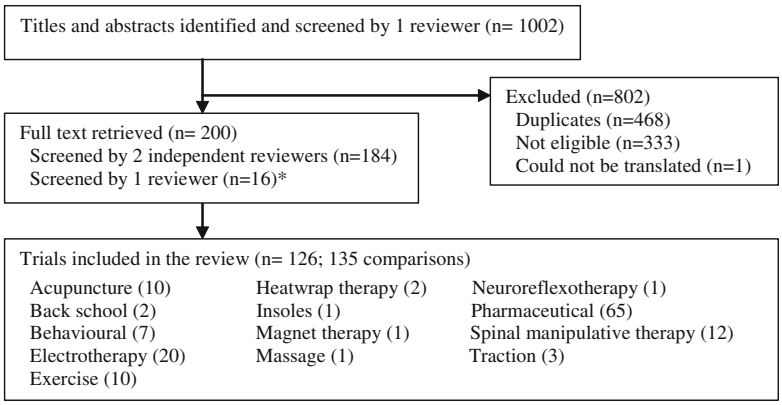

Fig. 1 Search and selection of papers. *Non-English papers

because we used the term "minimal intervention" in our search strategy. However, we only included trials in the review if the authors categorised the control intervention as a placebo intervention, or if they have stated in the manuscript that the intervention was designed to control for non-specific effects of treatment [29]. The use of non-inert placebos in trials is usually a consequence of an uncritical attempt to design placebos that are indistinguishable from real interventions. For example, among non-pharmaceutical trials, we found that indistinguishability was more frequent for trials of acupuncture but all these indistinguishable placebos consisted of potentially genuine treatments. In acupuncture trials, the use of invasive sham acupuncture techniques has been criticised because the mechanism behind the effects of acupuncture may not depend on the depth or location of needling, but on needling itself [98, 144]. Accordingly, the lack of a clear understanding on the mechanisms underlying specific therapeutic effects is also a challenge to the design of indistinguishable placebos in other complex interventions [66].

In pharmaceutical trials, "active placebos" are sometimes used to create intervention groups that are more closely matched. These placebos aim to mimic the side effects of drugs (e.g. dry mouth) while maintaining the same characteristics of other placebo types [115, 125]. However, pharmaceutical trials with improper choices of "active placebos" can also be at risk of spoiling their placebo comparisons. Two trials included in this review had a choice of "active placebo" (diphenhydramine) that might have acted as a genuine treatment because of its sedative properties. Thus, the results of these trials no longer reflect a placebo-controlled comparison but instead reflect a comparison of two genuine treatments. The decision on whether to use "active placebos" in pharmaceutical trials should be balanced with its risks. In antidepressant trials for example, their use may not be justifiable given that the incidence of side effects in experimental and placebo groups seems to be similar regardless of the use of an "active placebo" [4, 5].

The inclusion of naïve subjects in trials is one of the alternatives to enhance blinding when true indistinguishability is difficult to achieve. This is illustrated in a trial where TENS therapy is provided by a functioning device and the placebo via a non-functioning device (sham TENS group). Although both interventions will look the same, the electrical stimulation will only be detected by patients treated with the functioning device. In order to keep patients blinded in trials like this, researchers often tell them that they might or might not feel the stimulation regardless of whether the treatment provided was a placebo [27]. However, it is unlikely that such information will prevent patients who have previously received a course of TENS therapy from knowing the sensation of true treatment and consequently from becoming unblinded. For the same reason, the use of a crossover design in these trials might not be appropriate [50]. Deyo and colleagues [37] have argued for the inclusion of naïve subjects in electrotherapy trials and, consistent with this recommendation, our results showed that naïve subjects were used more frequently in electrotherapy trials than in trials of other interventions.

From the different strategies with the potential to facilitate blinding in placebo-controlled trials, we found that structural equivalence was the most frequently used. When experimental and placebo interventions are structurally equivalent, they might not look the same, but they involve similar degrees of therapeutic contact. Provision of structurally equivalent placebo interventions may control for placebo effects without the risk of having a placebo that is not inert. A meta-analysis of psychotherapy trials has provided some evidence that structural equivalence reduces bias in treatment estimates [9]. The meta-analysis showed that trials with structurally equivalent groups reported smaller effects of interventions than trials with groups that were not structurally equivalent. The "larger treatment effects" observed in the latter would reflect larger placebo effects in the experimental group due to the differential amount or quality of therapeutic contact. Nevertheless,

Table 1 Characteristics of included trials

Study	Placebo intervention	Assessment of blinding and expectations	Strategies to facilitate blinding			
			Indistinguishability	Inert placebo	Equivalence	Naïve subjects
Acupuncture						
Itoh et al. [74]	Mock insertion of a needle	⟨F⟩ Belief in the insertion of needles: no significant differences between groups		✔	✔	
Inoue et al. [73]	Mock insertion of a needle	⟨F⟩ Belief in the insertion of needles: no significant differences between groups		✔	✔	
Kerr et al. [85]	Detuned TENS	⟨F⟩ Willingness to try the treatment again in future: no significant differences between groups		✔	✔	
Molsberger et al. [106]	Superficial needling at non-acu points	Not assessed	✔		✔	✔
Leibing et al. [95]	Superficial needling at non-acu points	Not assessed	✔		✔	
Sherman et al. [128]	Mock insertion of a needle	⟨B⟩ Belief in the efficacy of acupuncture and ⟨F⟩ belief in the insertion of needles: no significant differences between groups; ⟨F⟩ Credibility scale: groups were different on item related to pain relief ($P = 0.01$)		✔	✔	✔
Carlsson and Sjölund [25]	Detuned TENS	Not assessed		✔	✔	
Macdonald et al. [99]	Detuned TENS	Not assessed		✔		
Duplan et al. [42]	Superficial needling at non-acu points	Not assessed	✔		✔	
Mendelson et al. [104]	Superficial needling at non-acu points	⟨B⟩ Expectation of pain relief: change in pain in response to treatment was not correlated to expectation of pain relief (no data provided)	✔		✔	
Back school						
Chenard et al. [28]	Detuned TENS	Not assessed		✔	✔	
Bergquist-Ullman and Larsson [11]	Lowest intensity SWD	Not assessed				
Behavioural						
Basler et al. [10]	Detuned US	Not assessed		✔	✔	
Snook et al. [130]	"Ineffective" exercises	Not assessed			✔	
Strong [132]	Health education video	⟨F⟩ Credibility scale: no significant differences between groups		✔	✔	
Goossens et al. [62]	Group discussion	Not assessed		✔	✔	
Nicholas et al. [111]	Group discussion	⟨B; F⟩ Expectation scale: no significant differences between groups at baseline; higher expectations in experimental group after treatment ($P < 0.05$)		✔	✔	

Table 1 continued

Study	Placebo intervention	Assessment of blinding and expectations	Strategies to facilitate blinding			
			Indistinguishability	Inert placebo	Equivalence	Naïve subjects
Stuckey et al. [133]	Encouragement to relax	Not assessed		✔	✔	
Bush et al. [21]	Biofeedback with "temperature tones"	Not assessed	✔	✔	✔	
Electrotherapy						
Lee et al. [94]	Detuned PEMT	Not assessed		✔	✔	
Bertalanffy et al. [15]	Detuned TENS	Not assessed		✔	✔	
Jarzem et al. [77]	Detuned TENS	Not assessed		✔	✔	✔
Jarzem et al. [76]	Detuned TENS	⟨F⟩ Evaluation of reported and actual use of TENS units: no significant differences between groups		✔		✔
Topuz et al. [137]	Detuned TENS	Not assessed		✔	✔	✔
Sator-Katzenschlager et al. [122]	Needling without electrical stimulation	⟨F⟩ Belief in provision of real stimulation: no significant differences between groups; ⟨F⟩ Willingness to repeat treatment if necessary: 87% of patients in experimental group and 0% in placebo group would repeat treatment			✔	✔
Weiner et al. [143]	Needling without electrical stimulation	Not assessed			✔	
Glaser et al. [57]	TENS	⟨B; F⟩ Expectation scale: no significant differences between groups			✔	✔
Carlsson and Sjölund [25]	Detuned TENS	Not assessed		✔	✔	
Hackenberg et al. [63]	Lowest intensity radiotherapy	Not assessed	✔	✔	✔	
Cheing and Hui-Chan [27]	Detuned TENS	Not assessed		✔	✔	
Basford et al. [8]	Inactive laser probes	Not assessed	✔	✔	✔	
Ghoname et al. [50]	Needling without electrical stimulation	⟨F⟩ Willingness to pay out-of-pocket for treatment: more patients in group receiving PENS therapy willing to pay compared to other groups ($P < 0.02$)			✔	✔
Ghoname et al. [49]	Needling without electrical stimulation	⟨F⟩ Willingness to pay out-of-pocket for treatment: more patients in group receiving electrical stimulation of 15–30 Hz willing to pay compared to other groups ($P < 0.05$)			✔	
Ghoname et al. [51]	Needling without electrical stimulation	Not assessed			✔	
Moore and Shurman [107]	Detuned TENS	⟨F⟩ Choice of therapy among those who would continue treatment: 38% NMES/TENS; 25% none; 21% NMES; 8% TENS; 8% placebo		✔	✔	✔

Table 1 continued

Study	Placebo intervention	Assessment of blinding and expectations	Strategies to facilitate blinding			
			Indistinguishability	Inert placebo	Equivalence	Naïve subjects
Herman et al. [69]	Detuned TENS	Not assessed		✔	✔	✔
Klein and Eek [89]	Inactive laser probes	Not assessed	✔	✔	✔	
Deyo et al. [37, 38]	Detuned TENS	⟨F⟩ Perception that TENS units were functioning properly: 84% of patients in placebo group guessed they had functioning units (blinding reported as partially successful)		✔	✔	✔
Gibson et al. [54]	Detuned SWD	Not assessed		✔	✔	
Exercise						
Goldby et al. [59]	Educational booklet	Not assessed				
Geisser et al. [48]	Nonspecific exercises/ positioning without muscle energy	⟨F⟩ Belief in provision of real treatment: no significant differences between groups			✔	
Tasleem et al. [136]	Lowest intensity SWD	Not assessed				
Preyde [116]	Inactive laser probes	Not assessed		✔	✔	
Ghoname et al. [50]	Needling without electrical stimulation	⟨F⟩ Willingness to pay extra money for therapy: no significant differences between groups receiving exercise and placebo			✔	✔
Cherkin et al. [29]	Educational booklet	Not assessed				
Spratt et al. [131]	Abdominal wrap/advice to walk/video	Not assessed		✔	✔	
Faas et al. [43]	US with lowest possible dose	Not assessed			✔	
Hansen et al. [67]	Semi hot pack/10% body weight traction	Not assessed		✔	✔	
Deyo et al. [37, 38]	Detuned TENS	⟨F⟩ Perception that TENS units were functioning properly: 84% of patients in placebo group guessed they had functioning units (blinding reported as partially successful)		✔		✔
Heatwrap therapy						
Nadler et al. [109]	Placebo tablets	Not assessed		✔		
Nadler et al. [110]	Placebo tablets	Not assessed		✔		
Insoles						
Shabat et al. [127]	Placebo insole	⟨F⟩ Choice of therapy among those who would continue treatment: majority of patients would prefer the true insole ($P < 0.05$)	✔	✔	✔	
Magnet therapy						
Collacott et al. [33]	Demagnetised device	Not assessed	✔	✔	✔	✔
Massage						
Preyde [116]	Inactive laser probes	Not assessed		✔	✔	

Table 1 continued

Study	Placebo intervention	Assessment of blinding and expectations	Strategies to facilitate blinding			
			Indistinguishability	Inert placebo	Equivalence	Naïve subjects
Neuroreflexotherapy						
Kovacs et al. [93]	Epidermal implants in adjacent points	Not assessed	✔	✔	✔	
Pharmaceutical (oral or topical)						
Muehlbacher et al. [108]	Matching placebo tablets	Not assessed	✔	✔	✔	
Bannwarth et al. [7]	Matching placebo tablets	Not assessed	✔	✔	✔	
Khoromi et al. [87]	Diphenhydramine tablets	Not assessed	✔		✔	
Ketenci et al. [86]	Placebo capsules	Not assessed	✔	✔	✔	
Katz et al. [82]	Matching placebo tablets	Not assessed	✔	✔	✔	✔
Brizzi et al. [20]	Drug-free hydroelectrophoresis	Not assessed	✔		✔	✔
Coats et al. [32]	Matching placebo tablets	Not assessed	✔	✔	✔	
Hoiriis et al. [72]	Matching placebo tablets	⟨F⟩ Belief in provision of real medication: no significant differences between groups	✔	✔	✔	
Pallay et al. [112]	Matching placebo tablets	Not assessed	✔	✔	✔	
Peloso et al. [114]	Matching placebo tablets	Not assessed	✔	✔	✔	
Frerick et al. [47]	Matching placebo plaster	Not assessed	✔	✔	✔	
Ruoff et al. [120]	Placebo tablets	Not assessed	✔	✔	✔	
Birbara et al. [17]	Matching placebo tablets	Not assessed	✔	✔	✔	
Dreiser et al. [41]	Placebo tablets	Not assessed	✔	✔	✔	
Katz et al. [83]	Placebo tablets	Not assessed	✔	✔	✔	
Dreiser et al. [40]	Placebo tablets	Not assessed	✔	✔	✔	
Keitel et al. [84]	Matching placebo plaster	Not assessed	✔	✔	✔	
Chrubasik et al. [30]	Matching placebo tablets	Not assessed	✔	✔	✔	
Dickens et al. [39]	Matching placebo capsules	Not assessed	✔	✔	✔	
Schnitzer et al. [124]	Placebo capsules	Not assessed	✔	✔	✔	
Atkinson et al. [4]	Diphenhydramine tablets	Not assessed	✔		✔	
Chrubasik et al. [31]	Matching lactose tablets	Not assessed	✔	✔	✔	
Atkinson et al. [5]	Matching placebo capsules	Not assessed	✔	✔	✔	
Worz et al. [145]	Placebo tablets	Not assessed	✔	✔	✔	
Weber et al. [142]	Matching placebo capsules	Not assessed	✔	✔	✔	
Goodkin et al. [60]	Matching placebo tablets	Not assessed	✔	✔	✔	

Table 1 continued

Study	Placebo intervention	Assessment of blinding and expectations	Strategies to facilitate blinding			
			Indistinguishability	Inert placebo	Equivalence	Naïve subjects
Marcel et al. [101]	Matching placebo tablets	Not assessed	✔	✔	✔	
Schnebel and Simmons [123]	Matching lactose capsules	Not assessed	✔	✔	✔	
Berry and Hutchinson [14]	Matching placebo tablets	Not assessed	✔	✔	✔	
Berry and Hutchinson [13]	Matching placebo tablets	Not assessed	✔	✔	✔	
Amlie et al. [2]	Matching placebo tablets	Not assessed	✔	✔	✔	
Ginsberg and Famaey [55]	Massage with placebo ointment	Not assessed	✔			
Haimovic and Beresford [64]	Matching placebo tablets	Not assessed	✔	✔	✔	
Dapas et al. [35]	Placebo tablets	Not assessed	✔	✔	✔	
Jagemann [75]	Placebo tablets	Not assessed	✔	✔	✔	
Pheasant et al. [115]	Atropine tablets	Not assessed	✔	✔	✔	
Berry et al. [12]	Matching placebo tablets	Not assessed	✔	✔	✔	
Alcoff et al. [1]	Placebo pills	Not assessed	✔	✔	✔	
Ghosh et al. [52]	Matching placebo tablets	Not assessed	✔	✔	✔	
Gold [58]	Placebo tablets	Not assessed	✔	✔	✔	
Pharmaceutical (injection or infusion)						
Finckh et al. [45]	0.9% saline infusion	Not assessed	✔	✔	✔	✔
Arden et al. [3]	Normal saline injection	⟨F⟩ Belief in the provision of real treatment: no significant differences between groups	✔	✔	✔	✔
Korhonen et al. [92]	Saline infusion	Not assessed	✔	✔	✔	✔
Wasan et al. [141]	Saline infusion	⟨B⟩ Expectation scale: expectations for pain relief significantly correlated with pain outcomes ($P < 0.05$)	✔	✔	✔	
Khot et al. [88]	Normal saline injection	Not assessed	✔	✔	✔	
Tuzun et al. [139]	Placebo injection	Not assessed	✔	✔	✔	
Mauro et al. [102]	Placebo injection	Not assessed	✔	✔	✔	
Dechow et al. [36]	Normal saline injection	Not assessed	✔	✔	✔	
Medrik-Goldberg et al. [103]	Normal saline infusion	⟨F⟩ Belief in provision of real treatment: no significant difference between groups	✔	✔	✔	
Tajiri et al. [135]	Physiologic saline injection	Not assessed	✔	✔	✔	
Revel et al. [118]	Saline injection	Not assessed	✔	✔	✔	
Carette et al. [23]	Isotonic saline injection	⟨F⟩ Belief in the provision of a placebo injection: no significant differences between groups	✔	✔	✔	

Table 1 continued

Study	Placebo intervention	Assessment of blinding and expectations	Strategies to facilitate blinding			
			Indistinguishability	Inert placebo	Equivalence	Naïve subjects
Ghozlan and Dropsy [53]	Isotonic saline injection/ matching placebo tablets	Not assessed	✔	✔	✔	
Babej-Dölle et al. [6]	Isotonic saline injection	Not assessed	✔	✔	✔	
Fine et al. [46]	Isotonic saline infusion	Not assessed	✔	✔	✔	
Szpalski and Hayez [134]	Placebo injection/ matching placebo tablets	Not assessed	✔	✔	✔	
Bush and Hillier [22]	Normal saline injection	Not assessed	✔	✔	✔	
Carette et al. [24]	Isotonic saline injection	Not assessed	✔	✔	✔	✔
Treves et al. [138]	Glucose infusion	Not assessed	✔	✔	✔	
Lilius et al. [97]	Physiologic saline injection	Not assessed	✔	✔	✔	
Ginsberg et al. [56]	Isotonic saline injection	Not assessed	✔	✔		
Klenerman et al. [90]	Normal saline injection	Not assessed	✔	✔	✔	✔
Chapman and Brena [26]	Normal saline injection	Not assessed	✔	✔	✔	
Hofferberth et al. [71]	Placebo injection	Not assessed	✔	✔	✔	
Brena et al. [19]	Saline injection	Not assessed	✔	✔	✔	
Spinal manipulative therapy						
Hall et al. [65]	Foot massage	⟨F⟩ Belief in provision of real treatment: no significant differences between groups		✔	✔	
Geisser et al. [48]	Nonspecific exercises/ positioning without muscle energy	⟨F⟩ Belief in provision of real treatment: no significant differences between groups			✔	
Hawk et al. [68]	Up to 12N postero-anterior force applied lateral to spine/ effleurage	⟨F⟩ Perception of group assignment: patients in placebo group more likely to accurately perceive their group assignment. ⟨B; F⟩ Expectation of improvement: no significant differences between groups at baseline; patients in placebo group had lower expectations at visit 4 ($P = 0.04$)			✔	
Hoiriis et al. [72]	Positioning and light pressure	⟨F⟩ Belief in provision of true chiropractic adjustments: more patients in chiropractic group believed real adjustments were provided ($P < 0.001$)	✔	✔		
Licciardone et al. [96]	Range of motion/light touch/simulated osteopathic techniques	Not assessed			✔	
Goodsell et al. [61]	Lying prone	Not assessed		✔		

Table 1 continued

Study	Placebo intervention	Assessment of blinding and expectations	Strategies to facilitate blinding			
			Indistinguishability	Inert placebo	Equivalence	Naïve subjects
Cherkin et al. [29]	Educational booklet	Not assessed				
Wreje et al. [146]	Gluteus medius transverse friction	Not assessed		✔		
Sanders et al. [121]	Light touch	Not assessed		✔	✔	✔
Gibson et al. [54]	Detuned SWD	Not assessed		✔		
Jayson et al. [78]	Microwave with lowest setting	Not assessed		✔		
Bergquist-Ullman and Larsson [11]	Low intensity SWD	Not assessed				
Traction						
Sherry et al. [129]	TENS	Not assessed			✔	
Beurskens et al. [16]	Traction up to 20% total body weight	⟨F⟩ Belief in provision of real treatment: no significant differences between groups	✔	✔	✔	✔
Reust et al. [117]	5 kg traction	Not assessed	✔	✔	✔	✔

TENS Transcutaneous electrical nerve stimulation, *SWD* short-wave diathermy, *PEMT* pulsed electromagnetic therapy, *PENS* percutaneous electrical nerve stimulation, *NMES* neuromuscular electrical stimulation, *US* ultra-sound

⟨B⟩ Measure taken at baseline. ⟨F⟩ Measure taken at follow-up

because potentially many factors influence the magnitude of placebo effects, it would seem unlikely that structural equivalence alone can control for all the factors that generate unbalanced placebo effects in trials.

The use of any strategy to facilitate blinding will be worthless if, ultimately, an acceptable level of blinding is not achieved. As noted by Schulz and colleagues [126], "blinding must succeed to reap its benefits". Accordingly, the CONSORT statement recommends that the success of blinding be reported [105]. Blinding success was poorly documented in a sample of general medicine and psychiatry trials [44]. Likewise, our results show that disappointingly few trials of low back pain report on blinding success. However, this fact is not sufficient to rule out successful blinding. Hill and colleagues [70] contacted the investigators of 40 rheumatology trials and found that the lack of reporting of randomisation, concealed allocation and blinding does not necessarily mean that these research methods have not been properly conducted. Nevertheless, although successful blinding might have been achieved in some trials where this was not reported, it would be clearer if future trials included the results of their blinding assessments in their reports.

One way of checking if blinding is successful is to measure how often the group assignment is guessed correctly. In a two-arm trial in which blinding is successful, guesses would be accurate 50% of the time. Nevertheless, in placebo-controlled trials, the success of blinding is better understood by the differences in the proportions of patients in each group who believed a "real" treatment was provided. That is, if patients in the placebo group are more likely to believe that the intervention received was a placebo, blinding was unsuccessful. The timing of blinding assessments also deserves special consideration. For instance, if the experimental intervention consists of a highly effective treatment, the difference in the proportion of patients believing in the provision of a "real" treatment will tend to be higher regardless of the use of adequate strategies to secure blinding. For this reason, it is preferable that blinding success is assessed earlier rather than latter in a course of treatment.

Some investigators supplement assessments of blinding success with measurements of expectations with treatment. While important imbalances in patients' expectations were reported in eight trials (out of 14), it is likely such imbalances are common across trials of this type because of the small number of trials in which assessments of expectations were performed. Health care providers may also transfer to patients their own expectations [125]. As noted by Critelli and Neumann [34], "there appears to be a tendency for experimental placebos to be in some sense weaker, less credible, or applied in a less enthusiastic manner than treatments that have been offered as actual therapies". However, in this review we have focused

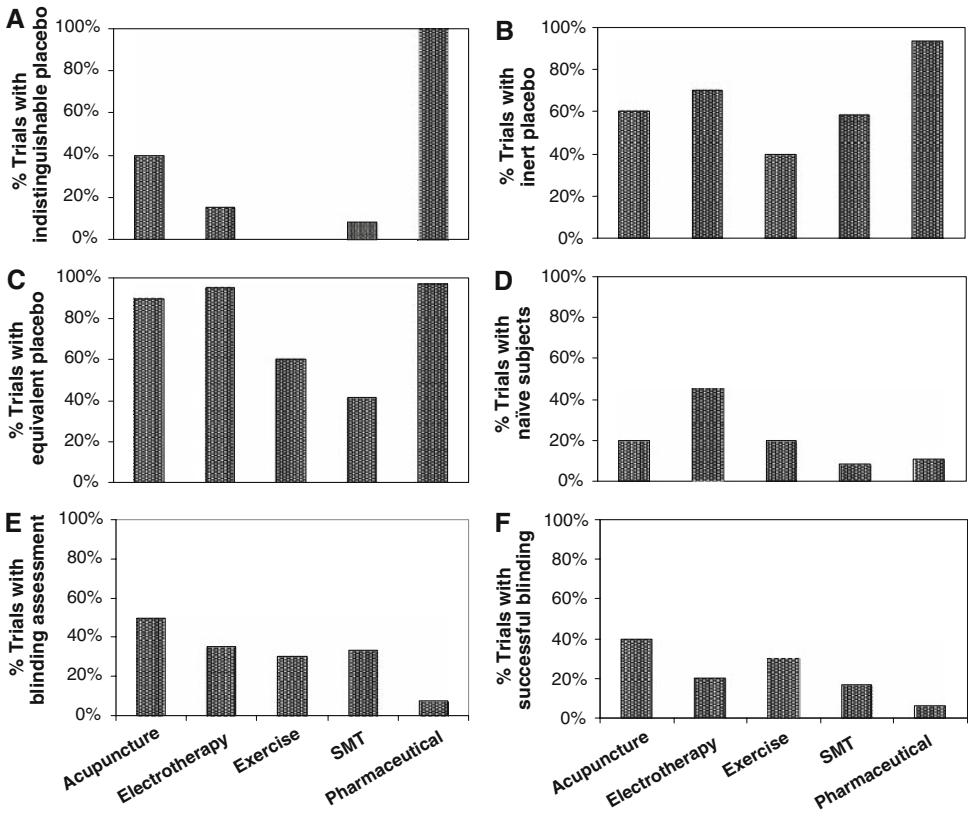

Fig. 2 Proportion of trials with (**a**) indistinguishable placebo, (**b**) inert placebo, (**c**) structurally equivalent placebo, (**d**) naïve subjects, (**e**) blinding assessment, (**f**) successful blinding (successful = both assessed and found to be successful; unsuccessful = not assessed or assessed and found to be unsuccessful). Assessments of patients' expectations were also considered under blinding assessment. Graphs report group of interventions investigated in ten or more trials. Acupuncture ($n = 10$), electrotherapy ($n = 20$), exercise ($n = 10$), SMT ($n = 12$), pharmaceutical ($n = 65$). *SMT* spinal manipulative therapy

exclusively on investigating this concept from a patient's perspective.

Despite the contribution of expectation measurements to the interpretability of the results in clinical trials, these measurements have important limitations. Firstly, there is no consensus on how expectations should be assessed in clinical trials, represented by the lack of standardisation in these assessments. In addition, deciding the best timing for these assessments is difficult and may explain the large variation encountered among the trials included in this review. As with assessment of blinding, treatment effects may confound ratings of patients' expectations obtained at follow-up. Thus, it is questionable whether assessments of expectations as late as 6 months after enrolment measure the same construct as assessments of expectations at baseline. If researchers choose to assess expectations at baseline, patients might find it difficult to describe their expectations associated with interventions to which they are unfamiliar. Optimal ways to assess expectations in trials and the standardisation of such measurements are a priority and should be addressed by future studies.

Conclusion

Our results illustrate the complexity inherent in design of suitable placebo interventions. Unfortunately many placebo-controlled trials evaluating treatment of low back pain are imperfect and so the trials potentially provide biased estimates of the efficacy of treatment. This finding has implications for the interpretation of published trials and the design of future trials in this area.

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