

# BMJ Open Placebo effects in trials evaluating 12 selected minimally invasive interventions: a systematic review and meta-analysis

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## ABSTRACT

**Objectives:** To analyse the impact of placebo effects on outcome in trials of selected minimally invasive procedures and to assess reported adverse events in both trial arms.

**Design:** A systematic review and meta-analysis.

**Data sources and study selection:** We searched MEDLINE and Cochrane library to identify systematic reviews of musculoskeletal, neurological and cardiac conditions published between January 2009 and January 2014 comparing selected minimally invasive with placebo (sham) procedures. We searched MEDLINE for additional randomised controlled trials published between January 2000 and January 2014.

**Data synthesis:** Effect sizes (ES) in the active and placebo arms in the trials' primary and pooled secondary end points were calculated. Linear regression was used to analyse the association between end points in the active and sham groups. Reported adverse events in both trial arms were registered.

**Results:** We included 21 trials involving 2519 adult participants. For primary end points, there was a large clinical effect ( $ES \geq 0.8$ ) after active treatment in 12 trials and after sham procedures in 11 trials. For secondary end points, 7 and 5 trials showed a large clinical effect. Three trials showed a moderate difference in ES between active treatment and sham on primary end points ( $ES \geq 0.5$ ) but no trials reported a large difference. No trials showed large or moderate differences in ES on pooled secondary end points. Regression analysis of end points in active treatment and sham arms estimated an  $R^2$  of 0.78 for primary and 0.84 for secondary end points. Adverse events after sham were in most cases minor and of short duration.

**Conclusions:** The generally small differences in ES between active treatment and sham suggest that non-specific mechanisms, including placebo, are major predictors of the observed effects. Adverse events related to sham procedures were mainly minor and short-lived. Ethical arguments frequently raised against sham-controlled trials were generally not substantiated.

## INTRODUCTION

It is normally assumed that medical practices are based on firm clinical evidence and that new practices or techniques are introduced

## Strengths and limitations of this study

- Selection of trials with low risk of bias.
- Calculation of effect sizes on primary and pooled secondary end points in active treatment as well as sham arms.
- Heterogeneous interventions, outcome measures and timing of assessment.

when superiority, or at least non-inferiority, has been demonstrated compared to established treatments. However, medical history reveals numerous examples contradicting this assumption. Forty-two per cent of 146 medical practices were found to be reversed in a recent review analysing 10 years of publication in a high-impact medical journal.<sup>1</sup> Large effects of an intervention in initial reports are often spurious findings, while the vast majority may represent substantial overestimations.<sup>2</sup>

Even though surgical and other invasive techniques generally have reached a high degree of sophistication through the last decades, not all invasive procedures have lived up to expectations. Promising results in initial observational studies have in some cases led to widespread clinical implementation, in spite of lack of documented effectiveness.<sup>3</sup> The reluctance to abandon contradicted medical practice is commonly ascribed to both culturally embedded medical practices and different forms of vested interests.<sup>4 5</sup> The continuation of unnecessary and potentially harmful interventions leads to major costs for both patients and society.

The randomised placebo-controlled trial is considered the gold standard for evaluating the effects of pharmacological treatments. However, there are relatively few controlled studies in peer-reviewed surgical journals and even fewer placebo (sham)-controlled studies.<sup>6-8</sup> Ethical concerns raised by the potential for harm to participants are usually cited as the main obstacle to sham-controlled

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studies.<sup>9</sup> Problems of a practical nature relate to patient blinding, differing technical expertise, the heterogeneity of the interventional techniques and variable outcome specifications, making standardisation difficult to achieve.<sup>10</sup>

A meaningful effect in clinical trials may result from a large effect in the active treatment group, a small effect in the placebo group or a combination of both. Even though a placebo effect has been documented in a range of clinical conditions, there are few studies assessing the magnitude of the placebo effect in surgical procedures. In the present study, we analysed placebo-controlled trials of minimally invasive interventions in musculoskeletal, neurological and cardiac conditions. The aims were threefold: (1) to assess the magnitude of change in outcome from baseline to trial end point in the active treatment as well as placebo (sham) arms; (2) to explore the contribution of non-specific factors, including placebo, to the outcome of active treatment and (3) to assess the level of reported adverse effects in both trial arms.

## METHODS

### Search strategy and selection criteria

We conducted electronic searches for randomised placebo-controlled trials of minimally invasive interventions for cardiac, neurological and musculoskeletal conditions. We defined minimally invasive procedures as interventions involving the introduction of a medical device, substance or other foreign material into the body through a cannula, catheter or arthroscope, thereby minimising damage to biological tissues at the point of entrance. We first used MEDLINE and Cochrane library to identify systematic reviews published between January 2009 and January 2014. The following key words were used in our search strategies: “randomi\* controlled trial”, “placebo OR sham” in combination with “low back pain”, “neck OR cervical pain”, “radiofrequency denervation”, “facet joint AND “nerve block” OR injection”, “intradiscal OR annular AND thermal”, “epidural AND corticosteroid\* AND sciatica OR radic\*”, “hyaluron\* OR viscosuppl\* AND knee AND osteoarthritis”, “vertebroplast\*”, “arthroscop\*”, “debridement AND lavage AND knee AND osteoarthr\*”, “meniscectomy AND knee”, “myocardial laser revascularization”, “transplantation OR gene OR stem cell OR deep brain stimulation AND Parkinson\* OR dystonia”, “spinal cord stimulation”, and “foramen ovale AND migraine”. We used the “core clinical journals” filter in PubMed, which is an index of journals particularly relevant to practicing physicians.

From the most recently published systematic review of each procedure, we selected randomised placebo-controlled trials published later than January 2000. We excluded trials published before January 2000 because our primary aim was to assess interventions that are currently, or until recently have been, in common use. We selected trials that according to the review fulfilled at least four of the following methodological criteria:

random allocation, allocation concealment, blinding of participant, blinding of assessor and intention-to-treat analysis. We chose these criteria because they were the most commonly used in the selected reviews, and because use of scales for assessing quality or risk of bias is explicitly discouraged in Cochrane reviews.<sup>11</sup> Two of the authors (RH and JIB) independently assessed the five methodological criteria in the RCTs included from systematic reviews.

We next searched MEDLINE for additional randomised placebo-controlled trials published between January 2000 and January 2014. Two of the reviewers (OT and JIB) independently assessed the five criteria aforementioned in the additional RCTs that were identified from this search.

Only English language journals were included. We excluded crossover trials, trials that did not report results as means, SD, SE or CIs in active and sham groups, as well as trials with only graphic representation of data. This review is reported in accordance with the PRISMA statement.<sup>12</sup>

### Data extraction

We registered all continuous primary end points. In trials without continuous primary end points, with multiple end points or no defined primary end point, we selected an outcome related to pain or condition-specific end point. The heterogeneity of trials did not allow for use of pain as a primary outcome. We used the RCTs’ defined primary outcome to avoid bias introduced by choosing our own end point. We also registered secondary end points in order to avoid potential bias from selective reporting in the included trials. End points describing medication, radiographic or physiological variables, social or psychological functions were not included. For the Parkinson’s trials, only end points in the off-medication state were registered. Results from the last follow-up until 12 months were extracted. The trials’ protocol registration, funding source, description of sham intervention, sample size, disease duration, length of follow-up and reported adverse events (AEs) in both trial arms were registered.

### Data synthesis

To assess clinically important change, we calculated effect size (ES, Cohen’s d) based on the means and SDs. We calculated ES for both the active and sham interventions to obtain information about the pre-to-post treatment change in both arms. Without first calculating ES of change in each trial arm, we would not be able to discern the relative contribution of placebo, which was one of the objectives of the study. Subtracting the average score after treatment from the average score before treatment and dividing the result by the average of the SDs before and after treatment calculates ES. An ES of 0.8 or more is assumed to be large, while an ES of 0.5–0.8 is considered moderate.<sup>13</sup> In trials with multiple secondary end points we calculated the pooled mean ES, without weighting.

Owing to the small sample sizes in most of the included trials, we calculated an adjusted ES in accordance with a recommended procedure.<sup>14</sup> Unadjusted linear regression analyses were used to explore the association between outcomes in the active and sham groups, both for primary and pooled secondary end points. For this analysis, we used Medcalc Statistical Software V.12.7.4.0.<sup>15</sup>

## RESULTS

### Selection of interventions and trials

The searches provided sham-controlled trials for the following interventions: percutaneous laser revascularisation of myocardium for angina pectoris (n=2), closure of foramen ovale for migraine (n=1), arthroscopic meniscectomy for meniscal tears (n=1), debridement (n=1) and injection of hyaluronic acid (n=3) for symptomatic osteoarthritis of the knee, injection or transplantation of biologically active material for Parkinson's disease (human retinal pigmental cells (n=1), fetal nigral cells (n=1) and neurturin (n=2)), epidural injections of corticosteroids for sciatica (caudal (n=1), interlaminar (n=2) and transforaminal (n=1)) routes, percutaneous heating of the intervertebral disc for chronic low back pain (intradiscal radiofrequency thermocoagulation (n=1), intradiscal electrothermal therapy (n=2)) and vertebroplasty for vertebral body fractures (n=2). We give a short description of each procedure's introduction, therapeutic rationale and history in web appendix table 1.

The searches provided no sham-controlled trials of cervical, thoracic or lumbar facet joint nerve blocks or joint injections, spinal cord stimulation for low back pain, cervical epidural injections, transmyocardial laser revascularisation for angina pectoris, deep brain stimulation for Parkinson's disease or dystonia or arthroscopic procedures other than knee conditions. We found six placebo-controlled trials of radiofrequency denervation for low back pain, but all were excluded as: SD not provided (n=1),<sup>16</sup> compound primary end point (n=1),<sup>17</sup> risk of false-positive response because of only one diagnostic block (n=4).<sup>18–21</sup>

The study selection process is summarised in figure 1. The search provided five systematic reviews, all identified through searches in MEDLINE; none were commercially funded.<sup>22–26</sup> It identified a total of 71 clinical trials, 12 of these were not identified from the systematic reviews. Forty-four trials were excluded for methodological reasons, principally risk of bias. Six additional trials were excluded because ES could not be calculated.<sup>27–32</sup> Web appendix table 2 shows the excluded trials and the reasons for exclusion. Finally, 21 clinical trials with a total of 2519 participants were included in the present review (table 1). Trial interventions in active treatment and sham arms are also shown.

Fourteen trials from the systematic reviews fulfilled at least four of the five methodological criteria.<sup>33–46</sup> Seven trials provided through searches in MEDLINE fulfilled the same criteria.<sup>47–53</sup> The included and excluded secondary end points are shown in web appendix table 3. All

trials reported approval of study protocol prior to patient enrolment (table 1). Seven trials were commercially funded.<sup>36 37 45 50–53</sup> Most of the trials had few participants, ranging from 20 to 346 (median 80).

### Clinical outcomes after active treatment and sham

Twelve of the 21 trials showed a large ES on primary end points after active treatment, while 11 trials showed a similar ES after the sham procedure (figure 2 and table 2).

ES on primary end points was moderate in three of the active treatment groups and in two of the sham groups.

On pooled secondary end points, a large ES was estimated in seven trials after active treatment and in five trials after sham, while a moderate ES was reported in four and three trials, respectively (table 2).

In none of the trials did the actively treated group show a deterioration of primary end point during treatment, while this was the case for two of the sham groups (not reported to be related to the procedure). On secondary end points, deterioration occurred in two active treatment and two sham groups (table 2).

### Differences in outcome between active treatment and sham

Better results on primary end points were reported with active treatment compared to sham in 14 of the 21 trials, but the differences were small. Three trials (1 epidural study,<sup>41</sup> 1 discogenic pain study<sup>44</sup> and 1 Parkinson's study<sup>52</sup>) reported a moderate effect but none showed a large effect (figure 3 and table 2). Seven trials reported a better primary end point outcome after sham than after active treatment.

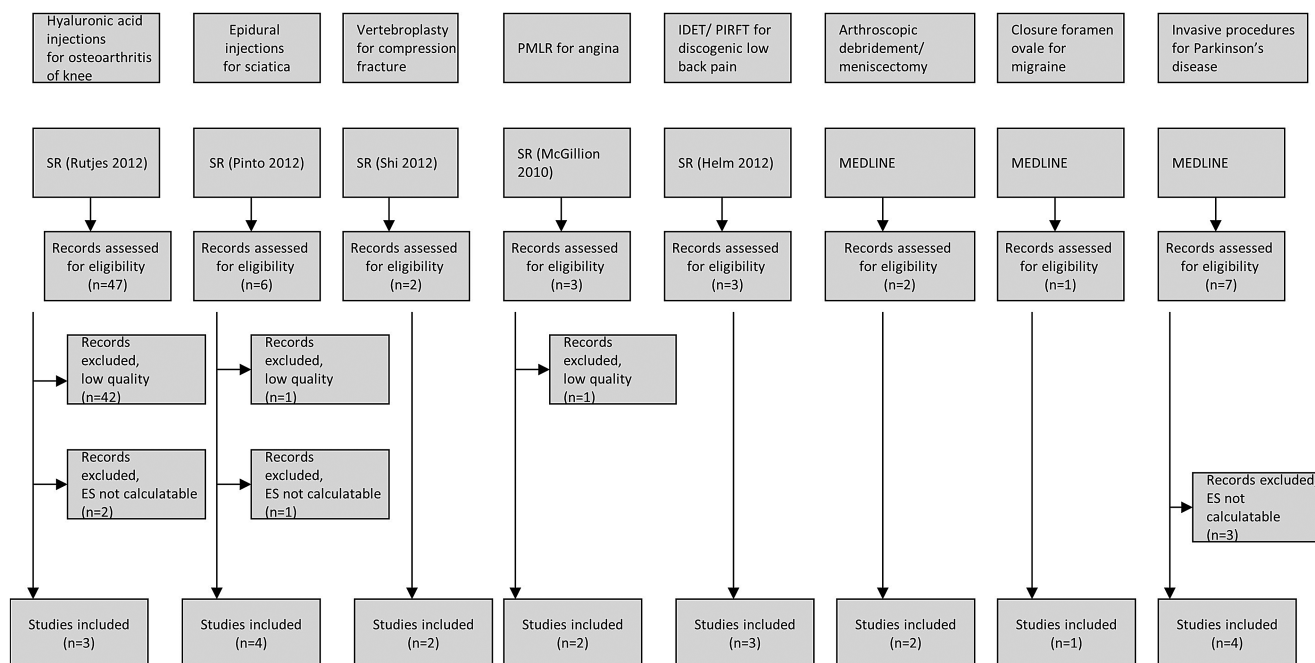
Nineteen trials reported secondary end points, 11 of these reported better outcome after active treatment than after sham, but in no case did the differences reach a moderate ES (figure 3 and table 2). In 12 trials, the outcome was better for primary than for pooled secondary end points. This bore no relation to funding source.

On regression analyses, ESs in the sham groups predicted about 80% of the variance of ES in the active treatment groups, both on primary and pooled secondary end points (figures 4 and 5).

### Adverse events

Eighteen studies provided information about AEs (table 1). Three of these trials reported no procedural AEs in any of the groups.<sup>33 39 47</sup> Major AEs were reported after active treatment in four trials<sup>34 50 51 53</sup> including one death in one of the Parkinson's studies.<sup>51</sup> In the sham groups, one trial<sup>53</sup> listed three major AEs possibly or probably related to the procedure, all presumed to be caused by antiplatelet medication, none of them life-threatening. Apart from this trial, there were no major AEs in the sham groups. The reported minor AEs were all of limited duration.





**Figure 1** Flow chart of study selection in the present meta-analysis (ES, effect size; IDET, intradiscal electrothermal therapy; PIRFT, percutaneous intradiscal radiofrequency thermocoagulation; PMLR, percutaneous myocardial laser revascularisation; SR, systematic review).

## DISCUSSION

### Principal findings

Analysis of 21 sham-controlled trials of minimally invasive procedures showed that the ESs in the active treatment arms were predicted by the ESs in the sham arms. There was a large ES on primary end points in about half of both the active and sham interventions, but none of the trials showed a large difference in ES between active treatment and sham groups, either on primary or secondary end points.

The magnitude of the effect in each trial arm varied considerably, both between different procedures and between trials using the same procedure. For instance, in the active treatment groups, ES for primary end points varied from around 0 to almost 2 after active treatment and from about -0.4 to 1.5 after sham. Disparate outcomes were reported even between trials where technical parameters were similar. For instance, ES in the sham group in the three hyaluronic acid trials varied by a factor of 3 and in the epidural trials by a factor of 2. This variability is probably related to differences in study design, duration of disability before inclusion, contextual factors, including the doctor-patient relationship, as well as other factors. The close association between end points in the active treatment and sham groups on regression analyses suggests that a large part of the reported outcomes in the active treatment groups are due to placebo effects, statistical regression to the mean or the natural course of the condition.

### Strengths and limitations of the study

It is our opinion that the calculation of ESs in active treatment as well as placebo arms is a strength of the

present study. This made it possible to assess the magnitude of change in arms as well as the contribution of non-specific factors to change in the active treatment arms. The calculation of ESs provides an alternative assessment to probability estimates. Another strength of the study is the supplementary analyses of pooled secondary end points, enabling a more comprehensive evaluation than using primary end points alone. Reports of tactically motivated use of primary and secondary end points before publication in order to improve study results strengthen the argument for registering all relevant secondary end points.<sup>54</sup> Our finding that a majority of trials reported better results on primary than on secondary end points might lend support to such a hypothesis, although all trials, according to the authors, had sought and gained approval of the protocol from ethics committee and/or review board (table 1).

The present review is limited to selected minimally invasive procedures in cardiology, neurology and musculoskeletal conditions. While some procedures are or have been in wide clinical use, some are still in the clinical trial phase. Other sources of heterogeneity are variable duration of disease before inclusion, selection of outcome measures and time to follow-up. Results cannot be generalised to minimally invasive procedures in all medical disciplines, but a similar methodology could be applied to more systematic analyses of the role of non-specific effects in other minimally invasive procedures.

We applied principles from guidelines for conducting systematic reviews and meta-analyses, and included an independent assessment of methodological trial quality by two of the authors. We cannot rule out that we have missed relevant trials because we limited our search to

**Table 1** Studies, protocol approval and funding, interventions in the active treatment and sham arms, and adverse events

Author	Protocol approval/ funding (commercial, non-commercial)	Invasive procedure/ indication	Sham intervention	Adverse events related to procedure, active treatment	Adverse events related to procedure, sham
Leon <i>et al</i> <sup>34</sup>	Food and Drug Administration/NC	Percutaneous myocardial laser revascularisation/	Laser turned on but no procedure performed	MAE in hospital (high dose): 4.1%	MAE in hospital: 0
Salem <i>et al</i> <sup>33</sup>	Ethics committee/NC	intractable angina pectoris		No procedural AE	
Sihvonen <i>et al</i> <sup>48</sup>	Review board/NC	Arthroscopic partial meniscectomy/degenerate meniscal tear	Routine arthroscopy, simulation of meniscectomy by manipulation etc	No MAE mAE: 6.6%	mAE: 2.9%
Moseley <i>et al</i> <sup>47</sup>	Review board/NC	Arthroscopic debridement/ knee osteoarthritis	Simulated arthroscopy preparation, intravenous anaesthesia, skin incisions, no instruments entered knee, knee manipulated	No procedural AE	
Pham <i>et al</i> <sup>35</sup>	Review board/NC	Hyaluronic acid/knee osteoarthritis	Intra-articular injection of saline solution	No MAE Any mAE: 81.7%	Any mAE: 1.2%
Altman <i>et al</i> <sup>36</sup>	Ethics committee/C			No MAE mAE: 12.8%	mAE: 8%
Chevalier <i>et al</i> <sup>37</sup>	ClinicalTrials.org/C			No MAE mAE: 35.8%	mAE: 33.8%
Kallmes <i>et al</i> <sup>38</sup>	Review board/NC	Percutaneous vertebroplasty with PMMA cement injection/ vertebral compression fracture	Conscious sedation + local anaesthesia, pressure put on spine, simulation of odour with mixing of PMMA to imitate the smell during the active procedure	No MAE mAE: 14%	mAE: 16%
Buchbinder <i>et al</i> <sup>39</sup>	Ethics committee at each participating center/NC		Conscious sedation + local anaesthesia, needle inserted to rest on the lamina, PMMA container opened to imitate the smell during the active procedure	No procedural AE	
Cohen <i>et al</i> <sup>41</sup>	Review board/NC	Epidural injection of corticosteroids/sciatica	2 mL sterile water at 1–2 injection sites, transforaminal approach	No MAE mAE: 36%	mAE: 20%
Arden <i>et al</i> <sup>42</sup>	Ethics committee/NC		2 mL saline into interspinous ligament	No MAE mAE: 9%	mAE: 10%
Valat <i>et al</i> <sup>43</sup>	Ethics committee/NC		2 mL saline into epidural space, interlaminar approach	No MAE mAE: 6%	mAE: 8%
Iversen <i>et al</i> <sup>40</sup>	Ethics committee/NC		Subcutaneous injection of 2 mL saline superficial to the sacral hiatus	Not reported	
Freeman <i>et al</i> <sup>45</sup>	Ethics committee/C	IDET/discogenic low back pain	17-gauge introducer needle inserted into disc under fluoroscopic guidance, catheter inserted but not connected to generator, both subject and surgeon blinded	No MAE mAE: 11%	mAE: 5%
Pauza <i>et al</i> <sup>44</sup>	Review board/NC		17-gauge needle introduced onto the outer annulus, mock electrode passage	Not reported	

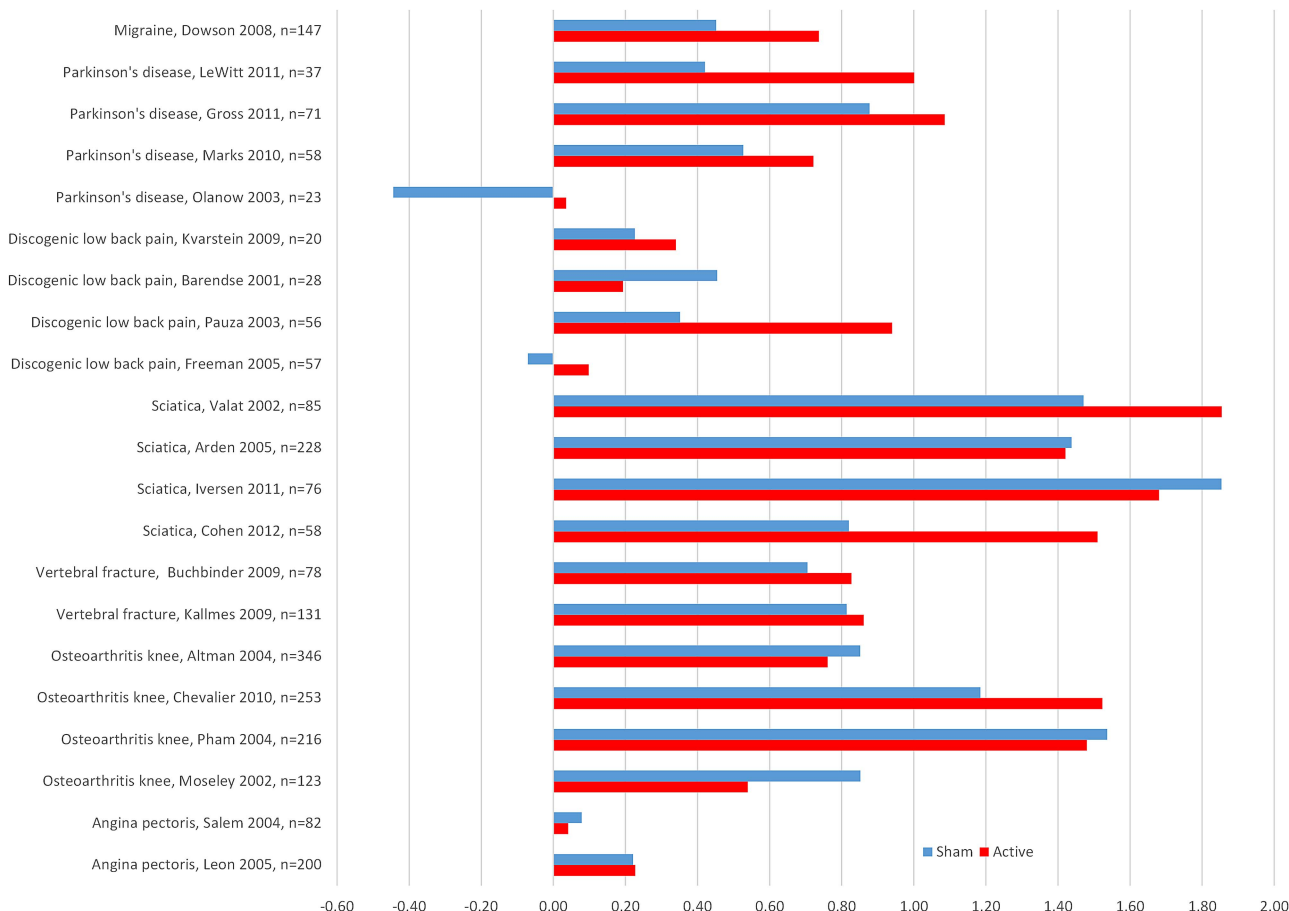
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Table 1 Continued

Author	Protocol approval/ funding (commercial, non-commercial)	Invasive procedure/ indication	Sham intervention	Adverse events related to procedure, active treatment	Adverse events related to procedure, sham
Kvarstein <i>et al</i> <sup>46</sup>		Ethics committee/NC	shown on monitor, generator noises produced PIRFT/discogenic low back pain	17-gauge canula and RF probe inserted into annulus, no RF current applied No MAE	Not reported
Olanow <i>et al</i> <sup>49</sup>	Review board/NC	Fetal nigral transplantation, 4 donors/Parkinson's disease	Scalp incisions, partial thickness burr holes, no cell transplantation, 6 months low-dose cyclosporine	mAE (rate/patient day: 0.66 MAE: 4	mAE (rate/patient day: 0.39 MAE: 0
Marks <i>et al</i> <sup>50</sup>	Review board/C	Gene delivery of AAV2-neurturin/Parkinson's disease	Scalp incisions, partial thickness burr holes, no intracranial injections	Most frequent mAE: headache: 68%	Most frequent mAE: headache: 50%
Gross <i>et al</i> <sup>51</sup>	Review board/C	Transplantation of human retinal pigmental cells/ Parkinson's disease	Scalp incisions, partial thickness burr holes, no cell transplantation	1 death MAE: 23%	0 deaths MAE: 0
LeWitt <i>et al</i> <sup>52</sup>	Review board/C	Insertion of AAV-GAD gene into subthalamic nucleus/ Parkinson's disease	Insertion of catheter caudal to nucleus, infusion of saline	No MAE mAE (probably related to procedure): 56%	mAE (probably related to procedure): 14%
Dowson <i>et al</i> <sup>53</sup>	Ethics committee/C	Patent foramen ovale closure with STARFlex Septal Repair Implant/migraine	General anaesthesia, skin incision in the groin	MAE (possibly or probably related to procedure): 11%	MAE (possibly or probably related to procedure): 4%

AAV2, adeno-associated; C, commercial; GAD, glutamic acid decarboxylase; IDET, intradiscal electrothermal therapy; MAE, major adverse events; mAE, minor adverse events; NC, non-commercial; PIRFT, percutaneous intradiscal radiofrequency thermocoagulation; PMMA, polymethylmethacrylate.



**Figure 2** Effect sizes of active treatment and sham, primary end points.

the Cochrane Library and MEDLINE, but the most relevant trials are likely to have been identified by our searches. By preferentially selecting core journals and trials that had previously been methodologically evaluated in systematic reviews, it was our intention to reduce the risk of bias by excluding studies of low quality. We realise that this selection process and the fact that we relied on previous methodological evaluations may have contributed to unrecognised selection bias.

The use of ES as a measure of clinical effect assumes a normal distribution of the data. This does not necessarily apply in the included trials because the majority of them are small. Including trials reporting non-parametric data would, however, necessitate other methods of statistical analysis. Small studies increase the likelihood of type-2 errors, though this is more relevant to probability estimates than analysis of ES.

### Adequate blinding and lack of physiological effects

We cannot rule out that treatment-specific effects in the actively treated groups may have jeopardised blinding, leading to overestimation of treatment effects through positive expectations. However, all the included trials gave a detailed description of the sham procedure, and both participant and assessor blinding seems to have been adequate.

On a more general level, it has been argued that sham procedures are not inert and may have specific physiological effects, thereby underestimating a treatment effect.<sup>55</sup> Recently, Bickett *et al* hypothesised that epidural injection of small volumes of saline might have physiological effects.<sup>56</sup> However, it is to be noted that in the four selected epidural trials in the present study, improvements in the sham group were greater in the two trials using non-epidural saline than in those using epidural saline, making a physiological effect less likely. In our opinion, physiological effects of the sham interventions are also unlikely in the remaining procedures.

Surgery and other invasive procedures are commonly believed to be associated with enhanced placebo effects, a phenomenon coined mega-placebo.<sup>57</sup> In spite of their heterogeneous nature, the 21 selected trials share a medicotechnological context in which an a priori enhanced placebo response could be expected. If an ES >0.8 is considered as mega-placebo, half of the included sham interventions reached this level. Factors such as the level of enthusiasm and conviction conveyed by the therapist, the impression of advanced procedures and the extent to which these factors succeed in activating a placebo response are probably crucial in explaining the improvements after sham interventions and the correlation of end points in the active treatment and sham

**Table 2** Effect size (ES) on primary and pooled secondary end points, showing differences between active treatment and sham arms.

Author/procedure	Limit disease duration/time to follow-up (months)	Trial arm/number of patients randomised	ES primary end point	ES pooled secondary end points (number of end points)
<b>Leon 2005</b> /percutaneous myocardial laser revascularisation	None/12		Exercise duration (s)	(10)
		Active/98	0.23	0.60
		Sham/102	0.22	0.54
ES active treatment vs sham			<b>0.01</b>	<b>0.07</b>
<b>Salem 2004</b> /percutaneous myocardial laser revascularisation	None/12		Exercise duration (s)	–
		Active/40	0.04	
		Sham/42	0.08	
ES active treatment vs sham			<b>–0.04</b>	
<b>Sihvonen 2013</b> /arthroscopic partial meniscectomy	>3/12		Lysholm knee score	(4)
		Active/70	0.86	0.58
		Sham/76	1.03	0.58
ES active treatment vs sham			<b>–0.17</b>	<b>0.00</b>
<b>Moseley 2002</b> /arthroscopic debridement	None/12		Knee Specific Pain Scale	(5)
		Active/59	0.54	0.11
		Sham/60	0.85	0.20
ES active treatment vs sham			<b>–0.31</b>	<b>–0.09</b>
<b>Pham 2004</b> /hyaluronic acid	None/12		VAS pain	(3)
		Active/131	1.48	1.35
		Sham/85	1.54	1.30
ES active treatment vs sham			<b>–0.06</b>	<b>0.05</b>
<b>Chevalier 2010</b> /hyaluronic acid	None/6		Womac A	Womac C function
		Active/124	1.52	1.13
		Sham/129	1.18	1.07
ES active treatment vs sham			<b>0.34</b>	<b>0.06</b>
<b>Altman 2004</b> /hyaluronic acid	None/6		Womac pain	(2)
		Active/172	0.76	0.38
		Sham/174	0.85	0.53
ES active treatment vs sham			<b>–0.09</b>	<b>–0.15</b>
<b>Kallmes 2009</b> /percutaneous vertebroplasty	<12/1		Roland-Morris Disability Questionnaire	(7)
		Active/68	0.86	0.72
		Sham/63	0.81	0.63
ES active treatment vs sham			<b>0.05</b>	<b>0.09</b>
<b>Buchbinder 2009</b> /percutaneous vertebroplasty	<12/6		Pain Score	(4)
		Active/38	0.83	0.46
		Sham/40	0.71	0.51

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Table 2 Continued

Author/procedure	Limit disease duration/time to follow-up (months)	Trial arm/number of patients randomised	ES primary end point	ES pooled secondary end points (number of end points)
ES active treatment vs sham <b>Cohen 2012</b> /epidural injection of corticosteroids	<6 /1	Active/28 Sham/30	<b>0.12</b> NRS leg pain 1.51 0.82	<b>-0.05</b> (2) 0.88 0.39
ES active treatment vs sham <b>Iversen 2011</b> /epidural injection of corticosteroids	>3/12	Active/36 Sham/40	<b>0.69</b> Oswestry Disability Index 1.68 1.85	<b>0.49</b> -   
ES active treatment vs sham <b>Arden 2005</b> /epidural injection of corticosteroids	>1<18/12	Active /120 Sham/108	<b>-0.17</b> Oswestry Disability Index 1.42 1.44	(2)   1.14 1.21
ES active treatment vs sham <b>Valat 2002</b> /epidural injection of corticosteroids	<6/1	Active/42 Sham/43	<b>-0.02</b> VAS Pain 1.85 1.47	<b>-0.07</b> (3) 1.10 0.99
ES active treatment vs sham <b>Freeman 2005</b> /intradiscal electrothermal therapy	≥3/6	Active/38 Sham/19	<b>0.38</b> Oswestry Disability Index 0.10 -0.07	<b>0.10</b> (6)  -0.03 0.12
ES active treatment vs sham <b>Pauza 2003</b> /intradiscal electrothermal therapy	>6/6	Active/32 Sham/24	<b>0.17</b> Oswestry Disability Index 0.94 0.35	<b>-0.15</b> (3)  0.90 0.46
ES active treatment vs sham <b>Kvarstein 2009</b> /percutaneous intradiscal radiofrequency thermocoagulation	>6/12	Active/10 Sham/10	<b>0.59</b> Brief Pain Inventory 0.34 0.23	<b>0.44</b> (5)  0.54 0.24
ES active treatment vs sham <b>Olanow 2003</b> /fetal nigral transplantation	None/24	Active/12 Sham/11	<b>0.11</b> UPDRS 3 off 0.04 -0.44	<b>0.30</b> (5) -0.24 -0.19
ES active treatment vs sham <b>Marks 2010</b> /gene delivery of AAV2-neurturin	≥60/12	Active/38 Sham/20	<b>0.48</b> UPDRS 3 off 0.72 0.53	<b>-0.06</b> (7) 0.23 -0.05

Continued

Table 2 Continued

Author/procedure	Limit disease duration/time to follow-up (months)	Trial arm/number of patients randomised	ES primary end point	ES pooled secondary end points (number of end points)
ES active treatment vs sham <b>Gross 2011</b> /transplantation of human retinal pigmental cells	≥60/12		<b>0.19</b> UPDRS 3 off	<b>0.28</b> (2)
ES active treatment vs sham <b>LeWitt 2011</b> /AAV-GAD gene into subthalamic nucleus	≥60/6	Active/35 Sham/36	1.09 0.88 <b>0.21</b> UPDRS 3 off	0.08 0.06 <b>0.02</b> (7)
ES active treatment vs sham <b>Dowson 2008</b> /patent foramen ovale closure	None/6	Active/16 Sham/21	1.00 0.42 <b>0.58</b> Frequency migraine/month (per protocol)	0.30 0.21 <b>0.08</b> Headache Impact Test
ES active treatment vs sham		Active/74 Sham/73	0.74 0.45 <b>0.28</b>	1.02 1.06 <b>0.04</b>
NRS, Numerical Rating Scale; UPDRS, Unified Parkinson's Disease Rating Scale; VAS, visual analogue scale; WOMAC, Western Ontario and McMaster Universities Osteoarthritis Index.				

groups. Participants' perception of whether they received active treatment or sham has been shown to contribute more to clinical improvement than the biological effects per se.<sup>32 58</sup>

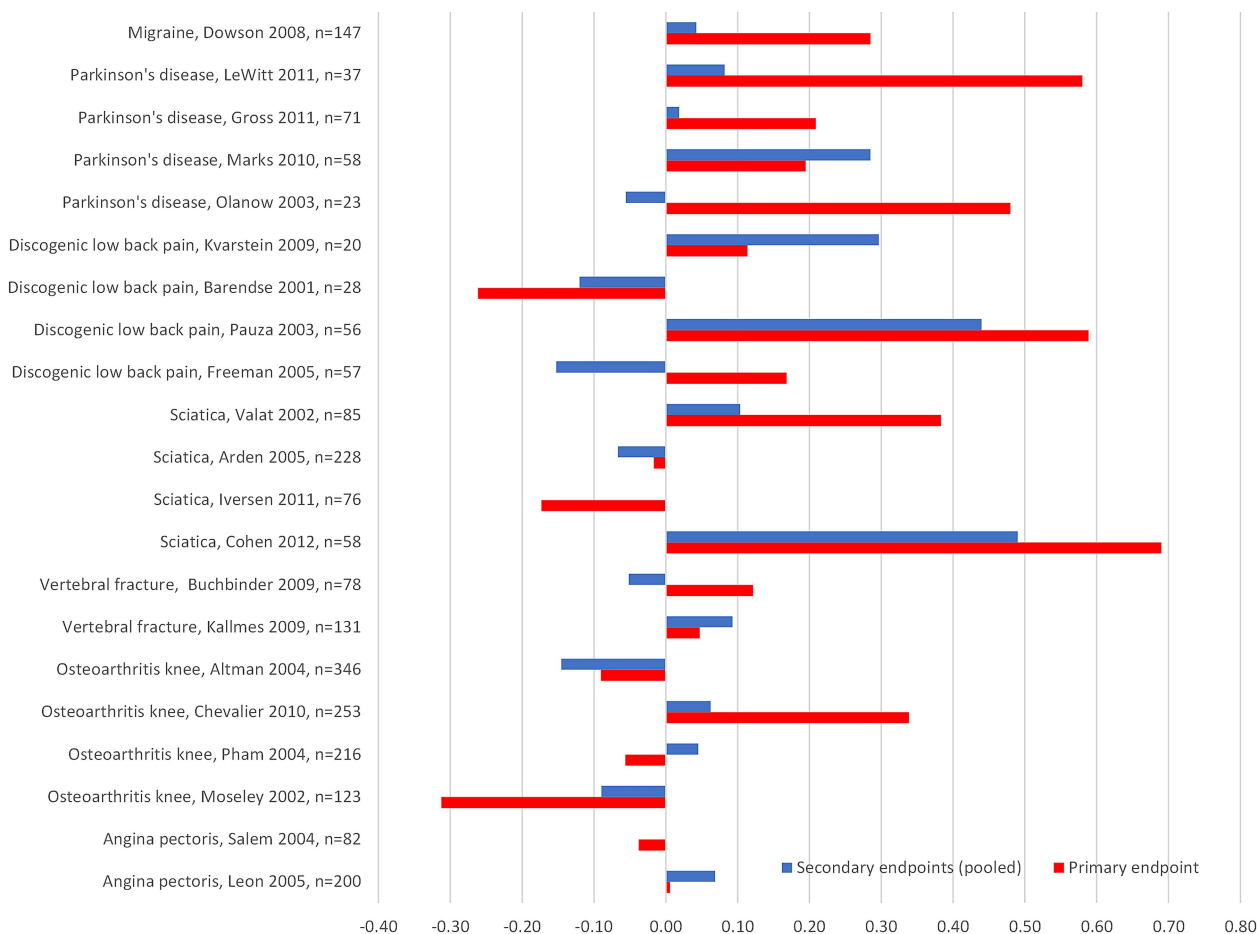
### Non-specific factors

The role of non-specific factors, primarily spontaneous remission or statistical regression to the mean in placebo-controlled studies is controversial.<sup>59</sup> A recent meta-analysis analysing 202 trials with an untreated group, spanning 60 different clinical conditions, found rather small differences between placebo and no treatment, with ESs in the range of 0.2–0.3.<sup>60</sup> Apart from acupuncture trials (mean ES 0.68), the authors did not include trials reporting the effectiveness of invasive procedures. Another meta-analysis studied the placebo effect of a range of treatments (pharmacological, non-pharmacological and surgical) for osteoarthritis of the hand, hip and knee.<sup>61</sup> Of 198 included trials, 14 had a no-treatment arm. The mean ES in the placebo groups was about 0.5, while it was only slightly above 0 in the no-treatment groups. The difference between the placebo and no-treatment groups was larger than the difference between the placebo and active treatment groups. Trials using injections, acupuncture and surgery had the largest placebo effects, and the effects were larger for subjective than objective end points. The authors concluded that there is a significant placebo effect on pain, stiffness and function in symptomatic osteoarthritis.

Because the trials in the present study did not include a no-treatment arm (ie, waiting list), we cannot rule out that the changes appearing during the trial period also reflect non-specific factors, that is, spontaneous improvement or regression to the mean. Such mechanisms would be expected to be most prominent in trials with brief illness duration before inclusion and with longer time to follow-up, while improvements in chronic, unremitting conditions such as Parkinson's disease would be more likely attributed to placebo. Interestingly, in three of the four included Parkinson's trials, there were moderate to large improvements in the sham groups even at 1-year follow-up.<sup>49 50 51</sup> Other authors have also found improvements several years after sham surgery, indistinguishable from conventional surgery.<sup>32 62</sup> This is in agreement with recent insights into the neurobiological effects of placebo and their relation to underlying psychological mechanisms, principally expectation and conditioning.<sup>63</sup>

### Are ethical objections to sham justified?

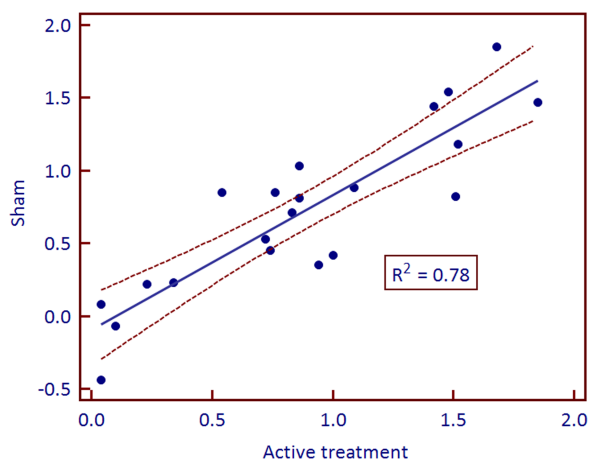
The use of sham in controlled surgical trials is a divisive issue, with scepticism, even frank opposition, being voiced by both ethics committees, involved surgeons and anaesthetists, and potential patients.<sup>10</sup> Ethical arguments include the inherent risks of sham procedures combined with the lack of obvious benefits to the participants. Barriers related primarily to feasibility include problems with patient and assessor blinding, differing technical expertise, the



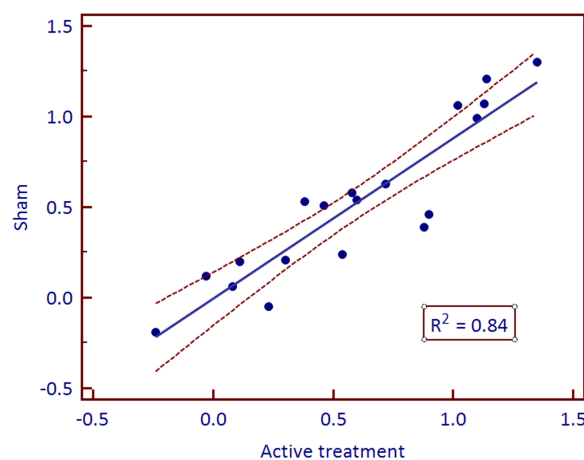
**Figure 3** Differences in effect size between active treatment and sham.

heterogeneity of the interventional techniques and variable outcome specifications, making standardisation difficult to achieve. Existing ethical guidelines accept the role of placebo-controlled trials when certain conditions are met.<sup>64</sup> There must be genuine equipoise, that is, conflicting or weak evidence of the effectiveness of a procedure. Blinding

of both participants and assessors must be assured and participants must freely consent to suspend knowledge of whether they are receiving sham or conventional treatment. The health risks and consequences of placebo or delayed treatment must be minimal, and outweighed by the societal importance of establishing the clinical utility of the intervention in question.<sup>65 66</sup>



**Figure 4** Association between effect sizes of primary end points in active treatment and sham arms. Linear regression, 95% CI; N=21.



**Figure 5** Association between effect sizes of pooled secondary end points in active treatment and sham arms. Linear regression, 95% CI; N=19.

The selected trials gave a detailed description of AEs in active as well as sham-treated groups (table 1). The safety concerns frequently raised as an argument against the use of sham were generally not supported. Major AEs related to the sham procedure were reported in only 1 of the trials<sup>53</sup> and they were short-lived and not life-threatening. Minor AEs were more frequent, but of limited duration. Positive placebo-induced effects generally outweighed AEs, thus weakening ethical arguments against the use of sham interventions. In our opinion, the consequences of the continued use of unproven invasive procedures are of a different magnitude. In the light of studies supporting the beneficial effects of sham procedures, at least for pain and Parkinson's symptoms, research ethics committees should consider such factors in their risk-benefit assessments of planned sham-controlled trials.<sup>67 68</sup>

### Clinical implications

The present results are pertinent to the ongoing discussion about wasteful and unproven medical practices, and underscore the necessity for a continual assessment of existing or novel unproven procedures. Minimally invasive techniques have lowered the threshold for interventions and led to their application to a wider clinical spectrum (indication creep) without an ongoing evaluation of effectiveness or safety.<sup>4</sup> The last two decades have seen dramatic increases in the use of several of the described procedures, as well as interventions we have not investigated, such as acromioplasty, percutaneous coronary intervention and recently, robotic surgery.<sup>69–74</sup> In light of the results in the present study, placebo effects might well explain a large part of the purported effects of such procedures. When clinicians and regulators are faced with claims of large treatment effects for insufficiently tested procedures, their default mode should be watchful scepticism. The standards of the evaluation process before approval and reimbursement for devices and procedures need to be strengthened, and economic or regulatory incentives that perpetuate the use of undocumented or harmful procedures should be abrogated.

### CONCLUSION

Sham-controlled trials are unique in their ability to discriminate between true treatment effects and non-specific effects. The results of the present study suggest that placebo and other non-specific effects explain a large part of their purported benefits. Further, results indicate that the risks of AEs in sham-controlled trials are over-rated and could be considered acceptable in view of the potential personal harm and societal costs associated with unproven minimally invasive interventions.

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Appendix table 1. Indications, postulated mechanisms and history of selected interventions

Invasive procedure / indication	Postulated mechanism	History	References
Percutaneous myocardial laser revascularization / intractable angina pectoris	Increasing the delivery of oxygenated blood to poorly perfused myocardium by creating channels	Introduced in the 1980s, initially transmyocardial route, later percutaneous route, now mostly abandoned	Schofield PM, McNab D. NICE evaluation of transmyocardial laser revascularisation and percutaneous laser revascularisation for refractory angina. <i>Heart</i> 2010;96:312-3.
Patent foramen ovale closure with STARFlex Septal Repair Implant / migraine	Improvement of migraine headache, believed to block the formation of microembolies to the brain	Developed in the 1990s for the prevention of stroke, later thought to cure migraine, never in clinical use for this indication	Gornall J. A very public break-up. <i>BMJ</i> 2010;340:c110
Arthroscopic debridement / Knee osteoarthritis	Unclear, no documented effect on arthritic process, but about 50% report relief of pain (Mosely)	Annually about 650.000 procedures in the USA in the mid-nineties, but 39% decrease between 2000 and 2008.	Holmes R, Moschetti W, Martin B, Tomek I, Finlayson S. Effect of evidence and changes in reimbursement on the rate of arthroscopy for osteoarthritis. <i>Am J Sports Med</i> 2013;41:1039-43.
Arthroscopic meniscectomy / degenerative meniscal lesions	Unclear, relief of symptoms attributed to trimming damaged meniscus down to viable meniscus and removing fragments.	The most common orthopedic procedure in the United States, 700.000 per year, up 50% last 15 years	Kim S, Bosque J, Meehan JP, Jamali A, Marder R. Increase in outpatient knee arthroscopy in the United States: a comparison of National Surveys of Ambulatory Surgery, 1996 and 2006. <i>J Bone Joint Surg Am</i> 2011;93:994-1000.
Viscosupplementation with hyaluronic acid / Knee osteoarthritis	Improve joint lubrication by increasing HA levels in joint, in spite of short half-lives (Marshall 2000)	Many positive reports since late 1980s, including sham-controlled trials. Still widely in use	Rutjes 2012 (15)
Percutaneous vertebroplasty with PMMA cement injection / vertebral compression fracture	Increase the strength of the damaged bone and alleviate pain by preventing microfractures	Numerous observational studies and single-blind trials reported substantial clinical benefits. Slight reduction of procedure since 2009	Manchikanti L, Pampati V, Hirsch JA. Analysis of utilization patterns of vertebroplasty and kyphoplasty in the Medicare population. <i>J Neurointerv Surg</i> 2013;5:467-72.
Epidural injection of corticosteroids / Sciatica	Dampen inflammatory reaction in nerve root sheaths caused by mechanical compression	Routinely used for sciatica since the 1950s (Pinto 2012). Since 2000 the number of injections increased by about 130% in the United States and 50% in the United Kingdom	Manchikanti L, Falco FJ, Singh V, Pampati V, Parr AT, Benyamin RM, Fellows B, Hirsch JA. Utilization of interventional techniques in managing chronic pain in the Medicare population: analysis of growth patterns from 2000 to 2011. <i>Pain Physician</i> 2012;15:E969-82

Percutaneous intradiscal radiofrequency and thermocoagulation (PIRFT and IDET) / discogenic low back pain	Placement of a electrode or RF-probe into the annulus and applying heat or current to destruct nociceptors/ annulus	Introduced in 1996 (IDET), later mostly abandoned	Helm 2012 (18)
Fetal nigral transplantation / Parkinson's disease			-
Gene delivery of AAV2-Neurturin / Parkinson's disease			
Transplantation of human retinal pigmental cells / Parkinson's disease	Restoration of dopamin levels in basal ganglia through injection of growth factors, GAD gene or nigral dopamine neurons	Based on animal models and a few small observational trials from about 2000. None in routine clinical use due to insufficient evidence	
Insertion of AAV-GAD gene into subthalamic nucleus / Parkinson's disease			

Appendix table 2. Search phrases, no of eligible studies and reasons for exclusion

Procedure	Search phrase MEDLINE	Source	Eligible studies	Excluded, ES not calculatable	Excluded, risk of bias	Included studies
PMLR	Percutaneous myocardial laser revascularization	McGillion 2010 (17)	3	-	1	Salem 2004, Leon 2005
PIRFT /IDET	Intradiscal OR annular AND thermal AND "low back pain"	Helm 2012 (18)	3	-	-	Kvarstein, 2009
				-	-	Freeman 2005, Pauza 2003
Epidural injection corticosteroids	Epidural AND corticosteroid* AND sciatica	Pinto 2012 (16)	6	Karppinen 2001	1	Iversen 2011, Valat 2002, Arden 2005, Cohen 2012
Intraarticular hyaluronic acid for osteoarthritis knee	Hyaluron* OR viscosuppl* AND knee AND osteoarthritis	Rutjes 2012 (15)	48	Lundsgaard 2008, Petrella 2008	41	Petrella 2006, Chevalier 2010, Altman 2004, Pham 2004
Vertebroplasty	vertebroplast*	Shi 2012 (19)	2	-	-	Kallmes 2009, Buchbinder 2009
Invasive treatment of Parkinson's disease	transplantation OR gene OR "stem cell" AND Parkinson*	MEDLINE	6	Freed 2001, Gordon 2004, McRae 2004	-	Marks 2010, Olanow 2003, Gross 2011, LeWitt 2011
Arthroscopic debridement knee osteoarthritis	debridement AND lavage AND knee AND osteoarthr*	MEDLINE	1	-	-	Moseley 2002
Meniscectomy knee	meniscectomy AND knee	MEDLINE	1	-	-	Sihvonen 2013
Foramen ovale closure for migraine	"foramen ovale" AND migraine	MEDLINE	1	-	-	Dowson 2008
<b>Number of trials</b>			<b>71</b>	<b>6</b>	<b>43</b>	<b>22</b>

Appendix table 3. Included and excluded secondary endpoints.

Author	Included secondary endpoints	Excluded secondary endpoints (means not reported, or irrelevant)
<b>Leon 2005</b>		
	Time to onset angina	Improvement in angina class
	Time to onset ST depression	Radioisotope imaging
	Overall health	
	Frequency angina	
	Stability angina	
	Physical functioning	
	Disease perception	
	Treatment satisfaction	
	PCS	
	MCS	
<b>Salem 2004</b>		
		Proportion improved CCS angina class
		Medication usage
		Seattle Angina Questionnaire
		Left EF
		Angina stability
		Angina frequency
		Physical limitation
		Treatment satisfaction
		Disease perception
<b>Sihvonen 2013</b>	WOMET score	-
	Knee pain at rest	
	Knee pain after exercise	
	15D score	
<b>Moseley 2002</b>		
	Arthritis Impact Scale	-
	Physical functioning Scale	
	Walking-bending	
	SF-36 Pain	
	SF-36 Physical functioning	
<b>Pham 2004</b>		
	Lequesne's algofunctional index	-
	Global assessment	
	% painful days	
<b>Chevalier 2010</b>		
	Womac C function	-
<b>Altman 2004</b>		
	Womac stiffness	-
	Womac physical	
<b>Kallmes 2009</b>		
	Pain Intensity	Opioid use



	SF-36 PCS	
	SF-36 MCS	
	Pain Frequency Index	
	Pain Bothersomeness Index	
	EQ-SD Index	
	SOF-ADL	
<b>Buchbinder 2009</b>		
	Roland-Morris Disability Questionnaire	-
	Life Questionnaire of the European Foundation	
	European Quality of Life-5 Dimensions	
<b>Cohen 2012</b>		
	Oswestry Disability Index	-
	Back pain	
<b>Arden 2005</b>		
	Leg pain	Analgesic use
	Back pain	
<b>Valat 2002</b>		
	Roland-Morris Disability Questionnaire	Dallas Pain Questionnaire
	Straight leg raising	
	Schober's test	
<b>Iversen 2011</b>		
		VAS back and leg pain, European Quality of Life scale
<b>Freeman 2005</b>		
	Modifiede Somatic Perception Questionnaire	SF-36 Mental, Role Physical/ Mental, Social Function
	Low Back Pain Outcome Score	
	SF-36 Physical Function	
	SF-36 Pain	
	SF-36 General Health	
	SF-36 Vitality	
<b>Pauza 2003</b>		
	VAS Pain	-
	SF-36 Physical Function	
	SF-36 Pain	
<b>Kvarstein 2009</b>		
	SF-36 Bodily pain	SF-36 Mental, Role Physical/ Mental, Social Function
	SF-36 Physical function	
	Oswestry Disability Index	
	SF-36 General health	
	SF-36 Vitality	
<b>Olanow 2003</b>		
	UPDRS motor on	Mean L-dopa dose equivalents
	UPDRS ADL off	
	UPDRS ADL on	

	% Off time day	
	% On time without dyskinesia	
<b>Marks 2010</b>		
	UPDRS OFF 1	Mean L-dopa dose equivalents
	UPDRS OFF 2	
	UPDRS ON 1	
	UPDRS ON 2	
	UPDRS ON 3	
	On without dyskinesia	
	On with dyskinesia	
<b>Gross 2011</b>		
	UPDRS ON	Mean L-dopa dose equivalents
	UPDRS ADL	
<b>LeWitt 2011</b>		
	UPDRS 1	Timed walking
	UPDRS2	BPRS other than taps
	UPDRS4	Dyskinesia rating scale
	Schwab and England ADL scale	Patient's diary
	BPRS taps 60 s	Clinical global impression
	Hoehan and Yahr stage	
	PDQ-39 total	
<b>Dowson 2008</b>		
	Headache Impact Test	-