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To what extent are surgery and invasive procedures effective beyond a placebo response? A systematic review with meta-analysis of randomised, sham controlled trials

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ABSTRACT

Objectives: To assess the quantity and quality of randomised, sham-controlled studies of surgery and invasive procedures and estimate the treatment-specific and non-specific effects of those procedures.

Design: Systematic review and meta-analysis.

Data sources: We searched PubMed, EMBASE, CINAHL, CENTRAL (Cochrane Library), PILOTS, PsycInfo, DoD Biomedical Research, clinicaltrials.gov, NLM catalog and NIH Grantee Publications Database from their inception through January 2015.

Study selection: We included randomised controlled trials of surgery and invasive procedures that penetrated the skin or an orifice and had a parallel sham procedure for comparison.

Data extraction and analysis: Three authors independently extracted data and assessed risk of bias. Studies reporting continuous outcomes were pooled and the standardised mean difference (SMD) with 95% CIs was calculated using a random effects model for difference between true and sham groups.

Results: 55 studies (3574 patients) were identified meeting inclusion criteria; 39 provided sufficient data for inclusion in the main analysis (2902 patients). The overall SMD of the continuous primary outcome between treatment/sham-control groups was 0.34 (95% CI 0.20 to 0.49; p<0.00001; I^2=67%). The SMD for surgery versus sham surgery was non-significant for pain-related conditions (n=15, SMD=0.13, p=0.08), marginally significant for studies on weight loss (n=10, SMD=0.52, p=0.05) and significant for gastroesophageal reflux disorder (GERD) studies (n=5, SMD=0.65, p<0.001) and for other conditions (n=8, SMD=0.44, p=0.004). Mean improvement in sham groups relative to active treatment was larger in pain-related conditions (78%) and obesity (71%) than in GERD (57%) and other conditions (57%), and was smaller in classical-surgery trials (21%) than in endoscopic trials (73%) and those using percutaneous procedures (64%).

Conclusions: The non-specific effects of surgery and other invasive procedures are generally large. Particularly in the field of pain-related conditions, more evidence from randomised placebo-controlled trials is needed to avoid continuation of ineffective treatments.

Strengths and limitations of this study

- This is the first systematic review using a meta-analysis approach to estimate both specific and non-specific components in sham-controlled surgical trials, and to what extent those effects differ among conditions and procedures.
- All sensitivity analyses showed similar results as the main analysis, except one, namely the sensitivity analysis for large studies (≥100 patients), which showed a smaller non-significant effect size.
- Our results have implications for clinical research and practice by arguing against the continued use of ineffective invasive treatments, especially in the field of chronic pain.
- One limitation might be that the conclusions from our meta-analysis are restricted to available published data on surgical interventions that have been tested in sham-controlled clinical trials.

INTRODUCTION

Surgery and other invasive procedures such as endoscopy and percutaneous procedures are widely used in medicine but their specific efficacy and risk-benefit profile are rarely assessed in rigorous and systematic ways. The development of minimally invasive procedures has expanded the use of such interventions for treating a variety of conditions such as low-back pain,[1] arthritis,[2] endometriosis,[3] Parkinson's disease,[4] gastro-oesophageal reflux[5] and obesity.[6]

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Rarely are these procedures evaluated using rigorous research designs involving randomisation, allocation concealment and blinding or placebo controls, which are considered gold standards for medical interventions. In the absence of controls for common sources of bias, studies on these procedures may give a false impression of their true efficacy. Is it possible to test invasive procedures using rigorous methods? Blinding of outcome assessment is challenging since mimicking a complex, invasive procedure such as surgery, or insertion of a scope or a needle, requires an elaborate sham procedure. Moreover, there is significant controversy over the ethics of using sham procedures, even with carefully informed patients, further restricting the number of such studies being carried out.[7 8] However, can we justify widespread use of these procedures without rigorous testing?

The use of blinded, sham procedures permits rigorous assessment of treatment efficacy by comparing the outcome in the treatment and sham groups. Specifically, sham procedures control for a variety of observed outcomes in the sham group that are distinct from the specific efficacy of the surgery or invasive procedure under investigation. These 'non-specific' outcomes include placebo responses (also sometimes called placebo effects), which we define here as the observed outcome changes in the sham groups. These changes are due to the natural history of the patient's condition or regression to the mean and a response to the ritual of medical treatments. Such rituals include the type of procedure (pill, needle, knife or touch), the status, authority and communication style of the provider, the setting and context of the treatment and the patient's and practitioners expectation about the outcome.[9]

Yet, invasive procedures are thought to incorporate many factors that may contribute to the placebo responses including use of a hospital-like setting; multiple, authoritative providers; frequent and repeated suggestions about expected outcomes; a physical invasion of the body; and an elaborate ritual of treatment delivery and recovery.[10] Thus, one would expect a significant contribution from surgical ritual and other non-specific factors to the observed outcomes during invasive procedures in clinical practice and in randomised trials without sham control groups. Several high profile studies support this hypothesis in which sham procedures involving only superficial anaesthesia were compared to the more invasive true procedure.[11–13] For example, Moseley *et al*[11] reported no greater pain improvement in patients with osteoarthritis of the knee that underwent arthroscopic knee surgery compared to a sham procedure in which a cut was made over the knee without introducing the arthroscope. Two more recent controlled studies of vertebroplasty for painful osteoporotic vertebral fractures reported similar degrees of pain relief from sham procedures involving only superficial anaesthesia compared to the more invasive active procedures.[12 13] In contrast, a systematic review comparing surgical with non-surgical treatments for painful osteoporotic vertebral fractures came to the conclusion that vertebroplasty and kyphoplasty are superior to non-surgical treatments.[14] Since invasive interventions frequently go along with larger non-specific effects than non-invasive treatments[15 16] surgical trials that do not include a sham surgery arm may give biased results. Thus, the efficacy of invasive procedures, for example, for chronic pain conditions, remains controversial.[17] In addition, many invasive procedures involve the risk of anaesthesia and high cost.[17] Therefore, it is important to estimate to what degree the observed outcomes from invasive procedures are due to specific efficacy of the treatments or to other factors.

To better understand these issues we conducted a systematic review and meta-analysis of studies on surgery and invasive procedures in which a parallel sham procedure was included for comparison. Our study aims were to: (1) assess the quantity and quality of such studies; (2) estimate the magnitude of specific effects over sham procedures; and, (3) estimate the contribution of the surgical ritual and other non-specific factors to outcomes from these procedures.

METHODS

Identification of studies

The following online databases were searched from their inception through January 2015: PubMed, EMBASE, CINAHL, CENTRAL (Cochrane Library), PILOTS, PsycInfo, DoD Biomedical Research, clinicaltrials.gov, NLM catalog, as well as NIH Grantee Publications Database. We used as our initial search terms: 'Diagnostic Techniques, Surgical' OR 'Orthopedic Procedures' OR 'Specialties, Surgical' OR 'Surgical Procedures, Operative' OR 'surgery' (Subheading) or surgery) AND ('Placebos' OR 'Placebo Effect' or sham surg* or placebo surg* or mock surg* or simulated surg* or placebo proc* or sham proc* or mock proc* or simulated proc*). We restricted our search to humans and randomised controlled trials. Variations of these search terms were made for MESH terms, where necessary, and are available on request from the first author.

The 'Grey literature' was searched by looking for relevant dissertations, conference proceedings, Google Scholar and searching the internet using the keyword scheme as well as searching all relevant reference lists of identified articles and related reviews. We also contacted and consulted with leading experts in the fields of surgery and placebo, and shared databases that these experts have collected over the years relating to placebo to make sure we captured all the relevant literature.

Eligibility criteria

Studies were included in the systematic review if they: (1) were randomised controlled trials; (2) involved a population for which there was a symptom-driven medical condition for which an invasive procedure or

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classical surgery as defined below was being performed; and (3) had a comparison group that used a sham procedure to mimic the real procedure.

Classical surgery was defined as a procedure that followed the typical surgical experience that uses preoperative preparation, anaesthesia, an incisional trauma (usually through muscle and fascia and into the peritoneum) and a postoperative recovery process. Invasive procedures were defined as when an instrument was inserted into the body (either endoscopically or percutaneously) for the purpose of manipulating tissue or changing anatomy. In all cases we selected studies where when these procedures were compared to a sham procedure that used the same surgical or invasive procedure, instrument and ritual, but eliminated the hypothesised active component of tissue manipulation. We excluded studies in which the procedure was used simply as a delivery mechanism for another ongoing active treatment such as a pacemaker, brain or cardiac stimulation, or delivery of a drug or biological product. Studies where an invasive procedure was implemented for prevention of a medical condition or there was no symptom-driven condition were also excluded.

Four investigators (CC, LC, KL and KM) screened titles and abstracts for relevance in two phases based on the inclusion criteria: phase one eliminated all clearly irrelevant studies, phase two applied all inclusion/exclusion criteria listed above for the remaining studies. Any disagreements about including a study were resolved through discussion and consensus, and approved by the first author (WJ). All reviewers were fully trained in systematic review methodology. At least two reviewers had to review each citation in order for it to progress to the next phase of the review. A Cohen's κ on agreement was attained for both phases above 88%.

Quality assessment and data extraction

The methodological quality of the individual studies (sequence generation, allocation concealment, was assessed independently by three reviewers using the Cochrane Risk of Bias (ROB) tool.[18] Descriptive data was independently extracted on the following items: population; condition for which surgery was performed; sample (population) entered; dropout rate; informed consent details; whether a power calculation was performed and achieved; intervention and sham procedure used; primary and secondary outcomes and the statistical data associated with these; whether expectation was reported; author conclusions; adverse events reported; funding source, and reviewer comments. We also extracted from each study, if available, a continuous and a dichotomous main outcome at two time points (intermediate and late), and a continuous and a dichotomous pain outcome (when applicable). The most important outcome measure (miOM) was defined as either: (1) the primary main outcome measure (pMOM) at a time point as predefined in the trial; or (if not 1), (2) the only major outcome of a trial at the latest available time point; or (if neither 1 nor 2), (3) the clearly most relevant outcome determined by two independent reviewers at the latest available time point. Secondary outcomes were intermediate time points of the most important outcome measure; pain outcomes at the latest available time point; or, pain outcomes at the intermediate time point. All discrepancies were tracked by the review manager and were resolved by consensus and discussions during team meetings. Data were entered into a web-based, secure, systematic review management programme called Mobius Analytics SRS (Mobius Analytics Inc, Ottawa, Ontario, Canada).

Data synthesis and analysis

According to our analysis plan, the meta-analyses focused on continuous outcomes. The primary analysis was based on trials reporting a most important continuous outcome measure in sufficient detail to be included in the meta-analysis. Secondary analyses were based on trials reporting (1) a continuous outcome measure at an intermediate time point, (2) a pain measure at a late time point, (3) a pain measure at an intermediate time point. Trials reporting only a dichotomous outcome measure (responder data) are noted in online supplementary table 1, and a sensitivity analysis was computed for these outcomes (see below).

Within-group and between-group effect sizes were based on Cohen's[19] d for change within one group, and Cohen's d for between-group effect measures, respectively, correcting for small-sample bias.[20] In order to keep the effect size framework coherent for within-group and between-group designs, change from baseline was used throughout. When SD was not reported, it was calculated from pre-SD and post-SD,[21] using r=0.5 for the product-moment correlation between pre and post measures.

Analyses of continuous data were performed with the generic inverse variance module of the Cochrane Collaboration's Review Manager software (V.5.1), using standardised mean difference (SMD) as the effect size measure. As we expected heterogeneity, a random effects model was used. Within-group effect sizes were pooled in such a way that positive values indicate improvement, while positive values of between-group effect sizes indicate superiority (more pronounced improvement) of the intervention group over the control (sham) group. To estimate the relative contribution of non-specific outcomes to treatment effects, the per cent ratio of the pooled within-group treatment effects in the sham and the treatment groups was calculated. We used Cochrane's Q test and calculated I^2 to examine statistical heterogeneity, with low, moderate and high I^2 values of 25%, 50%, and 75%.[22] Egger's test was used to assess funnel plot asymmetry.[23] A p value of less than 0.05 was set as the level of significance.[24 25]

Subgroup analyses were performed according to predefined categories of target diseases and types of

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surgery. To check the robustness of results, we performed sensitivity analyses with four criteria: (1) studies specifying a primary main outcome measure (pMOM); (2) imputing 0.3 and 0.7 for pre–post correlation coefficient r, when missing; (3) studies with total sample sizes ≥100; and, (4) studies with low risk of allocation concealment. An additional sensitivity analysis was performed for dichotomous outcomes of 12 studies that provided no continuous outcome (see online supplementary figure 1).

RESULTS

Eligible studies

Our search identified a total of 7360 citations. After excluding clearly irrelevant references the full text of 113 publications were obtained. Of these, 46 were excluded, mainly for not including an instrumental or surgical intervention or a sham procedure as defined above. A total of 55 studies (in 67 publications) involving a total of 3574 enrolled patients met our inclusion criteria for systematic review (figure 1).[26]

Characteristics and quality of included studies

Characteristics of the included studies are summarised in online supplementary table 1. About half (25) of the studies were carried out on pain-related conditions with back pain (7) being the most frequent[11 12 27–31] followed by arthritis (4),[13 32–34] angina from coronary artery disease (4),[35–39]) abdominal pain (3),[40–42] endometriosis (3),[43–47] cholia (2)[48 49] and migraine (2).[50 51]) The most frequently studied non-pain condition was obesity, especially when using balloon insertion (11).[52–62]) Other conditions that had more than one study included gastroesophageal reflux disease (GERD) (5),[63–67] Parkinson's Disease (2),[68–74] sleep apnoea (2),[75 76] dry eye (2)[77 78] and asthma (2).[79–81] Some other conditions were also studied (see online supplementary table 1).[80–90] Many (22) of the studies involved endoscopic or percutaneous procedures in which tissue was removed or altered or a material (eg, dye, cement, balloon) was inserted.[11–13 28 31 34 38 40–43 52 54 56 61 63 65 67 77–79 90] Some of these procedures used a catheter to reach an internal organ (such as the heart or gall bladder) or a needle to inject a material or cell (often into the lumbar spine or

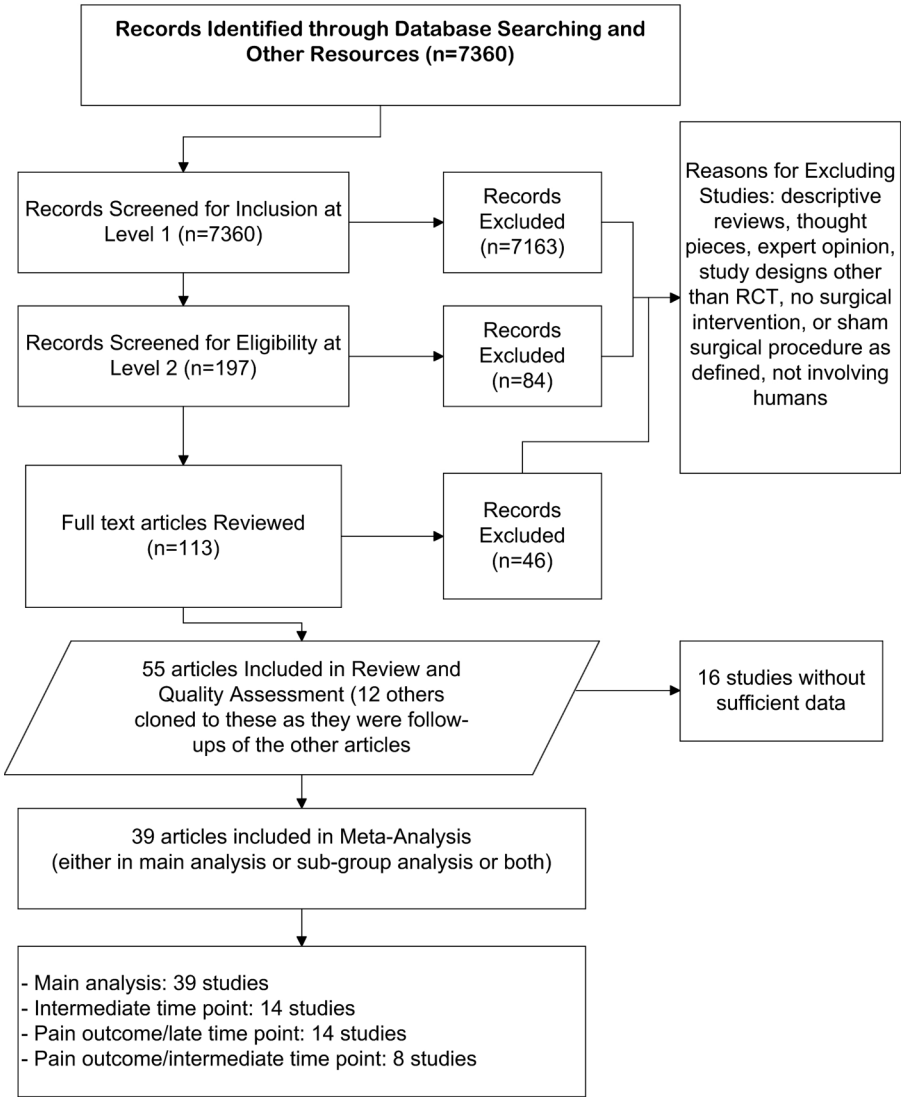

Figure 1 Flow chart of included studies. RCT, randomised controlled trial.

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brain).[27 29 30 32 53 55 57 59 60 62 64 66 85 89] Five studies evaluated more classical surgical procedures in which the body was opened with a scalpel or drill.[50 51 74–76]

In most studies, blinding was achieved using elaborate sham procedures. Those mimicking classical surgical procedures usually cut the body, leaving a scar but causing less damage than the real surgery. Sham percutaneous and endoscopic procedures often involved superficial insertion of a needle or a scope. For example, in the Parkinson's studies on surgical interventions on the brain, sham procedures involved placing burr holes without penetration of the skull.[68–74] Sham surgery for endometriosis would often involve 'diagnostic laparoscopy' with no internal tissue destruction. Sham balloon insertion for obesity treatment usually involved inserting the balloon but not inflating it.[52–62]

Overall, the risk of bias was low in these studies, with some exceptions. Of the 55 studies (67 publications) included in the systematic review, 34 studies (62%) reported an adequate method for generating the allocation sequence, however only 23 (42%) had adequate concealment of allocation. Blinding of the patients and outcome assessors was adequate in 48 (87%) studies and incomplete data was adequately addressed in 52 (95%). Fifty-two (95%) of the studies were free from suggestion of selective outcome reporting and 53 studies were judged to be free of other sources of bias.

Overall analyses

Thirty-nine studies (2902 patients) with continuous data were included in the main analysis. The overall effect of surgery compared to sham surgery was highly significant (SMD 0.34, 95% CI 0.20 to 0.49; p<0.00001), while heterogeneity was large (I^2=67%, p<0.00001). Excluding one outlier[52] reduced I^2 to 57% (SMD, 0.30, 95% CI 0.17 to 0.43; p<0.00001), indicating moderate heterogeneity. Sensitivity analyses provided comparable effect sizes (figure 2), except for studies with overall sample sizes of 100 participants or more, for which the SMD was non-significant at 0.15 (n=10; 95% CI −0.02 to 0.32; p=0.09; I^2=66%). Inspection of the funnel plot suggests the presence of biases in the meta-analysis, such as small study bias or publication bias (figure 3). Asymmetry in the funnel plot was confirmed by the Egger's test (asymmetry coefficient 1.7, p=0.017).

Non-significant SMD were found when combining available data for the most important continuous outcome measure at an intermediate time point (n=14; SMD 0.12, 95% CI −0.05 to 0.29; p=0.17; I^2=54%) as well as for specific pain outcomes at a late (n=14; SMD 0.12, 95% CI −0.03 to 0.27; p=0.11; I^2=29%;) or an intermediate time point (n=8; SMD 0.07, 95% CI −0.06 to 0.20; p=0.31; I^2=0%).

Subgroup analyses of most important outcome measures

Subgroups by condition

Figure 4 summarises the SMD and subgroup means for between-group changes and the 95% CIs for each condition. The overall test for subgroup differences was significant (χ^2=10.26, p=0.04), indicating significant heterogeneity of SMD between subgroups. Fifteen studies (analysing 1584 patients) included in the meta-analysis investigated pain-related conditions, the overall SMD was non-significant at 0.13 (95% CI −0.01 to 0.28; p=0.08; I^2=46%). Ten studies (287 patients) reported on weight loss, the SMD was marginally significant at 0.52 (95% CI 0.01 to 1.03; p=0.05; I^2=76%). Excluding one outlier[52] reduced I^2 to 14% (SMD 0.27, 95% CI 0.00 to 0.55; p=0.05). Most (nine) of these studies involved balloon and sham balloon insertion. Five studies (342 patients) involved GERD. They showed a significant SMD of 0.65 (95% CI 0.31 to 1.00; p=0.0002; I^2=55%). One study on Parkinson's (34 patients) showed an SMD of 0.36 (95% CI −0.37 to 1.09). Eight studies (655 patients) on other diseases yielded a pooled SMD of 0.44 (95% CI 0.14 to 0.74, p=0.004; I^2=57%).

Subgroups by type of procedure

Between-group SMD did not differ significantly between classical surgery, endoscopic surgery and percutaneous procedures (χ^2=1.10, p=0.58; results not shown).

Dichotomous outcomes

Twelve studies provided only a dichotomous outcome measure (see online supplementary table 1). Sensitivity analyses showed an overall effect of surgery compared to sham surgery (risk ratio 1.54, 95% CI 1.11 to 2.15; p=0.01), while heterogeneity was large (I^2=59%, p=0.005). Subgroup analyses according to condition revealed a significant effect of surgery versus sham surgery for pain studies (n=9; risk ratio 1.60, 95% CI 1.11 to 2.30; p=0.01; I^2=59%, p=0.01) but not for other studies (n=3; risk ratio 2.19, 95% CI 0.44 to 10.84; p=0.33; I^2=60%, p=0.08; see online supplementary figure 1).

Changes from baseline within sham and active groups

The pooled SMD for changes from baseline was 0.61 in the sham groups (95% CI 0.47 to 0.75, p<0.00001, n=39, I^2=76%) and 0.92 (95% CI 0.74 to 1.09, p<0.00001, n=39, I^2=86%) in the treatment groups. Thus, on average, the changes in the sham groups accounted for 65% of the overall improvement from the treatments. This proportion of specific to non-specific treatment effects was larger in pain-related conditions (78%) and obesity (71%) than in GERD (57%) and other conditions (57%), and was considerably smaller in classical surgery trials (21%) than in endoscopic trials (73%) and those using percutaneous procedures (64%; figure 4). Changes in the sham groups accounted for 89% and 82% of overall improvement in intermediate and late pain outcomes.

DISCUSSION

This is the first comprehensive systematic review with meta-analysis estimating the magnitude of the specific

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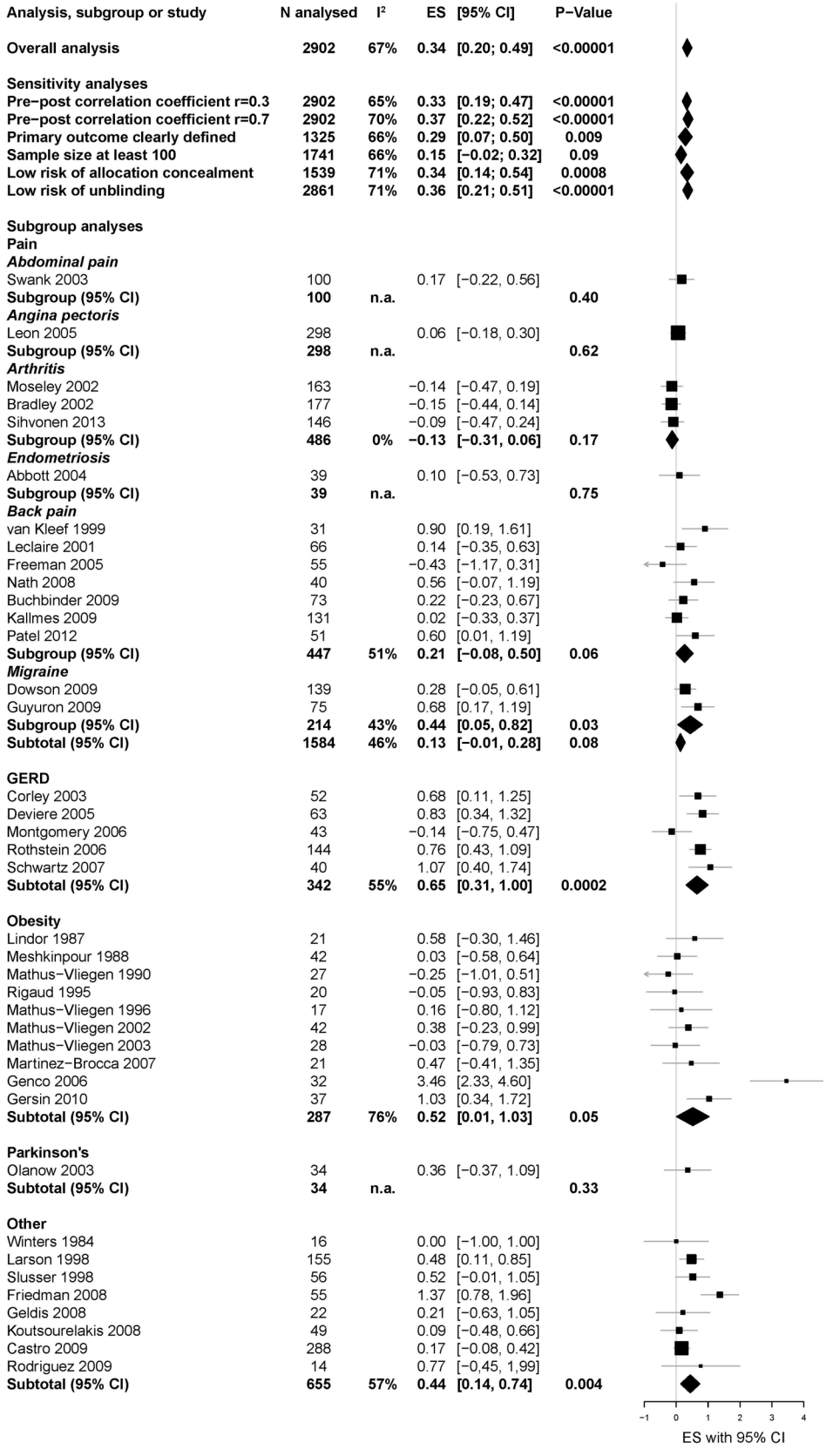

Figure 2 The specific effect of invasive procedures and surgery.

effects of surgery and invasive procedures for various conditions. While some high profile studies have reported no difference between treatment and sham procedures, we found a positive though modest overall effect size (Cohen's d) from the invasive procedures included in the analysis. When only larger studies (≥100 participants) are taken, the specific effects invasive procedures disappears, indicating the current evidence is

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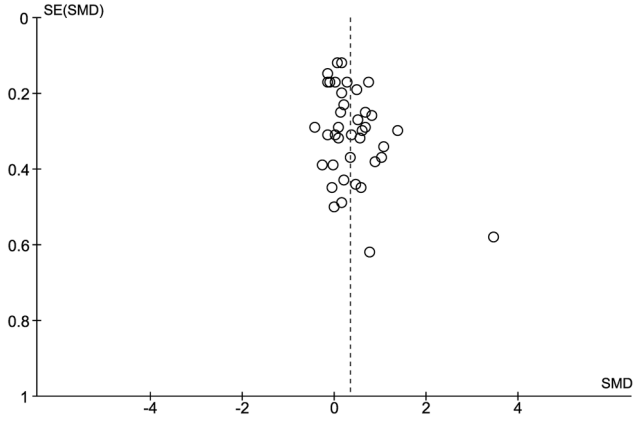

Figure 3 Funnel plot using continuous outcomes (effects of active vs sham treatment) of the 39 studies included in the main meta-analysis.

not strong and could be changed with more and better research. In addition, the contribution of non-specific effects is even more substantial for certain conditions and procedures. While non-specific effects accounted for approximately 65% of the effects from all invasive procedures, they made up to 78% of the active treatment effects in chronic pain conditions and 71% of the active treatment effects in obesity. These percentages are substantially higher than those observed in non-surgical trials, namely 40% for chronic pain conditions and 33% for obesity.[91] The higher contribution of non-specific effects in surgical trials could well be the result of higher placebo effects. However, the lack of no-treatment groups in our data set (and other data set)[92] allows no firm conclusion.[91] Our subgroup analyses indicate that the current evidence does not support the specific efficacy of invasive procedures for chronic pain conditions (p=0.08) and was borderline for obesity (p=0.05), but does support these procedures for GERD (p=0.0002). However, please note that the analysis of dichotomous outcomes showed a somewhat larger specific effect for pain studies (see online supplementary figure 1). There is insufficient data to make recommendations about the other conditions examined.

Strengths and weakness of this study

This study has several limitations. First, both the central strength and limitation of our study is that we pooled effect estimates of the included studies. We consider this a strength at is allows us to: (1) make an estimate of the overall effects of invasive procedures in sham-controlled surgical studies, (2) estimate the strength of confidence in the currently available data as to the specific efficacy of those procedures; and, (3) empirically investigate to what extent results differ between conditions and procedures. Obviously, it is not reasonable to expect that surgery has similar specific effects across conditions and outcomes so our subgroup estimates should not be interpreted clinically without considering how the interventions and outcomes varied. This is also indicated by the moderate-to-large heterogeneity in our meta-analyses, indicating more variation of effect sizes than would be expected by chance. Second, it is difficult to fully double-blind invasive procedures. While most studies successfully blinded patients and outcome assessors, physicians doing these procedures could not be blinded. Thus, it is possible that they communicated information to patients that biased the studies. Price and others have shown that physician expectations can influence pain outcomes even when restrictions are placed on verbal communication.[93 94] Third, publication bias may play a role in the accuracy of our estimates. It is known that negative studies (in this case, studies showing no difference between real and sham procedures) are not published as frequently as positive studies. However, our search strategy was comprehensive and the study selection process was reliable. We also conducted a thorough search of the grey literature, as described above, and had input by experts in placebo research, increasing the likelihood of capturing all studies in this area. This activity allowed for a cross-check in the end to ensure we captured most of the relevant published randomised controlled trials for this review. We did not find any unpublished reports that met our inclusion criteria appropriate for this review, however there were some publications that were not readily accessible through the search engines commonly accessed that we were able to

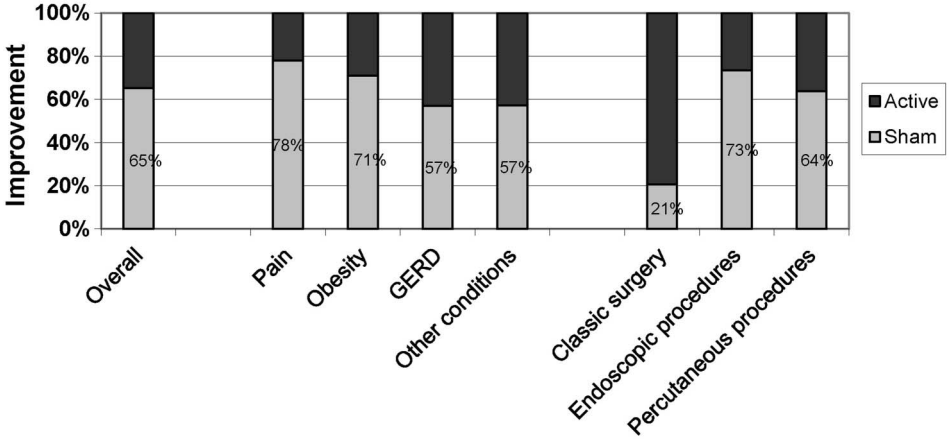

Figure 4 Relative contribution to improvement in the placebo and active treatment groups.

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capture through these methods. Our sensitivity analyses on study quality factors did not change our primary findings, except restricting the analyses to large studies with 100 participants and above, revealed a considerably smaller, non-significant SMD at 0.15 (95% CI −0.02 to 0.32; p=0.09). Egger's test for funnel plot asymmetry, however, suggested a small study bias in our data set. While our combined estimates of effect size must be considered crude for the overall meta-analysis, they are reasonable estimates for the pain, GERD and obesity subgroups. Meta-analyses of placebo-controlled drug studies in pain, depression, hypertension, ulcer treatment and other areas often report a similar magnitude of specific treatment effects compared to non-specific effects.[95–98] Those studies, however, usually have much larger sample sizes, increasing confidence in their estimates. Finally, we found only one three-armed study that included no treatment, active and sham groups.[67] Therefore, it is not possible to estimate the contribution that the ritual and context make to outcomes in invasive procedures compared to no treatment. Especially in the field of pain and obesity such three-armed studies would seem to be essential for making good evidence-based decisions.

Our findings are consistent with a systematic review published in the *BMJ* in 2014.[92] That study, however, used vote count and reported that 74% of 55 trials showed improvement in the placebo arm with 51% reporting no difference between surgery and placebo and 49% reporting surgery was superior to placebo. We have built on that study by doing a more comprehensive literature search and meta-analysis which allowed us to estimate the magnitude of surgical effects, the confidence in the current findings and to examine that magnitude across various quality parameters, conditions, procedures and outcomes. We can now conclude that at least chronic pain conditions lack clear evidence for the efficacy of the explored surgical interventions (eg, classic surgery and endoscopic procedures. Since these conditions represent a high public health burden worldwide we need to obtain better evidence for the use of these procedures. In addition, it is clear that the evidence from placebo controlled trials in the field as a whole is poor.

Implications for practice, research and policy

These results have a number of implications for practice, research and policy. The evidence from available sham-controlled trials indicates that invasive procedures are not clearly more effective than sham procedures for various chronic pain conditions including endometriosis, back pain, arthritis, angina and migraine. There is evidence to support surgical interventions for GERD and limited evidence to support the use of balloon insertion for obesity.

Given the large number of invasive and surgical procedures being performed, it is noteworthy that we could identify only 55 sham-controlled studies in the literature. Certainly, not all invasive procedures warrant sham-controlled comparisons; for example, when results demonstrate indisputable changes in objective parameters the risks of sham procedures would be excessive. However, given that non-specific factors make a large contribution to the effects from invasive procedures for conditions like pain, more rigorous evaluation is needed before their widespread use is recommended for these conditions. A recent survey of surgeon's attitudes about sham surgery may provide an opportunity to conduct more such research. Surgeons generally agreed that a placebo component to surgical intervention might exist.[99] Furthermore, results of a recent systematic review indicate that the risks of adverse effects associated with sham surgical procedures are small.[92] Thus, more well-designed sham-controlled surgical trials are warranted to avoid the continued use of ineffective invasive treatments.

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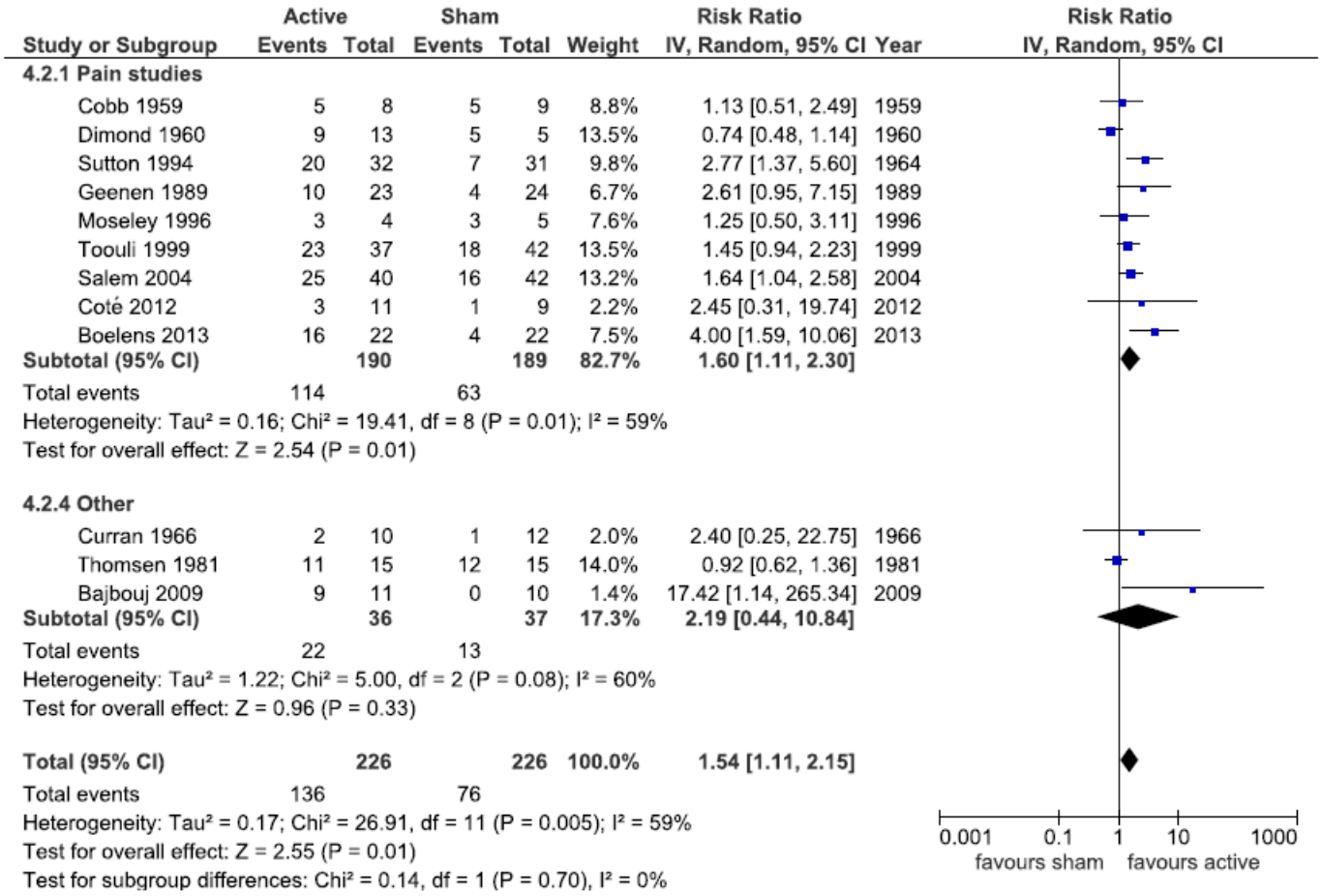
Supplemental Figure 1. Meta-analysis of dichotomous outcomes from 12 studies that provided no continuous outcome



Online Supplemental Material

Supplemental Table 1. Characteristics of Included Studies

Source	Condition	N Total Entered (Treatment/ Control)	Treatment	Sham Treatment	Concealment	Outcome for Main Analysis	Author Conclusions
PAIN							
Sutton et al,1994[46] Sutton et al,1997[45]	endometriosis	T32/ C 31	laprasocopic laser treatment of endometriosis	diagnostic laparoscopy with three incisions in the same locations as the active treatment and the removal of the serosanguinous fluid from the Pouch of Douglas to perform an inspection of the pelvic peritoneum	Unclear	patients with pain improvement at 6 months ‡	(+)
Abbott et al, 2004[42]	endometriosis	T 20/ C 19	laparoscopic excision of endometriosis tissues	diagnostic laparoscopic procedure with no laparoscopic excision of endometriosis tissues -(delayed surgery)	Adequate	overall pain reduction at 6 months †	(+)
Jarrell et al,2005[44] Jarrell et al, 2007[43]	endometriosis	T 8/ C 7	laparoscopy biopsy and excision	three incisions and a biopsy but no tissue excision	Adequate	§	(+)
Leclaire et al, 2001[27]	low back pain (> 3 months)	T 36/ C 34	percutaneous radiofrequency articular denervation done under fluoroscopic guidance	the same procedure without denervation	Adequate	change of Roland-Morris questionnaire score at 12 weeks *	0

Van Kleef et al, 1999[29]	chronic low back pain	T 15/ C 16	radiofrequency lumbar facet denervation (60-second radiofrequency lesion at 80 C of the medial branch of the posterior primary ramus of the segmental nerves L3–L5 on one or on both sides)	sham denervation where electrodes were introduced as in the active treatment but no radiofrequency lesion was made	Unclear	VAS pain score at 8 weeks †	(+)
Nath et al, 2008[28]	chronic low back pain	T 20/ C 20	percutaneous radiofrequency neurotomy	identical procedure except no current was used and the electrode tip remained at body temperature	Unclear	global improvement for back pain according to VAS at 6 months †	(+)
Freeman et al, 2005[26]	chronic discogenic low back pain	T 38/ C 19	positioning of IDET catheter and delivering of electrothermal energy	positioning of the IDET catheter without delivering electrothermal energy	Unclear	Low back pain outcome score (LBOS) at 6 months †	0
Buchbinder et al, 2009[12]	painful osteoporotic vertebral fractures	T 38/ C 40	vertebroplasty	same procedures up to the insertion of the 13-gauge needle to rest on the lamina. The central sharp stylet was then replaced with a blunt stylet. To simulate vertebroplasty, the vertebral body was gently tapped, and polymethylmethacrylate was prepared so that its smell permeated the room.	Adequate	overall pain score at 3 months *	0

Kallmes et al, 2009[13]	painful osteoporotic vertebral fractures	T 68/ C 63	vertebroplasty	simulated procedure without cement where methacrylate monomer was opened to simulate the odor associated with PMMA mixing but needles were not placed nor PMMA infused	Adequate	RDQ (Roland-Morris disability score) at 1 month †	0
Patel et al, 2012[30]	chronic sacroiliac joint pain	T 34/ C 17	lateral branch neurotomy using cooled radiofrequency	sham neurotomy where the treatment was identical, except that radiofrequency energy was not delivered.	Unclear	comparison of mean change from baseline in NRS pain score between treatment and sham groups at the 3-month follow-up time-point *	(+)
Cobb, 1959[34]	angina pectoris	T 8/ C 9	ligation of the internal mammary arteries after they had been isolated	sham ligation of the internal mammary arteries after they had been isolated	Unclear	subjective improvement in angina >40% ‡	0
Dimond, 1960[35]	angina pectoris	not stated	ligation of internal mammary artery	sham ligation (skin incision with exposure of the internal mammary arteries with no ligation)	Unclear	>=50% subjective improvement ‡	0
Salem et al, 2004[38] Salem et al, 2005[37]	angina pectoris	T 40/ C 42	Percutaneous Myocardial Laser Revascularization (PMLR) plus optimal medical therapy	sham procedure involving the laser catheter being inserted but connected to a hidden lead box plus optimal medical therapy	Adequate	mean Canadian Cardiovascular Society angina (CCS) class at 12 months ‡	(+)

Leon,et al, 2005[36]	angina pectoris	T 196/ C 102	Biosense direct myocardial revascularization (DMR) with laser catheter introduced and advanced to the left ventricular (LV)	the laser (already in the room) was turned on but no further procedure was performed	Unclear	exercise treadmill duration at 6 months *	0
Moseley et al, 1996[32]	arthritis	Lavage: 3/ Debribement: 2/ C 5	arthroscopic débridement or arthroscopic lavage	patients undergoing placebo arthroscopy were prepared, draped, examined, and injected with local anesthetic in the same manner as the other two groups. Three stab wounds were made in the skin with a scalpel, but no instruments of any kind were placed into the knee	Unclear	a "strongly agree" response to question "Do you feel the operation was worthwhile?" ‡	(-)
Moseley et al, 2002[11]	arthritis	Lavage: 61/ Debribement: 59/ C 60	arthroscopic débridement or arthroscopic lavage	as described above	Adequate	KSPS (knee-specific pain scale) at 24 months *	0
Bradley et al, 2002[31]	arthritis	T 89/ C 91	arthroscopic knee irridation	sham irridation (needle was advanced to, but not through, the joint capsule)	Unclear	WOMAC function score (Western Ontario and McMaster Universities Osteoarthritis Index) at 52 weeks †	(-)
Sihvonen et al., 2013[33]	arthritis	T 70/ C 76	arthroscopic partial meniscectomy	a standard arthroscopic partial meniscectomy was simulated with sham surgery	Adequate	the Lysholm knee score at 12 mos after surgery *	0
Dowson et al, 2008[49]	migraine with aura	T 74/ C 73	Patent foramen ovale (PFO) closure with the STARFlex septal repair implant	a sham procedure (skin incision in the groin only)	Adequate	migraine attacks/month at 4-6 months †	0

Guyuron et al, 2009[50]	migraine headache	T 49/ C 26	Surgery in the predominant trigger sites (frontal (F), temporal (T) and occipital (O)) with endoscopic removal of the glabellar muscles encasing the supraorbital and supratrochlear nerves, removal of a segment of the zygomaticotemporal branch of the trigeminal nerve, and removal of the greater occipital nerve	sham surgery with exposure of the muscles and nerves through a similar incision but the integrity of the structures was maintained	Adequate	change in frequency of migraine attacks at 12 months †	(+)
Geenen et al, 1989[47]	cholia	T 23/ C 24	endoscopic sphincterotomy	sham sphincterotomy was performed exactly as was the true sphincterotomy except that the sphincterotome was positioned in the duodenal lumen during activation of the electrocautery unit	Unclear	patients with "good" symptom scores at 12 months ‡	(+)
Toouli et al, 2000[48]	cholia	SO stenosis: Sham 13/ Endoscopic sphinctectomy (ES) 13/ SO dyskinesia: sham 10/ ES 11/ Normal manometry: Sham 19/ ES 13	endoscopic sphinctectomy (ES)	endoscopy with introduction of a papillotome into the duodenum after which the "noises" of sphincterotomy were created	Unclear	improvement in abdominal pain at 24 months ‡	(+)

Cote et al, 2012[39]	painful pancreatic sphincter dysfunction	T 11/ C 9	biliary endoscopic sphincterotomy (BES)	sham endoscopy (not described)	Adequate	patients with two or more distinct episodes of acute pancreatitis at follow up evaluation ‡	0
Boelens et al, 2013[40]	painful anterior cutaneous nerve entrapment syndrome	T 22/ C 22	Neurectomy of the intercostal nerve endings at the level of the abdominal wall	Sham surgery with the exposure to the abdominal wall and then closed with no further surgical procedure	Adequate	patients achieving a minimal 50% improvement in pain perception measured using a VAS ‡	(+)
Swank et al, 2003[41]	chronic abdominal pain and adhesions	T 52/ C 48	Laparoscopic adhesiolysis	diagnostic laparoscopy only	Adequate	pain relief after one year using a VAS *	0
Davys et al, 2005[83]	plantar callosities in rheumatoid arthritis	T 19/ C 19	normal callus treatment (NCT) comprised of sharp scalpel debridement of the callosity	NCT was simulated by the podiatrist using a bluntedged scalpel such that no callus tissue was debrided	Adequate	forefoot pain §	0
Obesity							
Lindor et al, 1987[53]	obesity	T 11/ C11	intragastric balloon placed	an empty introducer tube was inserted, its position was confirmed fluoroscopically and 200 ml of air was pumped into the stomach	Unclear	weight loss at 2-3 months †	0
Meshkinpour et al, 1988[60]	obesity	T 21/ C 21	the Garren-Edwards gastric bubble inserted	insertion of an unloaded introducer tube after having modified the slit and simulation of the bubble inflation process	Unclear	weight loss at 12 weeks †	0

Mathus-Vliegen et al, 1990[55]	obesity	T 14/ C 14	four treatment combinations were compared: group A: balloon-sham; group B: sham-balloon; group C balloon-balloon; and group D: sham-sham. the treatment included two periods of each of balloon or sham therapy for 4 months	sham groups involved insertion of a balloon where the balloon was empty	Unclear	weight loss at 1-17 weeks †	0
Rigaud et al, 1995[61]	obesity	T 11/ C 9	endoscopic air filled balloon insertion	sham involved empty balloon insersion	Unclear	weight †	0
Mathus-Vliegen et al, 1996[59]	obesity	T 8/ C 9	endoscopic balloon insertion	empty balloon insertion	Unclear	weight at 4 months †	0
Mathus-Vliegen et al, 2002[56]	obesity	T 20/ C 23	endoscopic balloon insertion	empty balloon insertion	Unclear	weight at 13 weeks †	0
Mathus-Vliegen et al, 2003[58]	obesity	T 11/ C 17	endoscopic balloon insertion	empty balloon insertion	Unclear	weight at 13 weeks †	0
Genco et al, 2006[51]	obesity	T 16/ C 16	endoscopic balloon insertion	endoscopic examination in sedated patients but no balloon insertion in the first 3 months of treatment	Unclear	body mass index †	(+)
Gersin et al, 2010[52]	obesity	T 21/ C 26	endoscopic insertion of a duodenojejunal bypass liner (DJBL)	conscious sedation during which an EGD and a mock procedure were performed	Unclear	percentage of excess weight loss at 12 weeks *	(+)

Mathus-Vliegen et al, 2005[57]	treatment-resistant obesity	T 12/ C 21	the placement assembly consisted of a sheath with the collapsed balloon and a balloon fill tube	the collapsed balloon was not present in the assembly but otherwise mimicked the balloon procedure	Adequate	§	0
Martinez-Brocca et al, 2007[54]	treatment-resistant obesity	T 11/ C 11	endoscopic balloon insertion	insertion of a deflated balloon	Unclear	weight at 12 weeks †	(+)
GERD							
Corley et al, 2003[62]	GERD	T 35/ C 29	radiofrequency energy delivery to the gastroesophageal junction at each deployment position	balloon inflation at each deployment position without needle deployment or energy delivery	Adequate	heartburn score at 6 months †	(+)
Deviere et al, 2005[63]	GERD	T 32/ C 32	endoscopic implantation of a biocompatible nonresorbable copolymer	diagnosic upper endoscopy only endoscopy	Adequate	GERD-HRQL heartburn score reduction at 3 months †	(+)
Montgomery et al, 2006[64]	GERD	T 22/ C 24	gastric plication with endoscopical placement of two to four sutures	endoscopy with patient anaesthetized for approximately 40 min (corresponding to the time needed to perform the real procedure)	Adequate	GSRS gastrointestinal symptom rating scale at 3 months †	0

Rothstein et al, 2006[65]	GERD	T 72/ C 72	gastric plication with endoscopical placement of one sutures	The sham procedure mimicked the treatment procedure through the positioning of the plicator but with no sutures placed	Adequate	GERD-HRQL (health-related quality of life) at 3 months †	(+)
Schwartz et al, 2007[66]	GERD	T 20/ C 20	endoscopic gastroplication along the lesser curvature and greater curvatures	the sham procedure was carried out using the same equipment, but without the suturing needle and thread loaded	Adequate	heartburn score at 3 months †	(+)
Parkinson's							
Freed et al, 2001[67] Nakamura et al, 2001[72] Greene et al, 2002[69] McRae et al, 2003[70] McRae et al, 2004[71] Gordon et al, 2004[68]	parkinson's disease	T 20/ C 20	deep brain implantation of embryonic dopamine neurons	identical procedure except that the dura mater was not penetrated after the twist-drill holes had been made in the frontal bone	Unclear	§	0
Olanow et al, 2003[73]	parkinson's disease	T 23/ C 11	bilateral fetal nigral transplantation into the brain	treated in an identical manner except that partial burr holes that did not penetrate the inner table of the skull, no needles were inserted and no tissue was implanted	Unclear	UPDRS motor score (Unified Parkinson's Disease Rating Scale) at 24 months *	0
Other							

Curran, 1966[80] Curran, 1971[79]	asthma	T 10/ C 13	standard glomectomy procedure	sham glomectomy in which the carotid bifurcation was only exposed and subcutaneous tissue was sent to the pathologist	Unclear	physician's opinion of "definite" improvement at 6 months ‡	0
Thomsen et al, 1983[86] Bretlau et al, 1984[82] Thomsen,1981 [85] Thomsen,1986 [87]	meniere's disease	T 15/ C 15	regular endolymphatic sac shunt operation with insertion of silastic into the sac draining out into the mastoid cavity	mastoidectomy with care was taken not to remove the bone over the endolymphatic sac in order to avoid a decompression	Unclear	investigator's evaluation of operative effect: "good effect" at 12 months ‡	(-)
Winters, 1984[88]	dialated esophagus	T 8/ C 8	bougienage (dilatation of esophagus) with a 54 F bougie	sham bougienage using a 24 F bougie	Unclear	chest pain score at 2 weeks †	0
Larson et al, 1998[84]	Benign Prostatic Hyperplasia (BPH)	T 125/ C 44	high efficiency microwave thermoablation	same procedure except without microwave power and coolant temperature was increased in increments from 8 to 20°C over the same time period as in the microwave group	Unclear	AUA score (American urological association) at 6 months †	(+)
Slusser et al, 1998[77]	dry eye	T 28/ C 28	Herrick lacrimal plugs were inserted into both canaliculi of one previously randomized eye	manipulation of eye without insertion of Herrick lacrimal plugs	Unclear	subjective dryness of eye (VAS) at 5 weeks †	(+)
Geldis et al, 2008[76]	dry eye	T 19/ C 19	insertion of punctal plug	tissue manipulation producing the same sensation to the eye with no plug insersion	Unclear	contact lens dry eye questionnaire (CLDEQ) score at 6 weeks †	0

Friedman et al, 2008[74]	sleep apnea	T 31/ C 31	palatal implant insertion	identical procedure with no insertion of palatal implants	Adequate	reduction in AHI (apnoea/hypopnoea index) at 95 days *	(+)
Koutsourelakis et al, 2008[75]	sleep apnea	T 27/ C 22	standard submucosal resection of the nasal septum	nasal tissue manipulation simulating the operation but with no resection of the nasal septum	Unclear	reduction in AHI (apnoea/hypopnoea index) at 3-4 months †	0
Bajbouj et al, 2009[81]	globus	T 11/ C 10	endoscopy performed and APC therapy applied	after endoscopy, patients were connected with APC applicator but current flow was disconnected as soon as patients were asleep	Adequate	patients with overall symptom improvement (yes or no) at 3 months ‡	(+)
Castro et al., 2009[79]	asthma	T 190/ C98	bronchoscopy with bronchial thermoplasty	bronchoscopy, which mimicked thermal bronchoplasty	Adequate	asthma quality of life (AQLQ) score, average of 6, 9 and 12 weeks †	(+)
Rodriguez et al, 2009[89]	Type II diabetes	T 12/ C 6	endoscopic insertion of a duodenal-jejunal bypass liner (DJBL)	sham endoscopy	Unclear	improvement in glycemic control as measured by HbA1c change from baseline to week 12 *	(+)

* primary main outcome measure used; † most important outcome measure used; ‡ only responder data available, not used in main analysis; § insufficient data to include in meta-analysis

author conclusions: (+) favors intervention, (0) no benefit, (-) favors placebo or "placebo effect noted in author conclusions"

T: real treatment; C: sham control