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Placebo interventions for all clinical conditions (Review)

Hróbjartsson A, Gøtzsche PC

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[Intervention Review]

Placebo interventions for all clinical conditions

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ABSTRACT

Background

Placebo interventions are often claimed to substantially improve patient-reported and observer-reported outcomes in many clinical conditions, but most reports on effects of placebos are based on studies that have not randomised patients to placebo or no treatment. Two previous versions of this review from 2001 and 2004 found that placebo interventions in general did not have clinically important effects, but that there were possible beneficial effects on patient-reported outcomes, especially pain. Since then several relevant trials have been published.

Objectives

Our primary aims were to assess the effect of placebo interventions in general across all clinical conditions, and to investigate the effects of placebo interventions on specific clinical conditions. Our secondary aims were to assess whether the effect of placebo treatments differed for patient-reported and observer-reported outcomes, and to explore other reasons for variations in effect.

Search methods

We searched the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library* Issue 4, 2007), MEDLINE (1966 to March 2008), EMBASE (1980 to March 2008), PsycINFO (1887 to March 2008) and Biological Abstracts (1986 to March 2008). We contacted experts on placebo research, and read references in the included trials.

Selection criteria

We included randomised placebo trials with a no-treatment control group investigating any health problem.

Data collection and analysis

Two authors independently assessed trial quality and extracted data. We contacted study authors for additional information. Trials with binary data were summarised using relative risk (a value of less than 1 indicates a beneficial effect of placebo), and trials with continuous outcomes were summarised using standardised mean difference (a negative value indicates a beneficial effect of placebo).

Main results

Outcome data were available in 202 out of 234 included trials, investigating 60 clinical conditions. We regarded the risk of bias as low in only 16 trials (8%), five of which had binary outcomes.

In 44 studies with binary outcomes (6041 patients), there was moderate heterogeneity ($P < 0.001$; I^2 45%) but no clear difference in effects between small and large trials (symmetrical funnel plot). The overall pooled effect of placebo was a relative risk of 0.93 (95% confidence interval (CI) 0.88 to 0.99). The pooled relative risk for patient-reported outcomes was 0.93 (95% CI 0.86 to 1.00) and for observer-reported outcomes 0.93 (95% CI 0.85 to 1.02). We found no statistically significant effect of placebo interventions in four clinical conditions that had

been investigated in three trials or more: pain, nausea, smoking, and depression, but confidence intervals were wide. The effect on pain varied considerably, even among trials with low risk of bias.

In 158 trials with continuous outcomes (10,525 patients), there was moderate heterogeneity ($P < 0.001$; I^2 42%), and considerable variation in effects between small and large trials (asymmetrical funnel plot). It is therefore a questionable procedure to pool all the trials, and we did so mainly as a basis for exploring causes for heterogeneity. We found an overall effect of placebo treatments, standardised mean difference (SMD) -0.23 (95% CI -0.28 to -0.17). The SMD for patient-reported outcomes was -0.26 (95% CI -0.32 to -0.19), and for observer-reported outcomes, SMD -0.13 (95% CI -0.24 to -0.02). We found an effect on pain, SMD -0.28 (95% CI -0.36 to -0.19)); nausea, SMD -0.25 (-0.46 to -0.04)), asthma (-0.35 (-0.70 to -0.01)), and phobia (SMD -0.63 (95% CI -1.17 to -0.08)). The effect on pain was very variable, also among trials with low risk of bias. Four similarly-designed acupuncture trials conducted by an overlapping group of authors reported large effects (SMD -0.68 (-0.85 to -0.50)) whereas three other pain trials reported low or no effect (SMD -0.13 (-0.28 to 0.03)). The pooled effect on nausea was small, but consistent. The effects on phobia and asthma were very uncertain due to high risk of bias. There was no statistically significant effect of placebo interventions in the seven other clinical conditions investigated in three trials or more: smoking, dementia, depression, obesity, hypertension, insomnia and anxiety, but confidence intervals were wide.

Meta-regression analyses showed that larger effects of placebo interventions were associated with physical placebo interventions (e.g. sham acupuncture), patient-involved outcomes (patient-reported outcomes and observer-reported outcomes involving patient cooperation), small trials, and trials with the explicit purpose of studying placebo. Larger effects of placebo were also found in trials that did not inform patients about the possible placebo intervention.

Authors' conclusions

We did not find that placebo interventions have important clinical effects in general. However, in certain settings placebo interventions can influence patient-reported outcomes, especially pain and nausea, though it is difficult to distinguish patient-reported effects of placebo from biased reporting. The effect on pain varied, even among trials with low risk of bias, from negligible to clinically important. Variations in the effect of placebo were partly explained by variations in how trials were conducted and how patients were informed.

PLAIN LANGUAGE SUMMARY

Placebo interventions for all clinical conditions

Placebo interventions are often claimed to substantially improve many clinical conditions. However, most reports on effects of placebos are based on unreliable studies that have not randomised patients to placebo or no treatment.

We studied the effect of placebo treatments by reviewing 202 trials comparing placebo treatment with no treatment covering 60 healthcare problems. In general, placebo treatments produced no major health benefits, although on average they had a modest effect on outcomes reported by patients, such as pain. However, the effect on pain varied from large to non-existent, even in well-conducted trials. Variations in the effect of placebo was partly explained by variations in how trials were conducted, the type of placebo used, and whether patients were informed that the trial involved placebo.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Effect of placebo interventions across all clinical conditions (main findings)

Outcomes	Effect [1] (95% CI)	No. of participants (studies)	Quality of the evidence	Comments
All clinical conditions (binary outcomes)	RR 0.93 (0.88 to 0.99)	6041 (44)	Moderate	Moderate heterogeneity. No statistically significant differences between patient-reported, and observer-reported binary outcomes. No statistically significant effect on: pain, nausea, smoking or depression [2]. Out of three pain trials with low risk of bias (1109 patients), one German acupuncture trial found a large effect, and two trials found no effect [3].
All clinical conditions (continuous outcomes)	SMD -0.23 (-0.28 to -0.17)	10,525 (158)	Moderate	Moderate heterogeneity. Statistically significant differences between patient-reported, and observer-reported outcomes, SMD -0.26 (-0.32 to -0.19) versus -0.13 (-0.24 to -0.02). Meta-regression explained 54% of the variation in effect [3].
Pain [2] (continuous outcomes)	SMD -0.28 (-0.36 to -0.19)	4154 (60)	Moderate	Moderate heterogeneity. Seven trials (1198 patients) had low risk of bias, but heterogeneity was substantial: four German acupuncture pain trials found large effects, and three other pain trials found negligible effects [3].
Nausea [2] (continuous outcomes)	SMD -0.25 (-0.46 to -0.04)	452 (7)	Moderate	Low heterogeneity. The pooled result for all nausea trials was similar to the pooled result of the two nausea trials with low risk of bias [3].
Depression [2] (continuous outcomes)	SMD -0.25 (-0.55 to 0.05)	324 (8)	Moderate	Moderate heterogeneity. The pooled result for all depression trials was similar to the result of the single depression trial with low risk of bias [3].
Other outcomes [2] (continuous outcomes) Smoking, dementia, obesity, hypertension, insomnia, anxiety, asthma, phobia)	Range of SMD: -0.63 (-1.17 to -0.08) to -0.16 (-0.48 to 0.16)	1317 (41)	Low	There was a statistically significant, but unreliable, effect on asthma and phobia [3].

[1]. RR: relative risk; SMD: standardised mean difference.
[2]. Clinical conditions studied in three trials or more.
[3]. See Additional tables.

BACKGROUND

There has been a widespread belief that placebo interventions have considerable and reliable effects. This view was influenced by the seminal paper 'The Powerful Placebo' (Beecher 1955), which was one of the first attempts to combine results from several randomised trials. Narrative reviews from the 1980s and 1990s similarly concluded that placebo interventions substantially improve both patient-reported and observer-reported outcomes in a large proportion of patients with a wide range of clinical conditions, such as pain, asthma, high blood pressure, and even myocardial infarction (Brown 1998; Lasagna 1986).

However, a careful analysis concluded that Beecher's paper is flawed (Kienle 1997). Most reports on placebo, including Beecher's and the reviews quoted above, have estimated the effect of placebo as the difference before and after treatment in a placebo arm of a randomised trial. Thus, though the information in a loose sense comes from randomised trials, the estimation of the effect is not based on a comparison between patients who have been randomly allocated to a placebo group and to a no-treatment group. Without such a comparison, the effect of a placebo intervention cannot be distinguished from the natural course of the disease, and other factors, for example regression to the mean (the tendency for extreme measurements to be closer to the mean when repeated) (Gøtzsche 1994; Hróbjartsson 2002b). The reported large effect of placebo interventions could therefore, at least in part, be an artefact of inadequate research methods.

There is no formal definition of placebo that most clinicians and researchers agree upon (Gøtzsche 1994; Hróbjartsson 2002b). In clinical trials placebos are generally control treatments with a similar appearance to the study treatments, but without their essential components. It is generally assumed that any effect of a placebo intervention, for instance a sugar pill, is unrelated to its essential component, the sugar, but caused by the special interaction between patient and healthcare provider associated with the treatment ritual. However, the phrase 'placebo' is also sometimes used more broadly to describe, for example, any psychologically-mediated factor that potentially influences health. In this review we evaluate the effect of placebo in its narrow sense, as an intervention, based on trials that randomise patients to a placebo intervention group and to a no-treatment control group.

The two previous versions of this review were published in 2001 (Hróbjartsson 2001) and in 2004 (Hróbjartsson 2004a). Both reviews found that placebo interventions in general do not have clinically important effects, but that there were possible beneficial effects on patient-reported outcomes, especially pain. Since then several relevant trials have been published.

OBJECTIVES

Our primary aims were to assess the effect of placebo interventions in general across all clinical conditions, and to investigate the effects of placebo interventions on specific clinical conditions.

Our secondary aims were to assess whether the effect of placebo treatments differed for patient-reported and observer-reported outcomes, and to explore other reasons for variations in effect

METHODS

Criteria for considering studies for this review

Types of studies

Randomised clinical trials with a placebo group and a no-treatment group were considered for inclusion. Both parallel and crossover trials, in any language, were included, as well as unpublished studies when methodology and results could be accessed in written form.

Trials were excluded if patients were allocated by a quasi-random method, e.g. day of month or date of birth. Trials were also excluded if it was clear that the person who assessed objective outcomes was aware of group assignments, or if the dropout rate exceeded 50%.

Types of participants

Patients with a health problem, defined broadly as any somatic or psychiatric disease or symptom. We also included trials testing the prophylactic effect of placebo in a clinical setting on healthy participants. Trials were excluded if they involved healthy participants who had a condition inflicted upon them, e.g. pain, in a non-clinical, experimental setting, or patients who were paid a fee.

Types of interventions

We pragmatically defined a placebo intervention as any intervention which was clearly labelled a placebo in a trial report (by using the term placebo or an analogous term, e.g. sham, fake, dummy, or non- or unspecific treatment).

Trials were excluded when it was very likely that the alleged placebo intervention had an effect which was not related to the treatment ritual alone (e.g. movement techniques for postoperative pain). The no-treatment control groups consisted of patients who did not receive placebo interventions. We included trials in which both the placebo and no-treatment control groups received the same basic treatment.

Types of outcome measures

One outcome per trial was extracted for the main analyses. We primarily chose the outcome indicated as the main outcome in a trial report (e.g. used for a power calculation). If a main outcome was not clearly indicated we chose the outcome measure we considered most relevant to patients. We preferred patient-reported to observer-reported outcomes, and binary to continuous outcomes because we find such outcomes are generally more relevant to patients. We preferred post-treatment data, since follow-up data may be more prone to bias because of patients leaving the trial and diminution of the effect. Outcomes were not selected based on effect size or statistical significance.

Search methods for identification of studies

The search strategy was based primarily on an electronic search of five databases. The references of all included articles and selected reviews and books on placebo were read systematically for citations of potentially eligible trials. Furthermore, we contacted 28 researchers who had made significant contributions to the field, and asked if they knew of relevant trials.

We searched the following databases:

- The Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library,* Issue 4 2007);
- MEDLINE (1966 to March 2008);
- EMBASE (1980 to March 2008);
- PsycINFO (1887 to March 2008); and
- Biological Abstracts (1986 to March 2008).

The search strategies were developed iteratively based on synonyms of 'placebo', randomised clinical trials', and 'no-treatment'. Our comments under each of the headings explain variations in the search strategy (see Appendix 1).

Data collection and analysis

Reports that described potentially eligible trials were read in full by one author (AH), who excluded all studies that clearly did not comply with the inclusion criteria. Both authors read all other potentially eligible trial reports in full and made a decision on study inclusion independently; any disagreement was resolved by discussion.

We extracted information from the trial reports using a pilot-tested standardised data chart. The decision about which outcome to choose was made by both authors independently, and disagreements were resolved by discussion. All outcomes of each trial were listed. If outcome data were not available, we contacted the trial authors. All binary outcomes events were converted so they represent 'failures' or unsuccessful events. Similarly for continuous outcomes, all scales were converted so that higher scores indicate more intense symptoms.

For trials with binary outcomes we calculated the relative risk (RR) (if less than 1, it indicates a positive effect of the placebo intervention). For trials with continuous outcomes (and with data on ranking scales, for simplicity also called continuous in the following), we calculated the standardised mean difference (SMD) (a negative value indicates a positive effect of the placebo intervention). Trials reporting results measured on an ordinal scale were analysed as if they were continuous. For crossover trials we used data from the first period only. If that was not possible we used the summary data as if they had been derived from a parallel trial. We preferred final values, but used change from baseline if these were the only available data.

As we expected heterogeneity, we calculated the pooled results with random effect models (Mantel-Haenszel method for RRs, and inverse variance method for SMDs). We estimated the degree of heterogeneity using the I^2 test. The I^2 statistic can be interpreted as the proportion of the observed discrepancy in the estimation of the effect, within a group of trials, which cannot be accounted for by random variation (Higgins 2003). All results are reported with 95% confidence intervals and all P values are two-tailed.

We calculated the pooled effect of placebo overall for trials with binary outcomes and for trials with continuous outcomes. We also calculated the pooled effect on separate clinical conditions when they had been studied in three trials or more, and the pooled effect of trials with patient-reported and observer-reported outcomes. The threshold of three trials was chosen pragmatically, inspired by Linde (Linde 1997), in order to reduce the risk of spurious positive or negative findings in single trials. For each trial we plotted the effect by its standard error. The symmetry of such 'funnel plots' was assessed both visually, and formally with Egger's test (Egger 1997), to see if the effect decreased with increasing sample size.

We defined trials with low risk of bias as those fulfilling the following three criteria: adequate concealment of allocation, dropout rate no more than 15%, and inclusion of at least 50 patients. We pre-specified these thresholds based on a pragmatic intention of providing a simple risk of bias assessment in a review with many trials. The role of trial size is debated, but was included because small trials are often more poorly conducted than larger trials.

To study whether specific subgroups of trials reported higher or lower effects of placebo we compared two or more subgroups, with tests of interaction, involving the following 14 factors:

1. Type of placebo: i) pharmacological placebo, e.g. a pill; versus. ii) physical placebo, e.g. a machine without current; versus iii) psychological placebo, e.g. a neutral conversation.
2. Type of outcome: i) patient-reported outcomes essentially private to a patient, e.g. pain; versus ii) patient-reported outcomes potentially observable by another person at the time they occurred, e.g. haematuria; versus iii) observer-reported outcomes dependent on the cooperation of a patient, e.g. measurement of forced expiratory volume); versus iv) observer-reported outcomes not dependent on patient cooperation, e.g. assessment of oedema); versus v) observer-reported outcomes in the form of laboratory data, e.g. blood sugar.
3. Placebo as add-on treatment: i) placebo treatment was the only intervention; versus ii) placebo treatment was an add-on treatment to a basic care treatment, also given to the patients in the no-treatment control group.
4. Dropout rate: i) the dropout rate exceeded 15% or was not reported; versus ii) the dropout rate was 15% or lower.
5. Blinding of observer: i) the trial report stated explicitly that the data collector of an observer-reported outcome was blinded; versus ii) the trial report did not state this explicitly.
6. Blinding of patients and treatment providers: i) placebo and active experimental groups were compared in a ‘double-blind’ design; versus ii) that was not the case, or not stated.
7. The trial’s objective: i) the trial report stated explicitly that the objective was to assess the effect of placebo treatment; versus ii) no such explicit objective was stated.
8. Concealment of allocation: i) the allocation of patients was clearly concealed; versus ii) the allocation of patients was not clearly concealed.
9. Type of distribution: i) clear signs of a non-Gaussian distribution, or of a difference in variance between the placebo and the no-treatment groups; versus ii) no such signs. We regarded it a clear sign of a non-Gaussian distribution when 1.64 standard deviations exceeded the mean of naturally positive outcomes (CCC Stat Pol 1999). A difference in variance was assessed using F tests.
10. Reporting of a primary outcome: i) clear indication of a primary outcome in the trial report; versus ii) no clear indication of a primary outcome (in which case we decided which outcome to extract).
11. Sample size: i) the analysis involved at least 50 patients; versus ii) the analysis involved less than 50 patients.

12. Risk of bias: i) clearly concealed allocation of patients, and dropout rate of 15% or lower, and sample size of at least 50 patients; versus ii) those criteria not fulfilled.
13. Information to patients: i) patients were not informed that the trial involved a placebo intervention (instead they were informed that the trial compared two active interventions with a control group); versus ii) the trial report was unclear on this point, or stated that patients were aware that the trial involved a placebo intervention.
14. Format of outcome: Final values versus change from baseline.

Subgroup analyses 1-12 were pre-specified before we started searching for trials for the present update. Subgroup analyses 13 and 14 were post-hoc (see Discussion).

We furthermore conducted supplementary meta-regression analyses involving the trials with continuous outcomes. We specified 11 co-variates: the factors involved in subgroup analysis 1-4, 6-10, and 13, as well as trial precision (1/SE). For the meta-regression we modified our initial categorisations in two cases. Type of placebo (pharmacological, psychological or physical) was redefined as a binary co-variate: physical placebo; versus not. Similarly, type of outcome was dichotomised so that we analysed patient-involved outcomes (patient-reported outcomes and observer-reported outcomes involving patient cooperation); versus not. The meta-regression analyses involved: a) multiple meta-regression with all 11 covariates, and b) multiple meta-regression with stepwise elimination of the co-variate with the highest P value until the analysis only included co-variates with $P < 0.05$.

RESULTS

Description of studies

The search strategy (Appendix 1) identified 1215 potentially eligible trial reports. We excluded 620 non-clinical or non-randomised trials, 252 without a placebo or a no-treatment group, 35 duplicate publications and 11 with clearly unblinded assessment of observer-reported outcomes. A further 63 trials were excluded for other reasons, e.g. dropout rates over 50%.

Thus, we included 234 trials. In 29 trials we were unable to extract relevant outcome data, and three trials involved assessment of harm. The main meta-analyses therefore included 202 trials.

There were 18 crossover trials of which 12 (330 patients) were handled as parallel trials. In 196 trials there was a third active treatment group in addition to the placebo and the no-treatment groups. In 164 of these trials, the effect of placebo was not mentioned as an objective of the study. The trial reports were published in five languages between 1946 and 2008.

Outcomes were binary in 44 trials, and continuous in 158. Counting only patients in the placebo and no-treatment groups, the trials with binary outcomes included 6041 patients, and had a median size of 54 patients (10 and 90 percentiles: 20 and 618); the trials with continuous outcomes included 10,525 patients and had a median size of 40 (10 and 90 percentiles: 18 and 149).

The typical pharmacological placebo intervention was a lactose tablet. The typical physical placebo implied a machine turned off, e.g. sham transcutaneous electrical nerve stimulation. The typical psychological placebo was a non-directional, neutral discussion between patient and treatment provider, a so-called 'attention placebo'. No-treatment typically implied 'observation only' or 'standard therapy'. In the latter case all patients received standard therapy, and the placebo intervention was an additional treatment.

The trials investigated 60 clinical conditions: alcohol abuse, allergy, anaemia, anxiety, aphtous ulcers, asthma, attention-deficit-hyperactivity disorder, bacterial infections, benign prostatic hyperplasia, blood donation reactions, breathlessness, bulimia nervosa, carpal tunnel syndrome, compulsive nail biting, dementia, depression, dermatitis, difficulty of colonoscopy, diabetes, dry eye, enuresis, epilepsy, faecal soiling, fatigue, gag reflex, herpes simplex infection, irritable bowel syndrome, hypercholesterolaemia, hyperglycaemia, hypertension, ileus, infertility, insomnia, insufficient cervical dilatation, jet lag, labour, marital discord, menopause, mental handicap, orgasmic difficulties, overweight, procedural discomfort during bronchoscopy, upper respiratory infection, venous ulcers, vitiligo, pain, nausea, Parkinson's disease, patient involvement in adolescent diabetic care, phobia, physical activity, poor oral hygiene, Raynaud's disease, schizophrenia, seasickness, secondary erectile dysfunction, smoking, stress related to dental treatment, treatment adherence, or undiagnosed ailments.

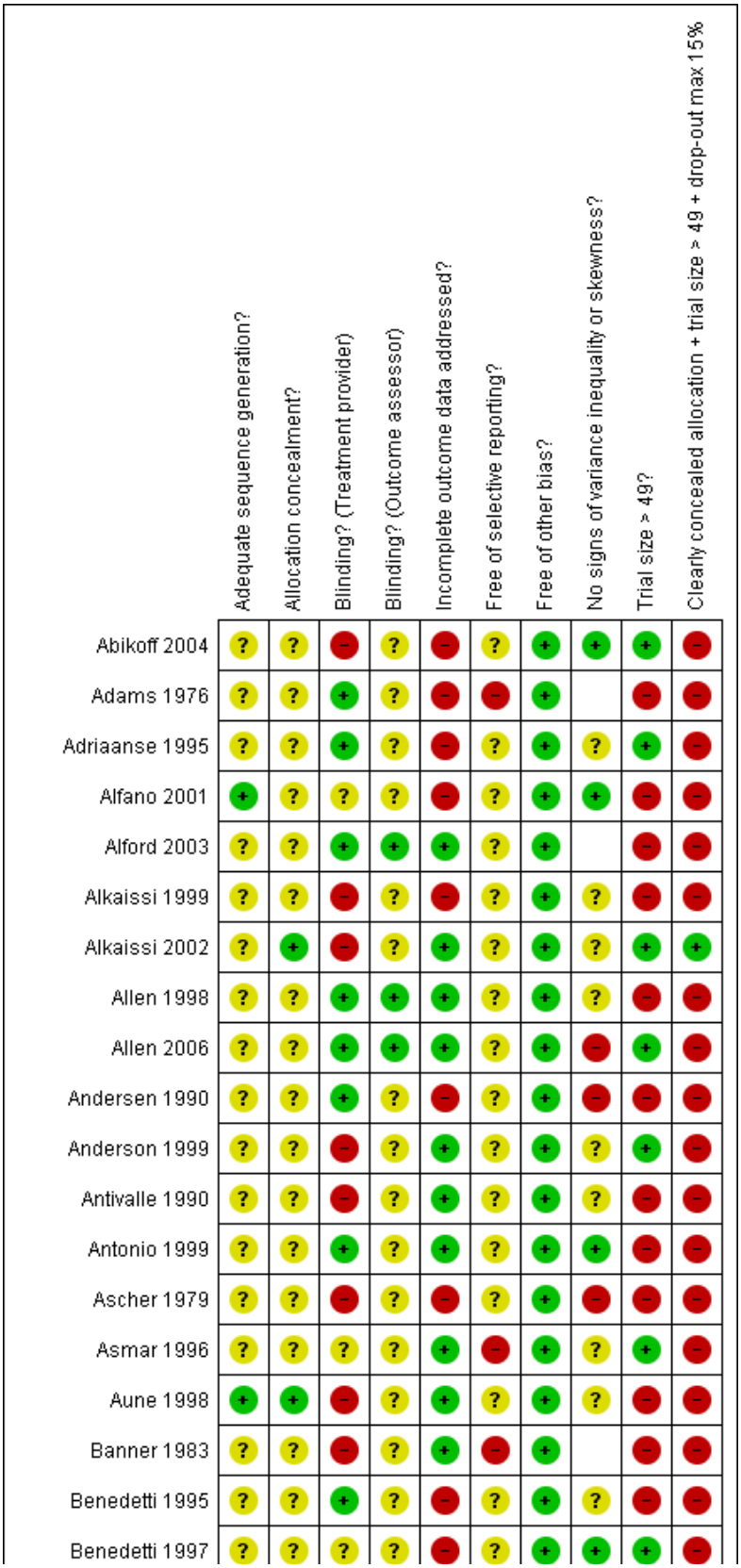
Five trials call for special attention (Brinkhaus 2006; Linde 2005; Melchart 2005; Witt 2005; Scharf 2006).The trials all studied the effect of acupuncture on pain. They were conducted in Germany, published between 2005 and 2007, had a very similar design, and four of the five trials had overlapping authors. In the following they are called 'the German acupuncture trials'. They studied the effect of 6 to 8 weeks of acupuncture and placebo acupuncture on osteoarthritis pain, low back pain, migraine, and tension type headache. The trials were medium-sized to large, their allocation concealment adequate and dropouts were below 15%. They reported substantial effects of placebo acupuncture, SMDs ranged from -0.56 to -0.82, and the single trial with a binary outcome reported an RR of 0.69. They differed from other trials in that they combined low risk of bias with large effects.

A more detailed description of the studies can be seen in the Characteristics of included studies table.

Risk of bias in included studies

The methodological quality of the trials was generally mediocre, but quite variable (Figure 1; Figure 2).

Figure 1. Methodological quality summary: review authors' judgments about each methodological quality item for each included study.



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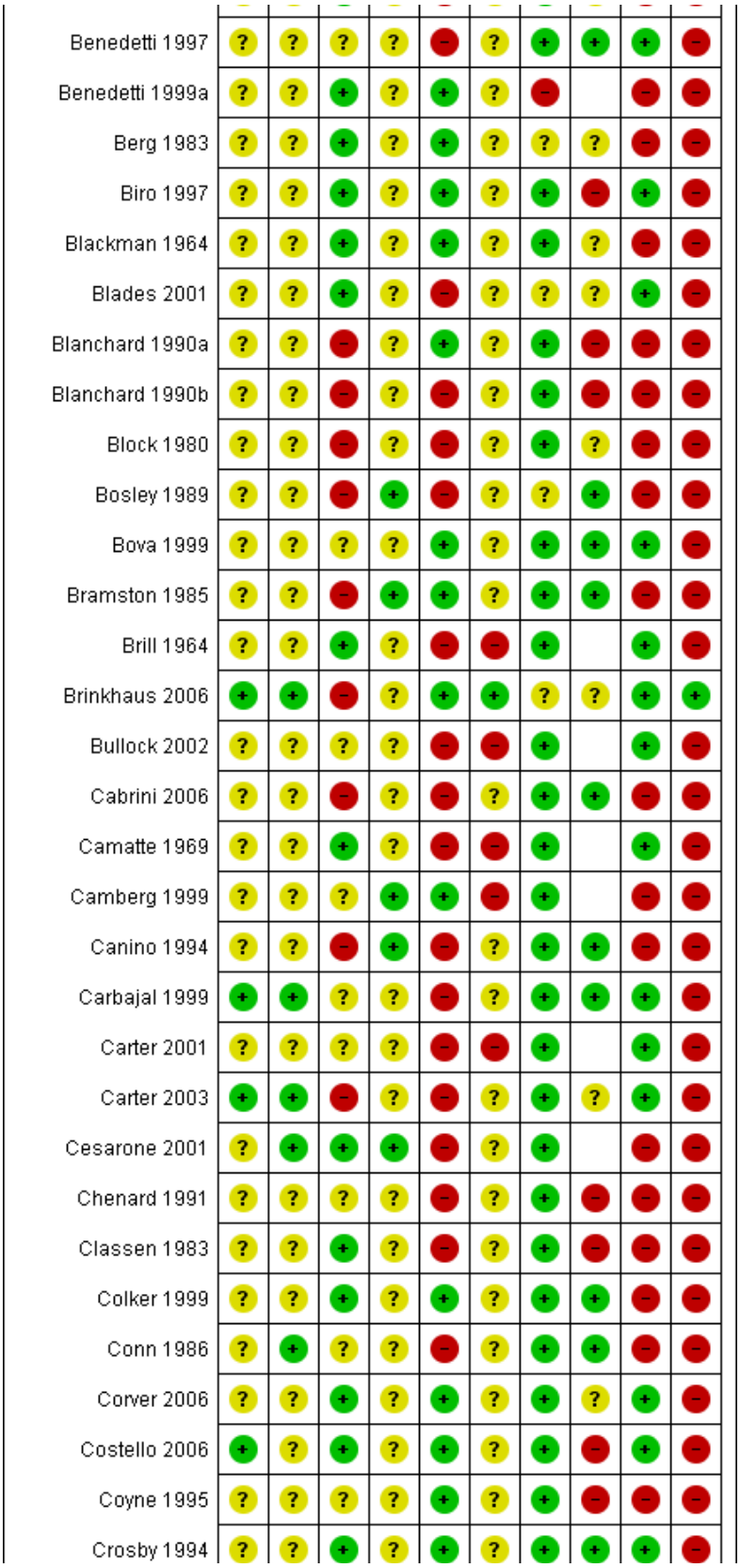

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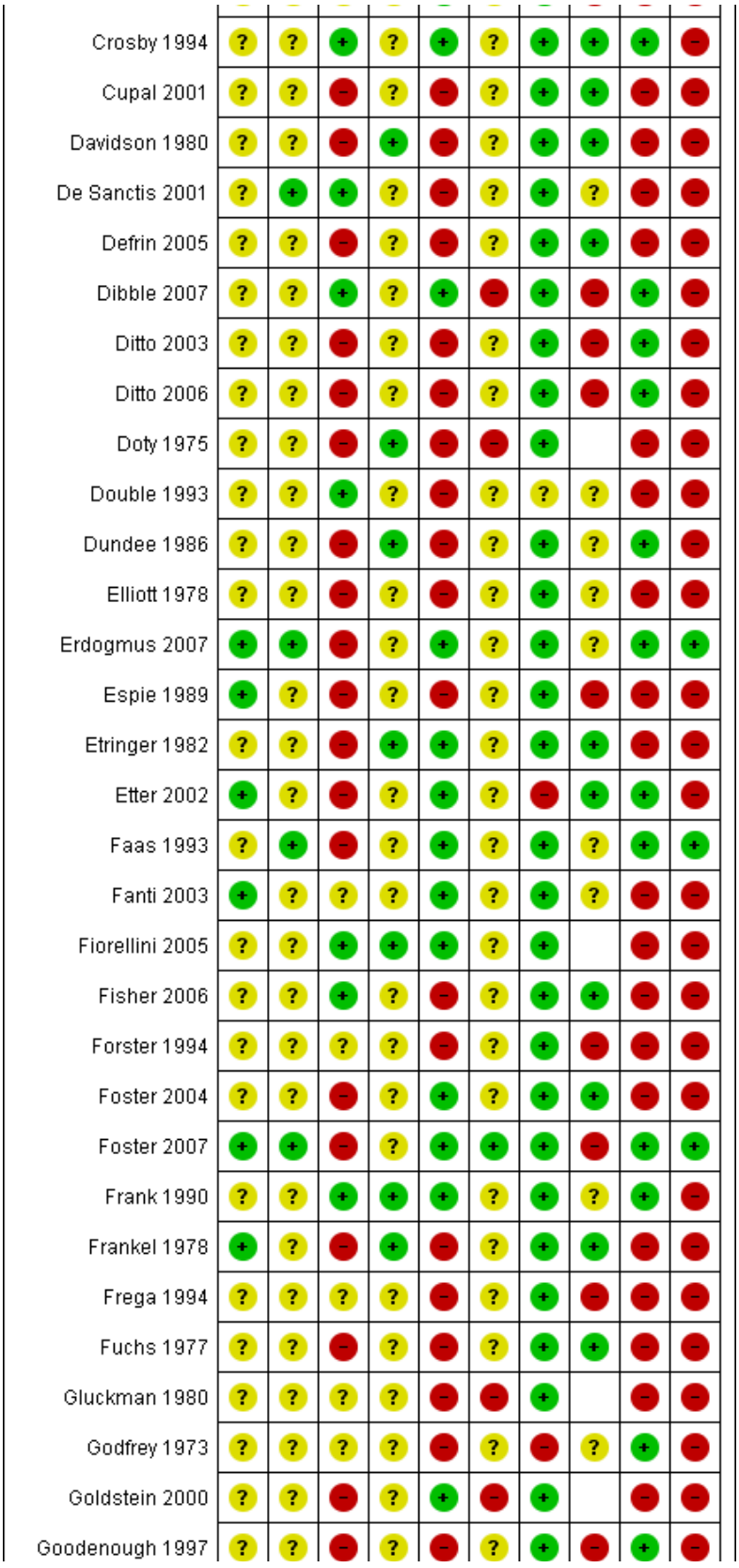

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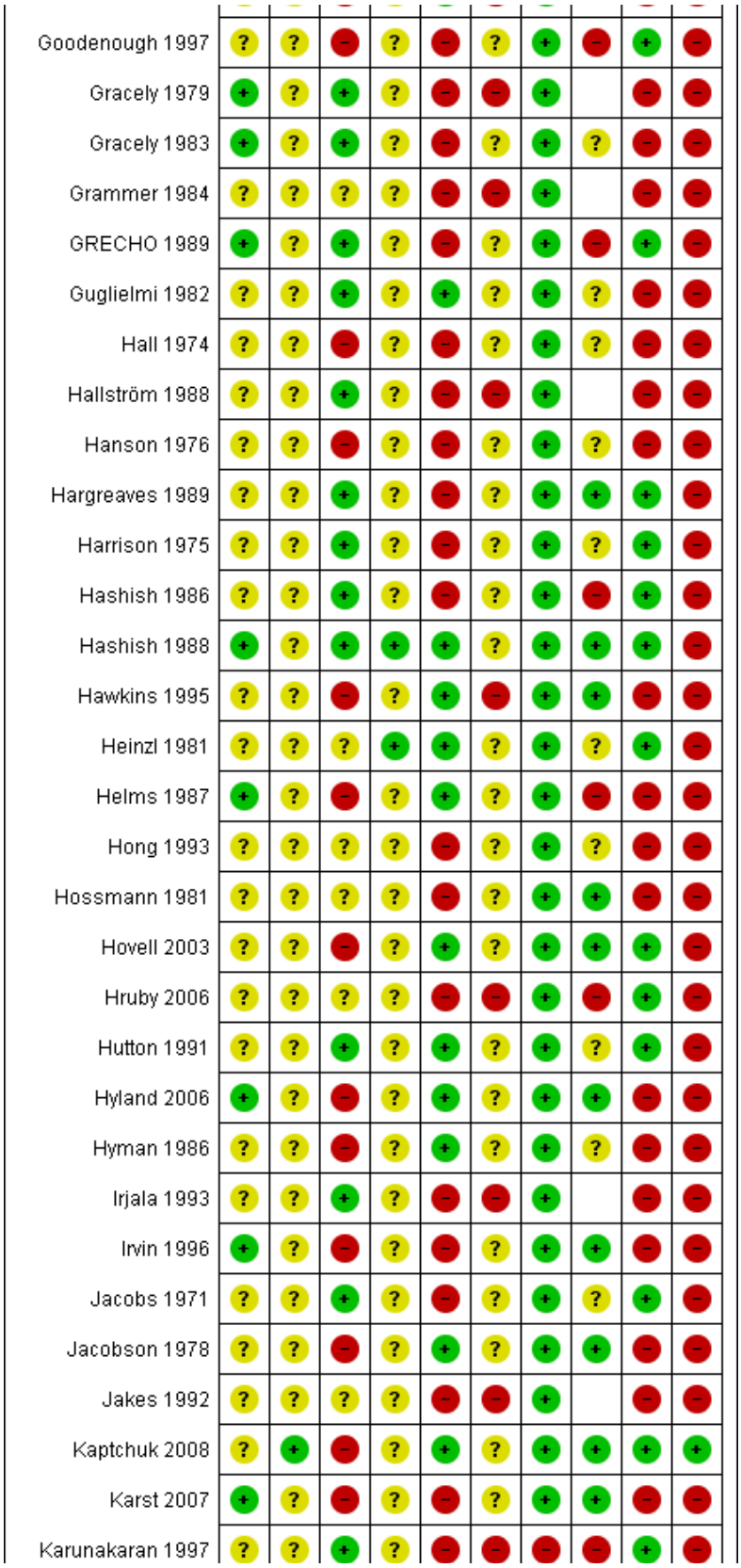

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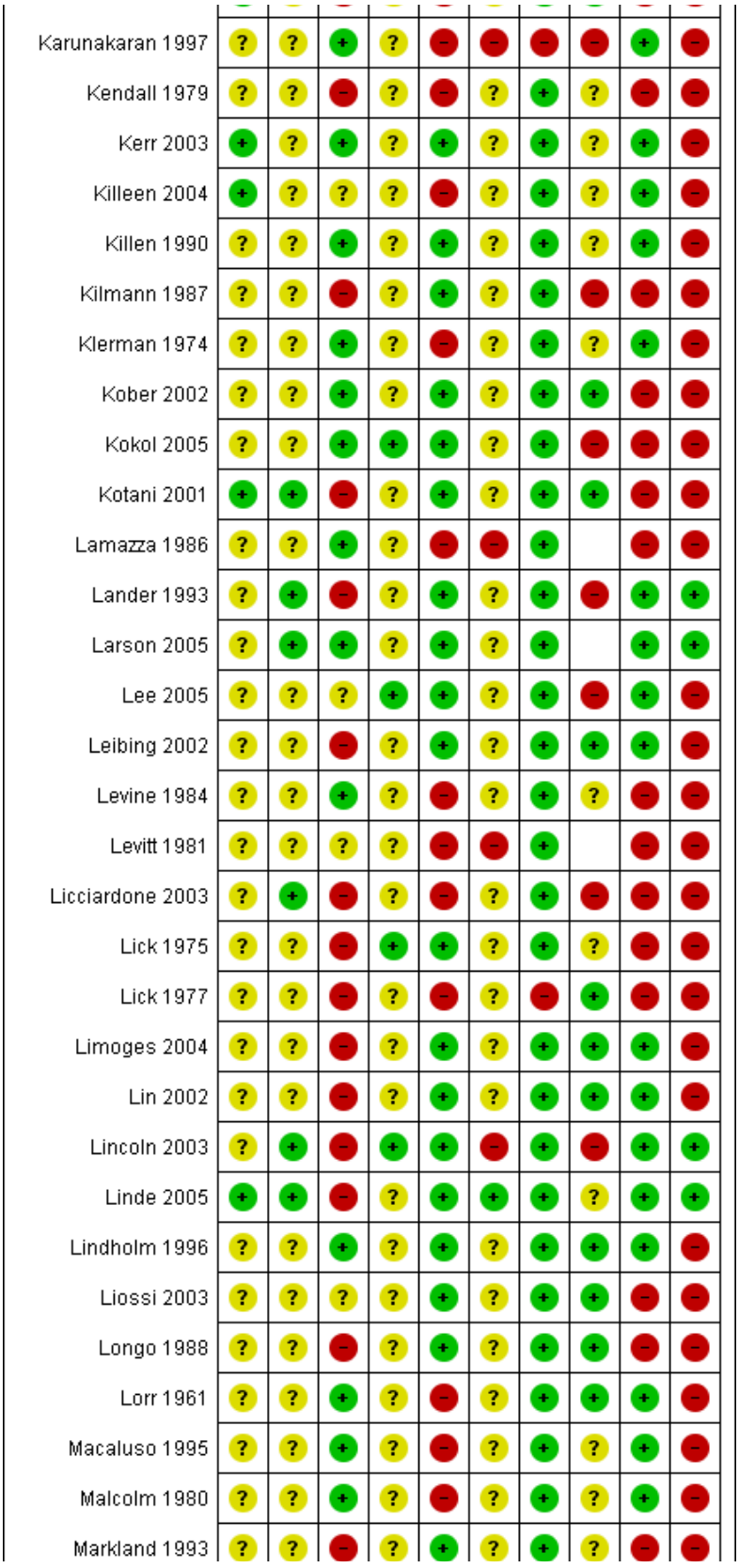

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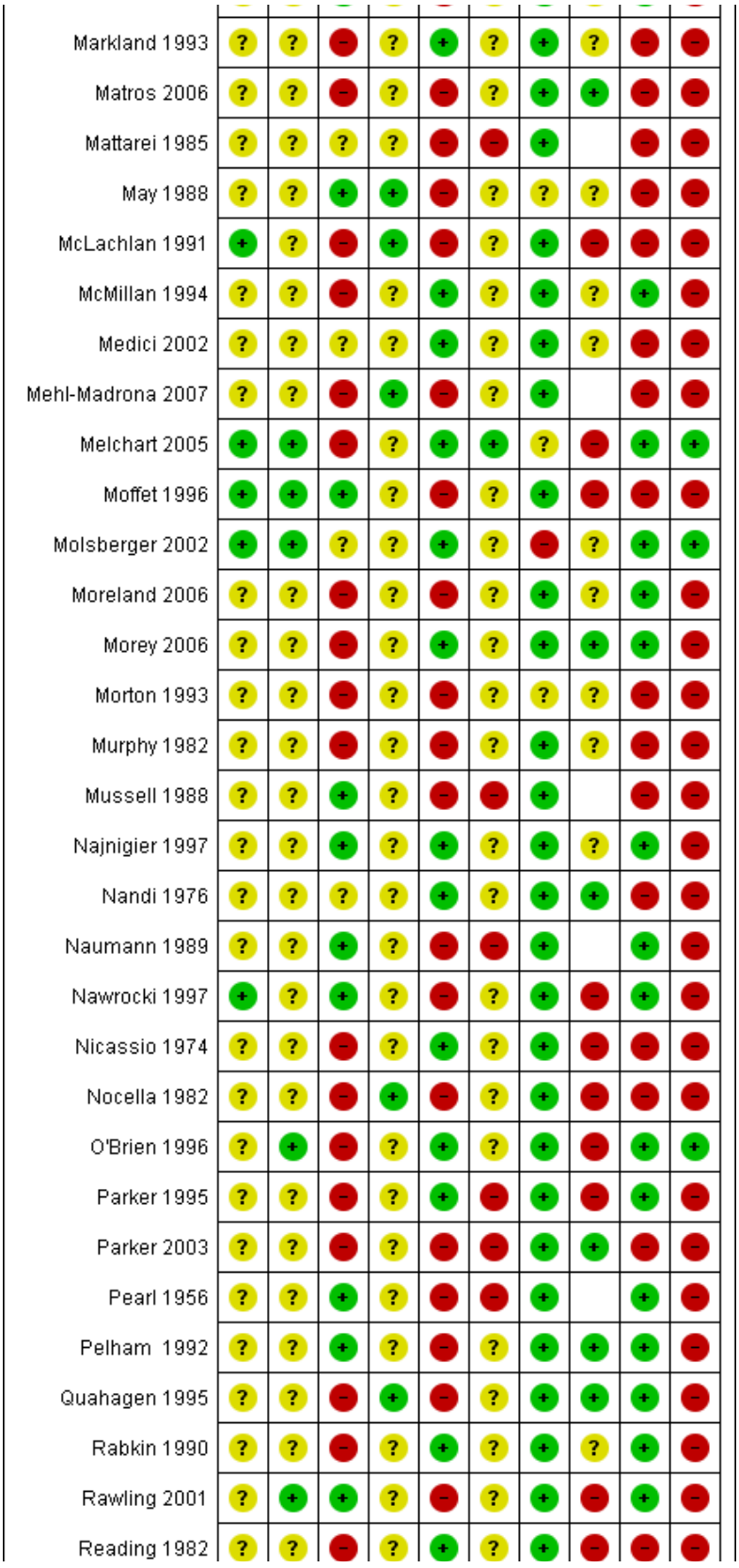

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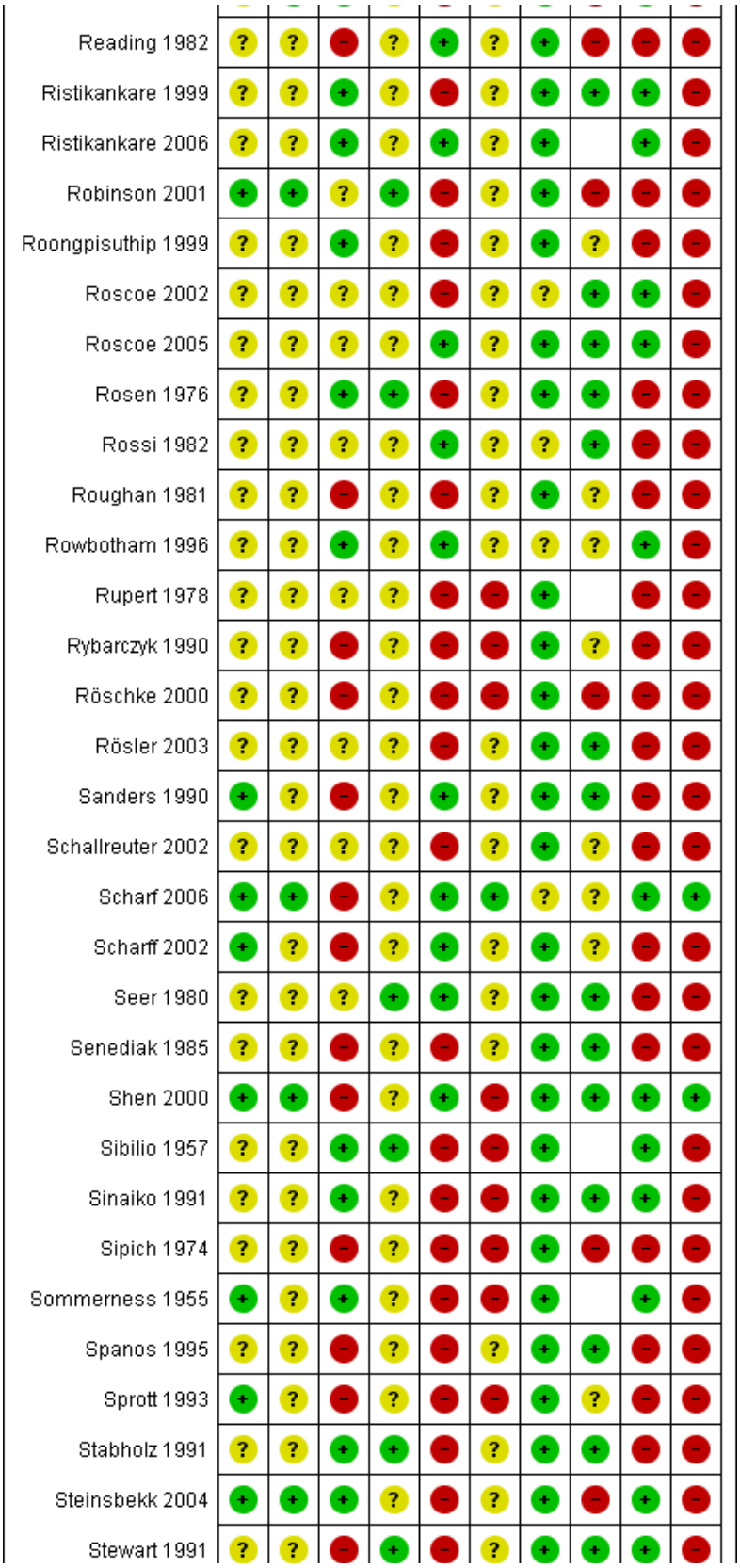

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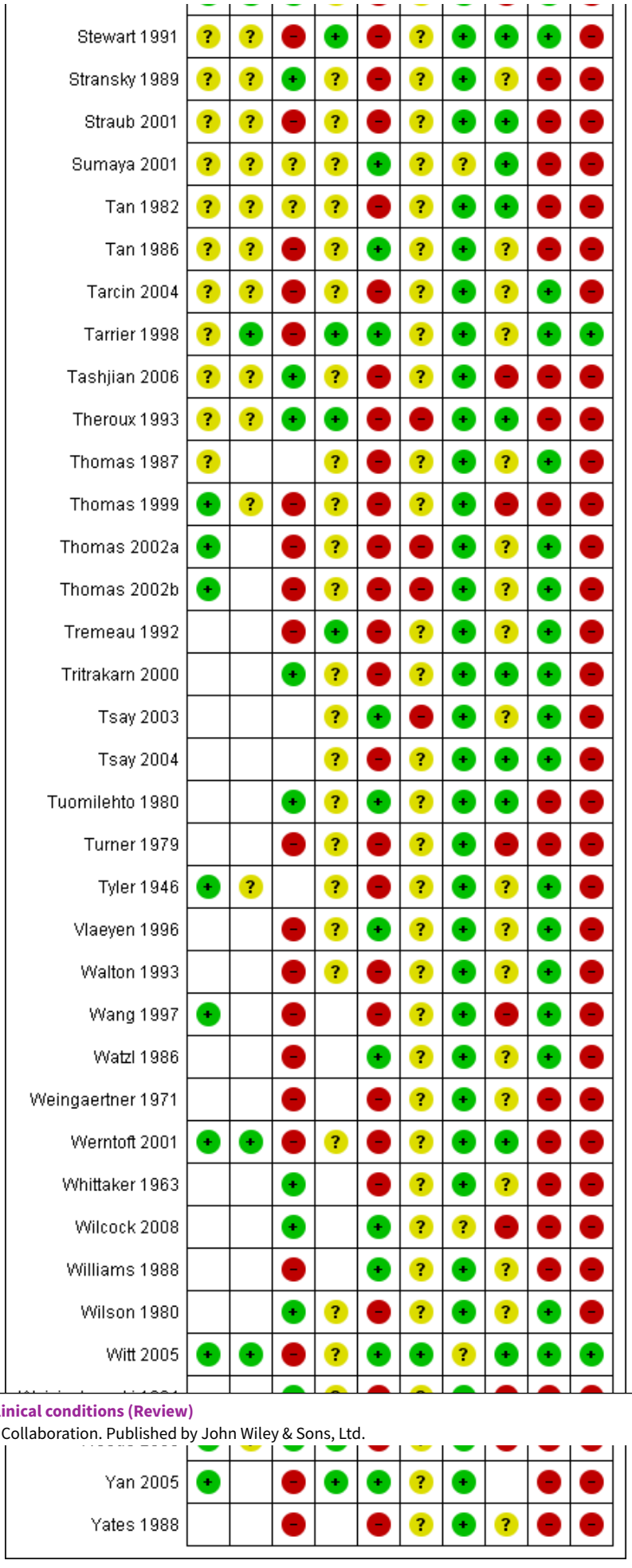
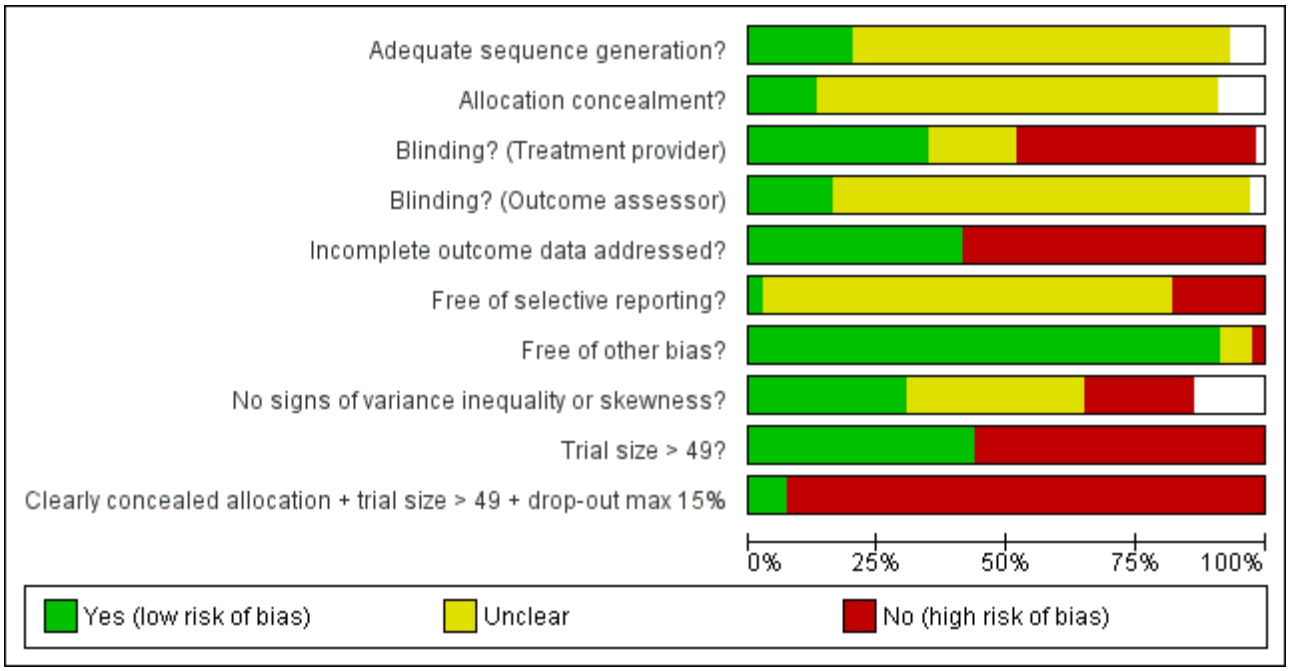


Figure 2. Methodological quality graph: review authors' judgments about each methodological quality item presented as percentages across all included studies.



All included trials were randomised, but in only 28 trials (12%) was it clear that patient allocation had been adequately concealed. In 88 trials the dropout rate was 15% or lower, and in the remaining 114 trials it was above 15% (or not reported). In 86 trials the sample size was 50 or more. We regarded the risk of bias as low in 16 trials (8%), five of which had binary outcomes.

In 61 trials the comparison between placebo and an experimental active treatment was described as 'double blind', whereas in the remaining 141 such trials comparisons were not double blind (or not reported). Observer-reported outcomes were clearly assessed by a blinded observer in 22 trials, but this was unclear in 41 trials.

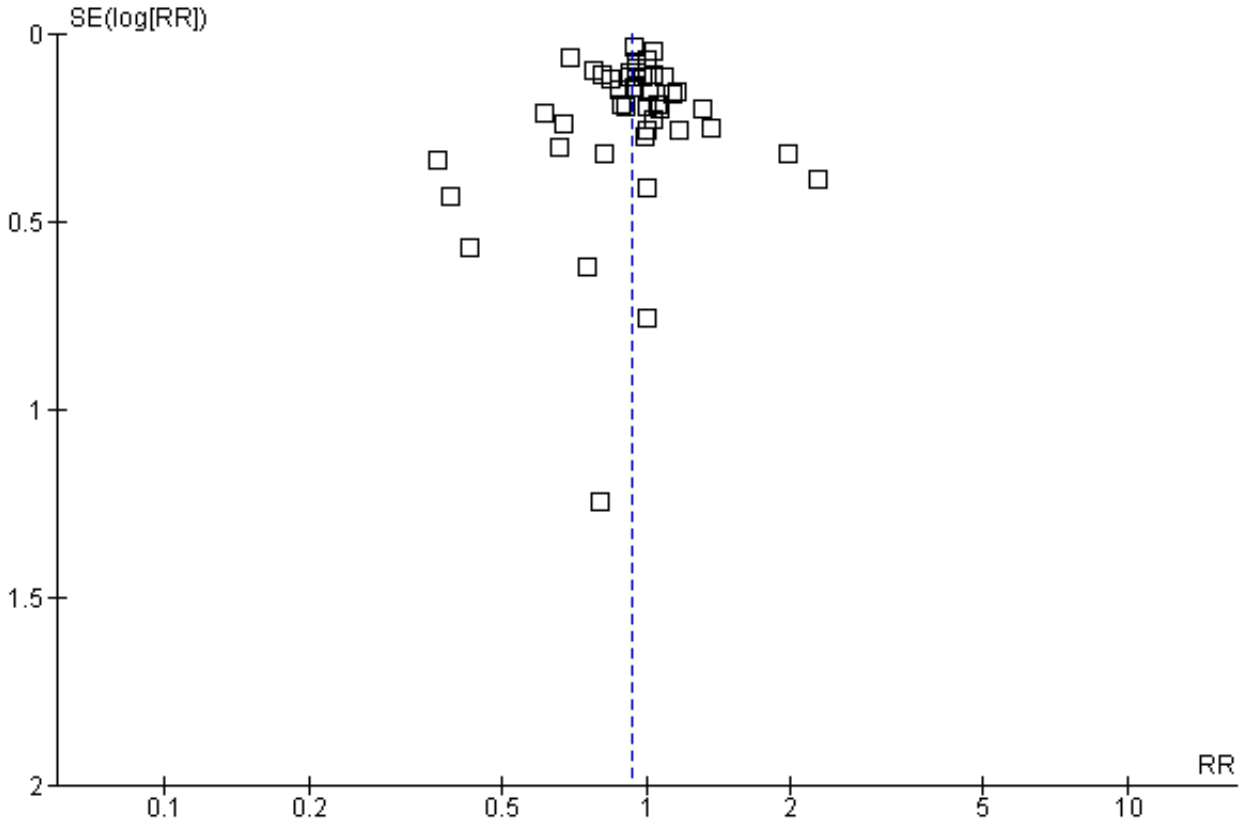
Effects of interventions

See: **Summary of findings for the main comparison** Effect of placebo interventions across all clinical conditions (main findings)

Binary outcomes (44 trials; 6041 patients)

The funnel plot was symmetrical around a single peak (Figure 3). There was no statistically significant difference between the results in small and large trials (Egger's test, P = 0.49). Heterogeneity was moderate (P < 0.001, I^2 45%).

Figure 3. Funnel plot of comparison: 1 Main analysis: overall pooled analyses, outcome: 1.1 Binary outcomes.



The pooled effect was RR 0.93 (0.88 to 0.99) (Analysis 1.1) (Summary of findings for the main comparison). The effect for patient-reported outcomes was RR 0.93 (0.86 to 1.00) and for observer-reported outcomes RR 0.93 (0.85 to 1.02) (Table 1).

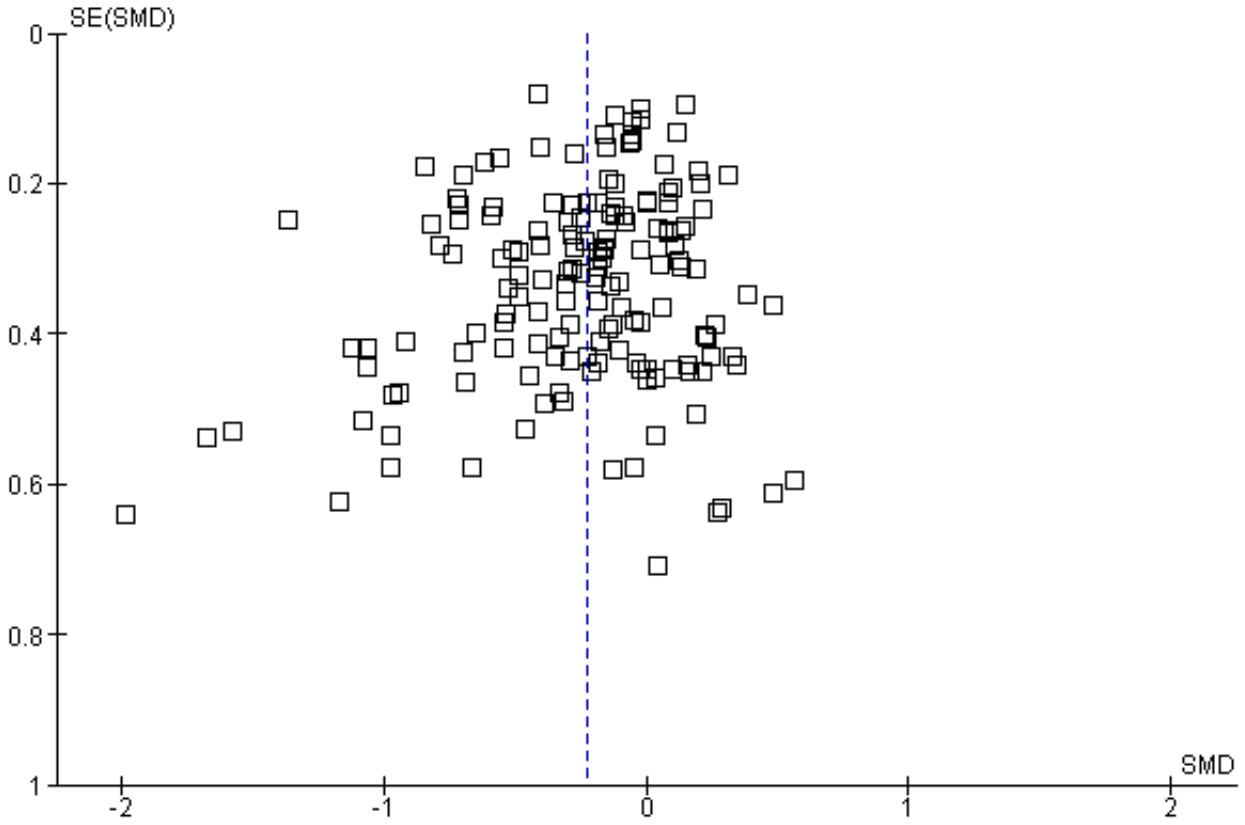
We categorised five trials as having low risk of bias. The pooled effect of these trials was RR 0.90 (0.76 to1.08). The analysis involved considerable heterogeneity (P < 0.001; I^2 78%) caused by one German acupuncture pain trial with a RR of 0.69 (0.61 to 0.78). The pooled effect of the other four trials was RR 0.96 (0.87 to 1.06) (P = 0.63; I^2 0%).

Four clinical problems had been investigated in at least three trials with binary outcomes: nausea, pain, and relapse in prevention of smoking and depression. Placebo interventions had no statistically significant effect on these clinical conditions, but confidence intervals were wide (Table 2).

Continuous outcomes (158 trials; 10,525 patients)

The funnel plot was asymmetrical (Figure 4). Small trials tended to report higher effects of placebo than larger trial (Egger's test, P = 0.03). There was moderate heterogeneity (P < 0.001, I^2 42%).

Figure 4. Funnel plot of comparison: 1 Main analysis: overall pooled analyses, outcome: 1.2 Continuous outcomes.



The effect estimates of the individual trials spanned roughly from SMD -2.0 to 0.5, and the effects of large trials varied considerably. Because of heterogeneity and funnel plot asymmetry it is a questionable procedure to pool all the trials, and we did so mainly as a basis for exploring causes for heterogeneity.

The pooled effect was SMD -0.23 (-0.28 to -0.17) (Analysis 1.2) (Summary of findings for the main comparison). The effect for patient-reported outcomes (SMD -0.26 (-0.32 to -0.19)) was statistically significantly different from the effect for observer-reported outcomes (SMD -0.13 (-0.24 to -0.02), (test of interaction, P = 0.045)) (Table 3).

We categorised 11 trials as having a low risk of bias. The pooled SMD for these trials was -0.38 (-0.55 to -0.22), but heterogeneity was considerable (P < 0.001; I^2 62%) and caused by four German acupuncture pain trials. The pooled effect of the other seven trials was -0.19 (-0.31 to 0.07) with no heterogeneity (P = 0.67; I^2 0%).

Eleven clinical problems had been investigated in at least three trials with continuous outcomes: anxiety, asthma, dementia, depression, hypertension, insomnia, nausea, overweight, pain, phobia, and smoking (Table 4). Confidence intervals were wide for most conditions. Placebo interventions had a statistically significant effect on pain, phobia, nausea, and asthma. Below we describe the results of these trials.

Pain

There were 60 trials with 4154 patients that evaluated the effect on pain based on continuous outcomes, e.g. pain intensity measured on a 100 milimetre (mm) visual analogue scale. The funnel plot was asymmetrical, as larger trials tended to report lower effects than smaller trials (Figure not shown). This tendency was not statistically significant (Egger's test, P = 0.20), but the intercept, which indicates the degree of asymmetry, was similar to the intercept for the analysis involving all trials with continuous outcomes. The statistically significant heterogeneity (P < 0.001) was moderate (I^2 42%).

The effect estimates of the individual trials spanned roughly from SMD -1.0 to SMD 0.5, with a peak around SMD -0.15, and with several medium-sized trials reporting effects between SMD -0.5 and -1.0. The pooled SMD was -0.28 (-0.36 to -0.19).

We categorised seven pain trials as having low risk of bias. Their pooled SMD was -0.45 (-0.69 to -0.21), but with substantial heterogeneity (I^2 75%). Four German acupuncture trials had a pooled effect of -0.68 (-0.85 to -0.50), whereas the other three pain trials had a pooled effect of SMD -0.13 (-0.28 to 0.03) (Analysis 18.3). When grouped this way neither had any heterogeneity (I^2 0%).

The mean standard deviation for the 16 trials with a 100 mm visual analogue pain scale was 24 mm. Thus, the effect on pain on a 100 mm scale based on the four German acupuncture trials was 16 mm, and 3 mm based on the other trials.

A similar pattern was seen among the six pain trials with binary outcomes, including 1207 patients. The pooled effect was RR 0.92 (0.77 to 1.11). There was substantial heterogeneity (P < 0.001; I^2 76%). The single German acupuncture trial reported a marked effect of RR 0.69 (0.61 to 0.78), whereas the five other trials had a pooled RR of 0.98 (0.88 to 1.09). When so grouped there was no heterogeneity (I^2 0%).

Nausea

Seven trials with 452 patients studied the effect of placebo on nausea based on continuous outcomes. No statistically significant heterogeneity (P = 0.30) was found (I^2 17%). The pooled SMD was -0.25 (-0.46 to -0.04). The mean standard deviation for trials using a 100 mm visual analogue scale (or similar) was 27 mm. The effect on reported nausea was thus 7 mm on a 100 mm scale. We categorised two nausea trials as having low risk of bias. They had a similar pooled effect, SMD = -0.19 (-0.49 to 0.11).

Six trials with 732 patients evaluated the effect of nausea on binary outcomes. No statistically significant heterogeneity was found (P = 0.95; I^2 0%). The pooled RR was 0.94 (0.82 to 1.07). We categorised one trial as having low risk of bias. This trial had a similar effect, RR 0.92 (0.75 to 1.12).

Phobia

Three trials with 57 patients evaluated the effect of placebo on phobia based on continuous outcomes, e.g. assessment of fear of snakes. No statistically significant heterogeneity (P = 0.52) was found (I^2= 0%).The pooled SMD was -0.63 (95% CI -1.17 to -0.08). The trials were very small with sample sizes of 14, 18 and 25 patients, and the concealment of allocation was unclear in all three cases. No trials with binary outcomes investigated phobia.

Asthma

Four trials with 203 patients evaluated the effect of placebo on asthma. No statistically significant heterogeneity was found (P = 0.52; I^2 0%). The pooled SMD was -0.35 (-0.70 to -0.01). The marginally statistically significant pooled result is primarily driven by one trial published in 1976 reporting an effect on children. No trial reported adequate concealment of allocation, and no trial with binary outcomes investigated asthma. The risk of bias is considerable in this analysis and we find it uncertain whether placebo has an effect on asthma.

Trials not reporting data necessary for meta-analyses

In 29 out of the 234 trials (12%), outcome data had not been reported in a way that was suited for meta-analysis, and three trials reported harms. Based on a qualitative assessment, there was no clear tendency for the findings in the 29 trials without outcome data to be different from the findings in the 202 trials we meta-analysed.

Trials studying harms

Three trials (1218 patients) studied harmful effects of placebo interventions. One trial with binary outcomes (1066 patients) found no statistically significant increase of nausea in patients treated with placebo (RR 1.36 (0.95 to 1.95)). The two trials with continuous outcomes (128 and 24 patients) also found no statistically significant harmful effect of placebo intervention (SMDs -0.19 (-0.53 to 1.06) and 0.83 (-0.01 to 1.67)).

Subgroup analyses and meta-regression analyses

We found no statistically significant differences between the subgroups of trials with binary outcomes (data not shown).

For trials with continuous outcomes the effect of physical placebo interventions, SMD -0.31 (-0.41 to -0.22) was higher than the effect of pharmacological placebo interventions, SMD -0.10 (-0.20 to -0.01), (test of interaction, P = 0.002). Furthermore, the observed difference between patient-reported outcomes and observer-reported outcomes was primarily driven by a small negative effect on laboratory outcomes, SMD 0.16 (0.01 to 0.30), and a small effect on observer-reported outcomes not involving the patients' cooperation, SMD -0.12 (-0.29 to 0.05). The effect on observer-reported outcomes involving the patients' cooperation, SMD -0.26 (-0.41 to -0.12), was very similar to the effects on patient-reported outcomes.

The pooled effect of the 23 trials that falsely informed the patients that they could receive two active treatments or no-treatment (i.e. the possibility of a placebo intervention was not revealed) was SMD -0.39 (-0.53 to -0.26). This effect was higher than in the trials that correctly informed patients that a placebo intervention was a possibility (or this aspects was not reported clearly) SMD -0.19 (-0.25 to -0.13) (test of interaction, P = 0.008). We also found a statistically significantly higher effect in the 28 trials with an aim of studying the effect of placebo, SMD -0.34 (-0.46 to -0.22) as compared with trials that did not state this aim, -0.20 (-0.26 to -0.14) (test of interaction, P = 0.04).

We found no statistically significant impact on results of the following methodological factors: whether the placebo treatment provider and patients had been blinded, whether placebo was an add-on treatment, whether observers had been blinded (when outcomes were observer-reported), whether the data indicated non-Normal distributions of continuous outcomes, or whether the trial report had defined a primary outcome. The effects of adequately concealed trials with continuous outcomes were somewhat larger than the effect of trials where concealment was unclear (test of interaction, P = 0.05). There was no statistically significant difference between the effect of placebo measured as final values, SMD -0.21 (-0.28 to -0.14), and change from baseline, SMD -0.27 (-0.37 to -0.16).

The results of the meta-regression analyses are shown in Table 5. The meta-regression model with stepwise elimination of co-variates with the highest P values, identified four co-variates with P values < 0.05: patient-involved outcomes (patient-reported outcomes and observer-reported outcomes involving patient cooperation), physical placebos, information to patients, and the aim of the trial. The model explained 54% of the variation in the analysis of all trials with continuous outcomes. In this analysis, small sample size was close to being statistically significant (P = 0.09), and the analysis of the funnel plot (Egger's test) did find such an association (P = 0.03). Thus, we regard sample size and effect as associated.

DISCUSSION

We found a small and uncertain pooled effect of placebo interventions in 44 trials with binary outcomes and no difference between patient-reported and observer-reported outcomes. For 158 trials with continuous outcomes we found higher effects in

small trials. The pooled effect of placebo on patient-reported outcomes was modest, and on observer-reported outcomes small and uncertain.

Out of 11 clinical conditions, investigated in three trials or more, there was a statistically significant effect of placebo on pain, nausea, phobia, and asthma. The pooled effect of placebo interventions on pain was very variable, also among trials with low risk of bias, spanning from clinically important to negligible. The pooled effect on nausea was modest, but consistent. The effect on phobia and asthma was very uncertain due to high risk of bias.

Larger effects of placebo interventions were associated with physical placebo interventions (e.g. sham acupuncture), patient-involved outcomes (patient-reported outcomes such as pain, and observer-reported outcomes involving patient cooperation, such as depression rating scales), small trials, and trials with the explicit purpose of studying placebo. Larger effects of placebo were also found in the trials that falsely informed patients that the study compared two active treatments with no-treatment.

Strengths and weaknesses

The two main strengths of our review are the randomised design of the included trials, and the large number of included trials. This enabled an comprehensive assessment of the clinical effect of placebo and provided a basis for analyses of the effect of placebo on specific clinical conditions, of the risk of bias, and of reasons for heterogeneity.

The main weakness of any review of the effect of placebo is that the comparison between placebo and no-treatment cannot be conducted blindly. Patients will know whether they receive a treatment or not, and this may affect both their reporting of symptoms and their use of concomitant therapy. In trials with patient-reported outcomes it is difficult to distinguish a true effect from biased reporting (response bias), as polite patients may tend to report what they think socially most acceptable. A review of signal detection analysis of experimental placebo studies on pain indicated that response bias was responsible for at least part of the patient-reported effects (Allan 2002). This is in accord with our findings that the effect of placebo was twice as high for patient-reported continuous outcomes as for observer-reported ones.

The effect of placebo could be underestimated if the patients in the no-treatment groups tended to seek treatment outside the trial more often than patients in the placebo groups. For example, the patients in the no-treatment group of a long-term pain trial could take more additional pain medication than the patients in the placebo group. Concomitant therapy was generally poorly reported, but in 13 three-armed acupuncture trials, patients in the no-treatment group reported taking more analgesic drugs than patients in the placebo group (Madsen 2009). The net direction of the two biases, response bias and co-intervention bias, is difficult to predict, but it seems likely that they partly cancel each other out.

The funnel plot of trials with continuous outcomes was asymmetrical and lacked a clear peak, as the effect of large trials also varied considerably. This could indicate that some small trials with a neutral or negative result had not been included. However, the publication of such trials is not directly linked to the effect of the placebo intervention (but to the effect of the active intervention), so we find it less likely that unidentified trials could explain the higher effects of placebo reported in small trials. It seems more likely that the asymmetry is caused by a combination of true heterogeneity and poor methodological quality in small trials. Regardless, the overall pooled effect of trials with continuous outcomes should be interpreted cautiously.

We carried out several subgroup and meta-regression analyses to explain the heterogeneity. Higher effects of placebo interventions were associated with patient-involved outcomes (patient-reported outcomes and observer-reported outcomes involving patient cooperation), physical placebos, small trials, and trials with the explicit purpose of studying placebo. Ten of eleven co-variates analysed were predefined before this update. The eleventh factor was whether patients had been falsely informed that they could receive two forms of active treatment or no-treatment (and were not informed about the possibility of a placebo intervention). The German acupuncture trials informed their patients in this way, which prompted us to re-read the other trial reports, extract relevant data, and include the factor in a post-hoc analysis. The factor was statistically significant only when the German acupuncture trials were included in the analyses, implying some uncertainty as to its general importance. Furthermore, pooling of final values and change from baseline may be problematic when outcomes are presented as standardised mean differences. However, in a sensitivity analysis we found no statistically significant difference between the pooled effect of 40 trials that reported change from baseline as compared with the 118 trials that reported final values.

The meta-regression model explained 54% of the initial variation found in the pooled analysis of trials with continuous outcomes. Subgroup analyses, and meta-regression, are observational and there is a risk of confounding. We have found one randomised trial that studied a co-variate involved in our meta-regression analyses. Placebo acupuncture was found to have somewhat larger effects than pill placebo on pain (Kaptchuk 2006), supporting our observation that physical placebos are associated with larger effects than pharmacological ones.

Other reviews

One previous systematic review of randomised trials with placebo and no-treatment groups identified 12 trials (Ernst 1995), which tended to report large effects of placebo.

Several laboratory studies indicate a neurobiological mechanism for the analgesic effect of placebo (Sauro 2005). These studies are often small, mostly based on healthy volunteers, and of short duration. The findings cannot easily be extrapolated to a clinical context, but they do elucidate the probable importance of, for example, endorphins in the analgesic response to placebo, and indicate that it is unlikely that response bias can account for all of the analgesic effect.

Other reviews have compared the effect of experimental treatments in trials that used placebo control groups, with similar trials that used no-treatment control groups (Dush 1986; Grissom 1996; Kirsch 1998; Shapiro 1982; Smith 1980). Such comparisons are indirect, prone to confounding and therefore less reliable.

The previous versions of our review prompted several independent re-analyses. Kamper and colleagues replicated our finding that the pooled effect of placebo on pain was low (Kamper 2008). Wampold

and colleagues replicated our overall findings for both binary and continuous outcomes, despite modified inclusion criteria and some disagreement about how such estimates should be interpreted (Wampold 2005; Hróbjartsson 2007). Meissner and colleagues replicated our findings that effects of placebo on laboratory outcomes tended to be lower than on other observer-reported outcomes (Meissner 2007). Vase and colleagues re-analysed the clinical pain trials included in our review, and reported low effects in ordinary clinical trials and high effects in clinical and laboratory based 'mechanism studies' (Vase 2002). We pointed out several methodological errors, and suggested that the difference could be less pronounced (Hróbjartsson 2006). The German acupuncture trials, which were not 'mechanism studies', also indicated that clinical non-mechanism trials can have quite substantial effects. Regardless, effects of placebo vary considerably, and the web of factors responsible for this variation is complex. Our regression analysis is one attempt to unfold the multifactorial background for effects of placebo.

Meaning of our review

This update confirms and modifies the findings of the previous versions of our review. Our approach can be seen as testing the hypothesis that placebo treatments have large effects across many clinical conditions and outcomes, and our results clearly indicate that this hypothesis is wrong.

However, our findings do not imply that placebo interventions have no effect. We found an effect on patient-reported outcomes, especially on pain. Several trials of low risk of bias reported large effects of placebo on pain, but other similar trials reported negligible effect of placebo, indicating the importance of background factors. We identified three clinical factors that were associated with higher effects of placebo: physical placebos, patient-involved outcomes (patient-reported outcomes and observer-reported outcomes involving patient cooperation), and falsely informing patients that the trial involved a comparison of two active treatments and no-treatment. Furthermore, two methodological factors were also associated with higher effects: small sample size and the explicit aim of studying effect of placebo. So, despite a general picture of low effects, and the risk of response bias and small sample size bias, it is likely that large effects of placebo interventions may occur in certain situations.

Extrapolation of our findings to settings outside clinical trials rests on the premise that the nature of the treatment ritual in an experimental and a clinical setting is not fundamentally different. To analyse this empirically is challenging, however, as it seems impossible to study the effect of placebo treatments in clinical practice reliably without introducing an experimental setting (Hróbjartsson 1996).

It can be difficult to interpret whether a pooled standardised mean difference is large enough to be of clinical relevance. A consensus paper found that an analgesic effect of 10 mm on a 100 mm visual analogue scale represented a ‘minimal effect’ (Dworkin 2008). The pooled effect of placebo on pain based on the four German acupuncture trials corresponded to 16 mm on a 100 mm visual analogue scale, which amounts to approximately 75% of the effect of non-steroidal anti-inflammatory drugs on arthritis-related pain (Gøtzsche 1990). However, the pooled effect of the three other pain trials with low risk of bias corresponded to 3 mm. Thus, the analgesic effect of placebo seems clinically relevant in some situations and not in others.

It is a question of definition whether our review evaluates the 'placebo effect'. This term does not only imply the effect of a placebo intervention as compared with a no-treatment group, but is also used to describe various other aspects of the patient-provider interaction, such as psychologically-mediated effects in general, the effect of the patient-provider interaction, the effect of suggestion, the effect of expectancies, and the effect of patients' experience of meaning (Hróbjartsson 2002b). As patients in the no-treatment group also interact with treatment providers, a no-treatment group is only untreated in the sense that they do not receive a placebo intervention (Hróbjartsson 1996). Our result is therefore neutral to many of the meanings of the term 'placebo effect' cited above, and we do not exclude the possibility of important effects of other aspects of the patient-provider interaction, though the methodological problems of studying such effects reliably are demanding.

Despite ethical concerns of the deceit inherent in most placebo prescriptions (Rawlinson 1985), the clinical use of placebo interventions has been advocated in editorials and articles in leading journals (Bignal 1994; Brown 1998; Ho 1994) and by influential commentators (Cochrane 1989). Questionnaire surveys indicate that placebo interventions are sometimes used in clinical practice, such as vitamin B for fatigue, or antibiotics for presumed viral infections (Hróbjartsson 2003; Tilburt 2008). In our opinion a clinical placebo intervention is ethically acceptable only if it fulfils two criteria. First, patients must be informed about the nature of the intervention. Second, the effect of placebo must be reliably demonstrated in trials that disclose to patients that they receive placebo. None of the trials included in this review tested the effect of fully disclosed placebo interventions. The tendency was the opposite, for higher effects in trials where the possibility of a placebo intervention was obscured. Thefore, placebo prescription seems to lack both ethical and empirical justification.

The use of placebos in blinded randomised trials is a precaution directed against many forms of bias, and not only against effects of placebo. Unblinded patients may differ from blinded ones in their way of reporting beneficial and harmful effects of treatment, in their tendency to seek additional treatment outside the study, and in their risk of dropping out of the study. Furthermore, unblinded staff may differ in their use of alternative forms of care and in their assessment of outcomes. Thus, even if there were no true effect of placebo, one would expect to record differences between placebo and no-treatment groups due to bias associated with lack of blinding.

AUTHORS' CONCLUSIONS

Implications for practice

We did not find that placebo interventions have important clinical effects in general. However, in certain settings placebo interventions may influence patient-reported outcomes, especially pain and nausea, though it is difficult to distinguish patient-reported effects of placebo from response bias.

Most clinical placebo prescriptions involve deceit and the effect of placebo has not been tested in trials after full disclosure that

the patients receive placebo. Therfore, we suggest that placebo interventions are not used outside clinical trials.

Implications for research

The results of this review do not imply that no-treatment control groups can replace placebo control groups in randomised clinical trials without a risk of bias.

Further research is needed to study the impact of bias (such as response bias and bias due to co-intervention) on the estimated effect of placebo, to study the association between type of outcome and bias, to explore which factors in the clinical setting are associated with different effects of placebo, and to explore the duration of effects.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Abikoff 2004

Methods	Design: three group parallel trial Purpose: study the effect of methylphenidate and multimodal psychological treatment on children with attention-deficit/hyperactivity disorder
Participants	Patients: children with attention-deficit/hyperactivity disorder Baseline comparability: yes (except for socioeconomic status)
Interventions	Placebo: sessions with attention control interventions with no social skills training Untreated: no sessions Experimental: sessions with social skills training (Co-intervention: All patients received methylphenidate)
Outcomes	Social skills rating scale (parents) Social skills rating scale (children) Taxonomy of problem situations (teachers) Direct school observations Parental practices Academic achievements Emotional status
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Abikoff 2004 *(Continued)*

Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (attention control placebo/multimodal psychological intervention)
Blinding? Outcome assessor	Unclear risk	Not relevant as patient (parents) reported outcome
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	Low risk	N = 69
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Drop-out > 15% or NS

Adams 1976

Methods	Design: three group parallel trial Purpose: examine the effect of adenine arabinoside on episodes of genital herpes
Participants	Patients: out-patients with episodes of genital herpes Baseline comparability: NS
Interventions	Placebo: ointment or gel without adenine arabinoside Untreated: no ointment or gel Experimental: ointment or gel with adenine arabinoside (Co-intervention: NS)
Outcomes	Pain Mean duration of pain Mean duration of viral shedding Mean duration of lesions Mean duration any new lesion during treatment
Notes	Relevant outcome data not reported in article

Risk of bias

Bias	Authors' judgement	Support for judgement

Adams 1976 *(Continued)*

Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'Thus ara-A or placebo ointment or gel were given in a double-blind fashion'
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	High risk	Relevant outcome data not reported in article
Free of other bias?	Low risk	
Trial size > 49?	High risk	N = 38
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Adriaanse 1995

Methods	Design: three group parallel trial Purpose: examine the effect of vaginal chlorhexidine disinfection on the transmission of group B streptococci from mother to child during labour
Participants	Patients: women during labour Baseline comparability: yes
Interventions	Placebo: vaginal gel without chlorhexidine Untreated: no vaginal gel Experimental: vaginal gel with chlorhexidine (Co-intervention: NS)
Outcomes	Bacterial transmission rate Infections
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	'Predefined block (10:10:10) allocation scheme'
Allocation concealment?	Unclear risk	NS

Adriaanse 1995 *(Continued)*

Blinding? Treatment provider	Low risk	'Two groups were treated in a double-blind manner with either a chlorhexidine or a placebo gel'
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	High risk	Drop-out >15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (binary outcome)
Trial size > 49?	Low risk	N = 654
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Drop-out >15% or NS

Alfano 2001

Methods	Design: five group parallel trial Purpose: examine the effect of static magnetic fields for treatment of fibromyalgia
Participants	Patients: subjects with fibromyalgia (American College of Rheumatology's diagnostic criteria) Baseline comparability: yes
Interventions	Placebo: pads that have no magnetic property inserted into the beds of the patients for 6 months Untreated: no pads Experimental: two types of pads with static magnetic properties (Co-intervention: NS)
Outcomes	Pain (11 point numeric rating scale, 0 to 10) at six months Number of tender points Tender point pain intensity Functional status (fibromyalgia impact questionnaire)
Notes	Results from two placebo groups reported as deriving from one group.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	'Computer-generated treatment list'
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Unclear risk	NS

Alfano 2001 *(Continued)*

Blinding? Outcome assessor	Unclear risk	Not relevant as patients reported outcome
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	High risk	N = 38
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Alford 2003

Methods	Design: three group parallel trial Purpose: to evaluate the efficacy of a continuous postoperative bupivacaine infusion pump for pain management after anterior cruciate ligament reconstruction
Participants	Patients: out-patients requiring ACL reconstruction Baseline comparability: NS
Interventions	Placebo: infusion catheter filled with saline Untreated: no catheter Experimental: infusion catheter filed with 0.25% bupivacaine solution. (Co-intervention: ipsilateral femoral nerve block with 30mL 0.25% bupivacaine and 20 mL 0.25% bupivacaine intra-articular injection. Postoperative pain management protocol: hydrocodone/acetaminophen, 5mg/500mg every 4 hours, and ibuprofen 800mg 3 times a day)
Outcomes	Pain (11 point numeric rating scale, 0 to 10) Medication consumption Physical therapy performance
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	'random number draw conducted in the operating suite'
Allocation concealment?	Unclear risk	'separate sealed notebook'
Blinding? Treatment provider	Low risk	'Both patient and investigators were blinded to the catheter contents and group assignment'
Blinding?	Low risk	'The therapists were blinded to patient group assignment'

Alford 2003 *(Continued)*

Outcome assessor		
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
Trial size > 49?	High risk	N = 16
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Alkaissi 1999

Methods	Design: three group parallel trial Purpose: examine the preventive effect of acupressure on nausea and vomiting after surgery
Participants	Patients: women undergoing minor gynaecological surgery Baseline comparability: yes
Interventions	Placebo: acupressure on a site which was not P6 during hospital stay Untreated: no acupressure Experimental: acupressure on P6 (Co-intervention: metoclopramide and droperidol at request)
Outcomes	Proportion of patients with complete response (no nausea, vomiting, or rescue medication) after 24 hours Nausea (only) Vomiting Rescue medication Nausea after 24 hours
Notes	In the no treatment group 6/20 had nausea at discharge, and 8/20 after 24 hours. The corresponding numbers for the placebo group were 7/20 and 1/20. According to protocol we extracted data at post-treatment (discharge). 10 out of 60 patients dropped out ('evenly distributed between the groups') and were replaced by 10 new patients

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	'The study was double-blind...' but this referred to blinding of patient and outcome assessor.
Blinding? Outcome assessor	Unclear risk	Not relevant as patients reported outcome

Alkaissi 1999 *(Continued)*

Incomplete outcome data addressed? All outcomes	High risk	Drop-out >15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (binary outcome)
Trial size > 49?	High risk	N = 40
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Drop-out >15% or NS

Alkaissi 2002

Methods	Design: three group parallel trial Purpose: examine the preventive effect of acupressure on nausea and vomiting after surgery
Participants	Patients: women undergoing minor gynaecological surgery Baseline comparability: yes
Interventions	Placebo: acupressure bands not on P6 for 24 hours Untreated: no acupressure Experimental: acupressure on P6 (Co-intervention: anaesthetic agents, rescue medication)
Outcomes	Proportion of patients with complete response (no nausea, vomiting or rescue medication), time NS Apfel risk score Satisfaction with treatment
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Low risk	'Sealed envelope'
Blinding? Treatment provider	High risk	Described as double-blind (Placebo/acupressure) but this referred to blinding of patient and outcome assessor.
Blinding? Outcome assessor	Unclear risk	Not relevant as patients reported outcomes
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out <15%

Alkaissi 2002 *(Continued)*

Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (binary outcome)
Trial size > 49?	Low risk	N = 275
Clearly concealed allocation + trial size > 49 + drop-out max 15%	Low risk	All three categories fulfilled

Allen 1998

Methods	Design: three group parallel trial Purpose: examine the effect of acupuncture on depression
Participants	Patients: out-patients with depression Baseline comparability: no (depression scores)
Interventions	Placebo: needling in acupuncture points not regarded having impact on depression Untreated: no needling Experimental: needling in acupuncture points regarded having impact on depression (Co-intervention: NS)
Outcomes	Hamilton Rating Scale for Depression (31-item version, HAM-D31) Proportion of patients with remission (50% reduction on HAM-D31) Inventory of Depressive Symptomatology Beck Depression Inventory Beck Hopelessness Scale
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'The treating acupuncturists were blind to the experimental hypotheses...' (Placebo/acupuncture)
Blinding? Outcome assessor	Low risk	'All patients were interviewed by trained raters blind to treatment condition...'
Incomplete outcome data addressed? All outcomes	Low risk	Drop out < 15%

Allen 1998 *(Continued)*

Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (not naturally positive continuous outcomes e.g. change)
Trial size > 49?	High risk	N = 22
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Allen 2006

Methods	Design: three group parallel trial Purpose: examine the effect of acupuncture on depression
Participants	Patients: out-patients with depression (score of 14 or more on the 17-item Hamilton rating scale for depression) Baseline comparability: yes
Interventions	Placebo: needling in acupuncture points not regarded having impact on depression Untreated: no needling Experimental: needling in acupuncture points regarded having impact on depression (Co-intervention: NS)
Outcomes	Hamilton Rating Scale for Depression (17 item) Beck Depression Inventory
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'The treating acupuncturists were blind to the experimental hypotheses...' (Placebo/acupuncture)
Blinding? Outcome assessor	Low risk	'Patients were blind to intervention condition, as were raters who assessed outcome'
Incomplete outcome data addressed? All outcomes	Low risk	Drop out < 15%
Free of selective reporting?	Unclear risk	No protocol available

Allen 2006 *(Continued)*

Free of other bias?	Low risk	
No signs of variance inequality or skewness?	High risk	Either variance inequality (F-test statistically significant) or skewness (1.64 standard deviations exceeds the mean)
Trial size > 49?	Low risk	N = 89
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Allocation not clearly concealed

Andersen 1990

Methods	Design: three group parallel trial Purpose: examine the effect of bromocriptine on breast pain and milk secretion after abortion
Participants	Patients: women having undergone a second-trimester abortion Baseline comparability: yes
Interventions	Placebo: a tablet without bromocriptine Untreated: no tablet Experimental: a tablet containing bromocriptine (Co-intervention: no)
Outcomes	Breast pain (VAS) and serum prolactin (micro g/l) Breast tenderness Milk secretion
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'The part of the study that involved bromocriptine and placebo was carried out 'double-blind''
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	High risk	Drop out > 15 % or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	

Andersen 1990 *(Continued)*

No signs of variance inequality or skewness?	High risk	Either variance inequality (F-test statistically significant) or skewness (1.64 standard deviations exceeds the mean)
Trial size > 49?	High risk	N = 34
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Anderson 1999

Methods	Design: three group parallel trial Purpose: examine the effect of an office based intervention to maintain parent-adolescent teamwork in diabetes management
Participants	Patients: families with a young person with type 1 diabetes Baseline comparability: yes (age, gender, HbA1c, etc)
Interventions	Placebo: over six months four 20 to 30 minute sessions with 'traditional' diabetic education with no focus on parental involvement Untreated: no sessions Experimental: sessions of parental-adolescent teamwork therapy (Co-intervention: standard diabetic care)
Outcomes	Insulin routine score for parental involvement (4 point Likert scale) HbA1c (%) Blood glucose monitoring score Diabetes family conflict scale Diabetic family behavior checklist
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/teamwork intervention)
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	Low risk	Drop out < 15 %
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	

Anderson 1999 *(Continued)*

No signs of variance inequality or skewness?	Unclear risk	Not relevant (not naturally positive continuous outcomes e.g. change)
Trial size > 49?	Low risk	N = 57
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Not clearly concealed allocation

Antivalle 1990

Methods	Design: Two group, two period cross-over trial Purpose: examine the effect of placebo intervention on blood pressure
Participants	Patients: previously untreated out-patients suffering from essential arterial hypertension Baseline comparability: yes (age, sex, blood pressure)
Interventions	Placebo: 'tablet x 2 daily' Untreated: no tablet Experimental : no (Co-intervention: no)
Outcomes	Diastolic blood pressure reduction (mm Hg)
Notes	The first period was considered a parallel trial. Results from the second period were disregarded.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/ultrasound)
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	Low risk	Drop out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (not naturally positive continuous outcomes e.g. change)
Trial size > 49?	High risk	N = 21

Antivalle 1990 *(Continued)*

Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Antonio 1999

Methods	Design: three group parallel trial Purpose: examine the effect of 'guggulsterone phosphate compound' on the body composition and mood in obese adults
Participants	Patients: out-patients with body mass index >25 kg per square meter Baseline comparability: yes
Interventions	Placebo: maltodextrin capsules daily for 6 weeks Untreated: no capsules Experimental: capsules with a compound of guggulsterone phosphate (Co-intervention: dietary and exercise program)
Outcomes	Weight (kg) Lean body mass Fat mass Percentage body fat Profile of Mood States questionnaire (POMS)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'In this double-masked, randomized study...'
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	Low risk	Drop out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	High risk	N = 12

Antonio 1999 *(Continued)*

Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Ascher 1979

Methods	Design: three group parallel trial Purpose: examine the effect of paradoxical intention on insomnia
Participants	Patients: out-patients suffering from insomnia Baseline comparability: yes (sleep parameters)
Interventions	Placebo: sessions of 'quasi-desensitization' (neutral images paired with bedtime activity) Untreated: no sessions Experimental: paradoxical intention: (instructed to remain awake as long as possible and presented with the true theoretical background) (Co-intervention: NS)
Outcomes	Sleep latency (minutes) Awakenings Restedness rating Difficulty falling asleep
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/paradoxical intention)
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	Drop out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	High risk	Either variance inequality (F-test statistically significant) or skewness (1.64 standard deviations exceeds the mean)
Trial size > 49?	High risk	N = 17

Ascher 1979 *(Continued)*

Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Asmar 1996

Methods	Design: two period, two group, cross-over trial Purpose: examine the effect of placebo on arterial hypertension
Participants	Patients: out-patients with untreated mild-to-moderate hypertension
Interventions	Placebo: NS Untreated: no placebo (Co-intervention: NS)
Outcomes	Diastolic blood pressure (mm Hg) Systolic blood pressure (mm Hg)
Notes	The outcome data was not available from the first period only, and was calculated as deriving from a parallel group trial. The results from the trial were reported in two publications (without cross reference). In the original report there were 36 included patients, but in the subsequent report there appears only 26. The reported effect of placebo on diastolic blood pressure was higher in the second trial report. We decided to include the results from the original publication.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Unclear risk	NS
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	Low risk	Drop out < 15%
Free of selective reporting?	High risk	No protocol available. Authors were contacted. They shared data after request from the involved journal.
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (not naturally positive continuous outcomes e.g. change)
Trial size > 49?	Low risk	N = 68

Asmar 1996 *(Continued)*

Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Not clearly concealed allocation

Aune 1998

Methods	Design: three group parallel trial Purpose: examine the prophylactic effect of acupuncture on recurrent lower urinary tract infection (UTI)
Participants	Patients: female out-patients with recurrent UTI Baseline comparability: yes (age, number of UTI last 5 years)
Interventions	Placebo: needling in areas that are not known acupuncture sites Untreated: no needling Experimental: needling in areas that are known acupuncture sites (Co-intervention: NS)
Outcomes	Number of patients who had infections during 6 months Number of infections during 6 months
Notes	Patients were randomised to placebo and no treatment in a 2:1 ratio

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	'computer based schedule'
Allocation concealment?	Low risk	'sealed envelopes'
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/acupuncture)
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome. (Urine was tested when patients reported UTI symptoms)
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (binary outcome)
Trial size > 49?	High risk	N = 40
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Banner 1983

Methods	Design: six group parallel trial Purpose: examine the effect of various techniques for reducing tension
Participants	Patients: media recruited out-patients who regularly experienced feelings of tension they wanted to reduce Baseline comparability: yes
Interventions	Placebo: sessions where relaxation was enhanced by listening to soft music Untreated: no sessions Experimental: sessions with -visual and auditory feedback on the tension in the frontalis muscle -visual and auditory feedback on the finger temperature -combination of frontalis and temperature feedback procedures -relaxation enhanced by listening to a autogenic relaxation tape (Co-intervention: NS)
Outcomes	Tension rating scale EMG Finger temperature Frequency of problems
Notes	Relevant outcome data not accessible: data lost (personal communication Banner CN)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/active)
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	High risk	Relevant outcome data not accessible: data lost (personal communication Banner CN)
Free of other bias?	Low risk	
Trial size > 49?	High risk	N = 19
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Benedetti 1995

Methods	Design: eight group parallel trial Purpose: examine the effect of placebo and proglumide on postoperative pain
Participants	Patients: postoperative in-patients after thoracotomy Baseline comparability: yes (pain intensity)
Interventions	Placebo: open infusion of saline Untreated: hidden infusion of saline Experimental: -open infusion of proglumide (0.05 mg, 0.5 mg, 5 mg) -hidden infusion of proglumide (0.05 mg, 0.5 mg, 5 mg) (Co-intervention: NS)
Outcomes	Pain (VAS)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'double-blind randomized study'
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	Drop-out >15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (not naturally positive continuous outcomes e.g. change)
Trial size > 49?	High risk	N = 24
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Benedetti 1997

Methods	Design: three group parallel trial in five sub-studies Purpose: examine the effect of transcutaneous electrical nerve stimulation (TENS) on acute postoperative pain

Benedetti 1997 *(Continued)*

Participants	Patients: postoperative in-patients after thoracotomy Baseline comparability: yes (sex and age)
Interventions	Placebo: TENS without batteries Untreated: no TENS Experimental: TENS with batteries (Co-intervention: analgesics on demand, see outcome)
Outcomes	Pain (overall analgesic medication within 12 hours)
Notes	The results from five sub-studies have been pooled

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Unclear risk	NS
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	Low risk	N = 221
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Drop-out > 15% or NS

Benedetti 1999a

Methods	Design: five group parallel trial Purpose: examine the respiratory depressant response of placebo in patients newly treated with opioids
Participants	Patients: lung cancer patients undergoing posterolateral thoracotomy, having repeatedly been treated with buprenorphine for three days, and were 'almost pain-free' Baseline comparability: yes (age, gender, weight)

Benedetti 1999a *(Continued)*

Interventions	Placebo: saline injection (patients told it was continuation of analgesic medication) Untreated: no injection Experimental: naloxone injection (open and hidden) (Co-intervention: additional doses of buprenorphine were administered and resulted in exclusion of the patient from the study, numbers NS)
Outcomes	Respiratory depression (ventilation per minute) 73 hours after surgery Pain (11 point numerical scale, 0 to 10)
Notes	The trial investigated the negative effect of placebo (respiratory depression). We included the trial in the review in a separate category (adverse effects), but not in the main analyses.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'The 60 patients... were investigated according to a randomized double-blind design'
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	High risk	See notes
Trial size > 49?	High risk	N = 24
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Berg 1983

Methods	Design: three group parallel trial Purpose: examine the effect of the additional treatment of an oral laxative 'Senokot' in patients with faecal soiling already treated with behavioural therapy
Participants	Patients: children with severe and persistent faecal incontinence Baseline comparability: yes
Interventions	Placebo: tablet without laxative Untreated: no tablet Experimental: tablet with laxative 'Senokot' (Co-intervention: behavioural therapy)

Berg 1983 *(Continued)*

Outcomes	Number of children soiling more than once weekly
Notes	Tablets delivered in packs marked A and B; selection bias may therefore have occurred, if the code was broken

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'...the psychiatrist and psychologists did not know which tablets actually contained the laxative'
Blinding? Outcome assessor	Unclear risk	Not relevant as patient (parents) reported outcome
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Unclear risk	Tablets delivered in packs marked A and B; selection bias may therefore have occurred, if the code was broken
No signs of variance inequality or skewness?	Unclear risk	Not relevant (binary outcome)
Trial size > 49?	High risk	N = 26
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Biro 1997

Methods	Design: five group parallel trial Purpose: examine the effect of topical anaesthesia methods for venous cannulation in adults
Participants	Patients: patients in need of cannulation Baseline comparability: yes ('demographic data')
Interventions	Placebo: cream without EMLA Untreated: no cream Experimental: -cream with EMLA -ethylchloride spray -lidocaine infiltration (Co-intervention: yes, midazolam)
Outcomes	Pain ratings (VAS)

Biro 1997 *(Continued)*

	Number of patients with difficult punctures
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	Unclear information
Allocation concealment?	Unclear risk	Unclear information
Blinding? Treatment provider	Low risk	'The study was double-blinded to the degree that the methodologies allowed'
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcomes
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	High risk	Either variance inequality (F-test statistically significant) or skewness (1.64 standard deviations exceeds the mean)
Trial size > 49?	Low risk	N = 58
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Unclear allocation concealment

Blackman 1964

Methods	Design: three group parallel trial Purpose: examine the effect of imipramine on enuresis
Participants	Patients: army recruits referred to a 'Mental Hygiene Consultation Service' with the complaint of enuresis Baseline comparability: yes (frequency of enuresis)
Interventions	Placebo: tablet without imipramine Untreated: no tablet (observational group) Experimental: tablet with imipramine (Co-intervention: NS)
Outcomes	Number of patients with reduced frequency of enuresis
Notes	

Blackman 1964 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'The subjects and experimenters were blind to which pills were the active medication'
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (binary outcome)
Trial size > 49?	High risk	N = 24
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Blades 2001

Methods	Design: three group, three period cross-over trial Purpose: study the effect of oral antioxidant therapy on marginal dry eye
Participants	Patients: out-patients with marginal dry eyes
Interventions	Placebo: capsules without antioxidants Untreated: no capsules Experimental: capsules with antioxidants (Co-intervention: NS)
Outcomes	Glasgow Caledonian University threads phenol read thread test (G-CUT) Tear thinning time McMonnies dry eye questionnaire Squamous cell metaplasia Goblet cell density
Notes	The outcome data from this cross-over trial was not available from the first period only, and was calculated as deriving from a parallel group trial.

Risk of bias

Blades 2001 *(Continued)*

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	'Latin squares'
Allocation concealment?	Unclear risk	No stated
Blinding? Treatment provider	Low risk	'This trial was double-masked...'
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Unclear risk	The outcome data from this cross-over trial was not available from the first period only, and was calculated as deriving from a parallel group trial.
No signs of variance inequality or skewness?	Unclear risk	Not relevant (not naturally positive continuous outcomes e.g. change)
Trial size > 49?	Low risk	N = 80
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Drop-out > 15% or NS

Blanchard 1990a

Methods	Design: four group parallel trial Purpose: study the effect of abbreviated progressive muscle relaxation (PMR) and cognitive therapy on headache
Participants	Patients: out-patients with tension headache Baseline comparability: NS
Interventions	Placebo: sessions of 'pseudomeditation' Untreated: no sessions Experimental: -sessions of abbreviated progressive muscle relaxation plus cognitive therapy -sessions of abbreviated progressive muscle relaxation (Co-intervention: headache medication)
Outcomes	Medication Index Headache Index Frequency of patients with headache reduction
Notes	
Risk of bias	

Blanchard 1990a *(Continued)*

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/PMR)
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	High risk	Either variance inequality (F-test statistically significant) or skewness (1.64 standard deviations exceeds the mean)
Trial size > 49?	High risk	N = 24
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Blanchard 1990b

Methods	Design: four group parallel trial Purpose: study the effect of thermal biofeedback and cognitive therapy on headache
Participants	Patients: out-patients with vascular headache Baseline comparability: NS
Interventions	Placebo: sessions of 'pseudomeditation' Untreated: no sessions Experimental: -sessions of thermal biofeedback and cognitive therapy -sessions of thermal biofeedback (Co-intervention: headache medication)
Outcomes	Medication Index Headache Index Frequency of patients with headache reduction
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Blanchard 1990b *(Continued)*

Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/thermal biofeedback)
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	High risk	Either variance inequality (F-test statistically significant) or skewness (1.64 standard deviations exceeds the mean)
Trial size > 49?	High risk	N = 42
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Block 1980

Methods	Design: three group parallel trial Purpose: examine the effect of rational emotive therapy on obese persons
Participants	Patients: overweight adults Baseline comparability: yes (weight)
Interventions	Placebo: sessions of deep muscle relaxation & discussions Untreated: no sessions Experimental: sessions with rational emotive therapy (Co-intervention: information booklet on nutrition)
Outcomes	Overweight (pounds)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS

Block 1980 *(Continued)*

Blinding? Treatment provider	High risk	Not described as double-blind (placebo/rational emotive therapy)
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (not naturally positive continuous outcomes e.g. change)
Trial size > 49?	High risk	N = 24
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Bosley 1989

Methods	Design: three group parallel trial Purpose: examine the effect of cognitive self-management training on hypertension
Participants	Patients: out-patients with essential arterial hypertension Baseline comparability: NS
Interventions	Placebo: general information on stress with no direct training suggestions Untreated: no training or information Experimental: cognitive self-management training (Co-intervention: antihypertensive medication, fixed ordination scheme: NS)
Outcomes	Diastolic blood pressure (mm Hg) Psychological distress Coping style
Notes	Standard deviations (SD) on diastolic blood pressure (mm Hg) not reported. SD estimated from another blood pressure study (Seer 1980: SD ˜ 10 mm Hg)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/training)

Bosley 1989 *(Continued)*

Blinding? Outcome assessor	Low risk	'The nurses were blind to the treatment group to which subjects were assigned'
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Unclear risk	Standard deviations (SD) on diastolic blood pressure (mm Hg) not reported. SD estimated from another blood pressure study (Seer 1980: SD ˜ 10 mm Hg)
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	High risk	N = 27
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Bova 1999

Methods	Design: three group parallel trial Purpose: evaluate the usefulness of premedication with an oral anticholinergic for relief of pain associated with barium enema
Participants	Patients: patients undergoing a pain inducing medical procedure (barium enema) Baseline comparability: NS
Interventions	Placebo: tablet with no hyoscyamine 15 to 30 minutes before procedure Untreated: no tablet Experimental: tablet with hyoscyamine (Co-intervention: NS)
Outcomes	Pain (0 to 10 analogue scale) reported immediately after enema Side effects
Notes	Patients with contraindications to hyoscyamine were 'moved to the placebo and no-treatment group'.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Unclear risk	NS
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome

Bova 1999 *(Continued)*

Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15 %
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	Low risk	N = 70
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Allocation NOT clearly concealed

Bramston 1985

Methods	Design: four group parallel trial Purpose: examine the effect of cognitive and behavioural social skills training with intellectually handicapped adults
Participants	Patients: institutionalised intellectually handicapped adults Baseline comparability: yes (outcomes)
Interventions	Placebo: unstructured training in 'money management' Untreated: no training Experimental: -cognitive social skills training -behavioural social skills training (Co-intervention: standard care)
Outcomes	Social skills assessment chart Staff questionnaire on social skills Preschool interpersonal problem solving
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/training)
Blinding? Outcome assessor	Low risk	'None of the raters participated in the training programme or were aware of S-group allocation'

Bramston 1985 *(Continued)*

Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	High risk	N = 24
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Brill 1964

Methods	Design: six group parallel trial Purpose: to examine the effect of psycho- and pharmacotherapy on psychiatric out-patients
Participants	Patients: out-patients with neuroses, borderline schizophrenia or personality disorders Baseline comparability: yes (rating scales)
Interventions	Placebo: capsule without meprobamate, phenobarbital or prochlorperazine Untreated: no capsule (waiting list group) Experimental: capsule with -meprobamate -phenobarbital -prochlorperazine (Co-intervention: NS)
Outcomes	Patient's rating (anxiety, tension, irritability, concentration, alertness, mood, sleep, appetite, general feeling) Rating by relative and patient (getting along, nervousness, happiness, ability to handle personal problems, energy, physical health, presenting symptoms or problems, ability to work, ability to enjoy life, overall condition) MMPI (Minnesota Multi phasic Personality Inventory) Social Worker Interview Evaluation
Notes	Number of patients assigned to untreated group was 34 contrasting the number in the other groups which had 50 to 54 patients. Relevant outcome data not accessible

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding?	Low risk	'Used a double-blind method of administration of drugs'

Brill 1964 *(Continued)*

Treatment provider		
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	Drop-out >15% or NS
Free of selective reporting?	High risk	Relevant outcome data not accessible
Free of other bias?	Low risk	
Trial size > 49?	Low risk	N = 89
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Drop-out >15% or NS

Brinkhaus 2006

Methods	Design: three group parallel trial Purpose: examine the effect of acupuncture in patients with chronic low back pain
Participants	Patients: patients with chronic low back pain Baseline comparability: yes (age, gender, pain intensity)
Interventions	Placebo: acupuncture on sites not regarded acupuncture sites Untreated: no acupuncture Experimental: acupuncture on sites regarded acupuncture sites (Co-intervention: All patients were allowed to take non-steroid anti-inflammatory drugs if necessary)
Outcomes	Pain (VAS) Back function (Funktionsfragebogen Hannover-Rücken) Global assessment of effect Pain disability Index Emotional aspects of pain (Schmertzempfindungsskala) Depression (Allgemeine Depressionsskala) Quality of life (SF-36) Number of days with pain Number of days with pain medication
Notes	Patients in the no-treatment group took medication on 6.3 days whereas the placebo group did so on 4.9 days (weeks 5 to 8) .

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	‘a randomised list was generated using computer software [SAMPSIZE V2.0]’
Allocation concealment?	Low risk	'Centralised telephone randomization procedure'
Blinding?	High risk	Not described as double-blind (placebo/acupressure)

Brinkhaus 2006 *(Continued)*

Treatment provider		
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Low risk	Primary outcome specified in protocol
Free of other bias?	Unclear risk	Patients in the no-treatment group took medication on 6.3 days whereas the placebo group did so on 4.9 days (weeks 5 to 8) .
No signs of variance inequality or skewness?	Unclear risk	Not relevant (not naturally positive continuous outcomes e.g. change)
Trial size > 49?	Low risk	N = 144
Clearly concealed allocation + trial size > 49 + drop-out max 15%	Low risk	

Bullock 2002

Methods	Design: three group parallel trial Purpose: to study the effect of auricular acupuncture for alcohol dependence
Participants	Patients: in-patients with alcohol dependence Baseline comparability: yes (age, gender)
Interventions	Placebo: needling on sites not regarded acupuncture sites Untreated: no needling Experimental: needling on sites regarded acupuncture sites (Co-intervention: conventional alcohol dependence treatment according to the 'Minnesota Model')
Outcomes	Alcohol use (Timeline Follow-back) Addiction severity index (ASI) Alcohol dependence scale Breathalyzer Alcohol desire (5-point Likert scale) Health status (SF36 and Medical status composite score part of ASI) Beck depression inventory Self-rating anxiety scale
Notes	Outcome not reported so that meta-analysis is possible.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS

Bullock 2002 *(Continued)*

Blinding? Treatment provider	Unclear risk	NS
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	High risk	Outcome not reported so that meta-analysis is possible.
Free of other bias?	Low risk	
Trial size > 49?	Low risk	N = 267
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Drop-out > 15% or NS

Cabrini 2006

Methods	Design: three group parallel trial Purpose: examine the effect of acupuncture in reducing discomfort during fibreoptic bronchoscopy
Participants	Patients undergoing diagnostic bronchoscopy Baseline comparability: yes
Interventions	Placebo: acupuncture on sites not regarded acupuncture sites Untreated: no acupuncture Experimental: acupuncture on sites regarded acupuncture sites (Co-intervention: All patients were treated with airway topical anaesthesia)
Outcomes	Discomfort (VAS) Anxiety Heart rate and pulse oximetry
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Acupuncturist aware of treatment group
Blinding?	Unclear risk	Not relevant as outcome was patient-reported

Cabrini 2006 *(Continued)*

Outcome assessor		
Incomplete outcome data addressed? All outcomes	High risk	Drop-outs not described
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	SD x 1.64 < mean
Trial size > 49?	High risk	N = 32
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Camatte 1969

Methods	Design: ten group parallel trial Purpose: examine the effect of various forms of drugs and placebo on the pain associated with peptic ulcer disease
Participants	Patients: patients with radiologically confirmed gastric ulcers Baseline comparability: NS
Interventions	Placebo: patches without active substance Untreated: no patches, capsules or injections Experimental: patches, capsules, and injections with various drugs, e.g. bismuth (Co-intervention: NS)
Outcomes	Pain (number of days in pain)
Notes	Outcome not reported so that meta-analysis is possible.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'Nei Gruppi 2 e 10 il placebo veniva presentato sotto forma di compresse aventi il medesimo aspetto ed il medesimo colore di uno dei medicamenti impiegati nei Gruppi 3 e 9'
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed?	High risk	Drop-out > 15% or NS

Camatte 1969 *(Continued)*
All outcomes

Free of selective reporting?	High risk	Outcome not reported so that meta-analysis is possible.
Free of other bias?	Low risk	
Trial size > 49?	Low risk	N = 72
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Drop-out > 15% or NS

Camberg 1999

Methods	Design: three group three period cross-over trial Purpose: examine the effect of 'Simulated Presence' (SimPres) on well-being in nursing home residents with Alzheimer's disease
Participants	Patients: nursing home residents with Alzheimer's disease
Interventions	Placebo: audio tape of a person reading a text that is not personal nor interactive Untreated: no audio tape Experimental: personalised interactive audio tape that contains a telephone conversation with a family member or surrogate. (Co-intervention: normal nursing home care)
Outcomes	Mood (multidimensional observation scale for elderly) Interest (multidimensional observation scale for elderly) Prevalence of agitated behaviour Prevalence of withdrawn behaviour Agitation scale (Cohen-Mansfield) Scale for observation of agitation in persons with dementia Positive affect rating scale Facial diagrams of mood (FACE)
Notes	Outcome not reported so that meta-analysis is possible.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	'Latin squares'
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Unclear risk	NS
Blinding? Outcome assessor	Low risk	'Observers were blinded to the study intervention'
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%

Camberg 1999 *(Continued)*

Free of selective reporting?	High risk	Outcome not reported so that meta-analysis is possible.
Free of other bias?	Low risk	
Trial size > 49?	High risk	N = 36
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Allocation not clearly concealed

Canino 1994

Methods	Design: three group parallel trial Purpose: examine the effect of behavioural treatment on hypertension
Participants	Patients: out-patients with primary hypertension Baseline comparability: yes (blood pressure)
Interventions	Placebo: stressful life events were recorded and participants instructed to relax at home some time every day without any formal relaxation training Untreated: waiting list Experimental: 'Behavioural program' (deep muscle relaxation technique and anxiety management training) (Co-intervention: no)
Outcomes	Diastolic blood pressure (mm Hg) Urinary catecholamine concentration Anxiety
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/behavioural program)
Blinding? Outcome assessor	Low risk	Automatic blood pressure measurement
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	

Canino 1994 *(Continued)*

No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	High risk	N = 13
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Carbajal 1999

Methods	Design: three group parallel trial Purpose: examine the analgesic effect of glucose, sucrose and pacifiers in term infants
Participants	Patients: newborn infants in need of venipunctures Baseline comparability: yes
Interventions	Placebo: 2 minutes before venipuncture sterile water was given to the infant orally with a syringe for 30 seconds Untreated: no sugar, pacifier or water Experimental: -glucose in syringe -sucrose in syringe -pacifier -sucrose in syringe and pacifier (Co-intervention: no)
Outcomes	Pain (Douleur Aiguë du Nouveau-né (DAN) scale (0 to 10 points)) during venipuncture
Notes	Outcome reported as medians (both placebo and no treatment: 7) and interquartile ranges (6-10, and 5-10)). Individual results were reported, and we recalculated the outcome as means and SD

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	'random numbers table'
Allocation concealment?	Low risk	'treatment allocations inserted in opaque sealed envelopes numbered 1-150. Investigators were blind to these allocations.'
Blinding? Treatment provider	Unclear risk	NS
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available

Carbajal 1999 *(Continued)*

Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	Low risk	N = 50
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Drop-out > 15% or NS

Carter 2001

Methods	Design: three group parallel trial Purpose: examine the effect of allergen avoidance for asthma among inner-city children
Participants	Patients: Children (5 to 16 years) with asthma Baseline comparability: yes
Interventions	Placebo: mattresses permeable for allergens, ineffective roach traps Untreated: no mattresses Experimental: mattresses impermeable for allergens and effective roach bait (Co-intervention: NS)
Outcomes	Number of acute visits for asthma (hospitalisation, emergency department visits, unscheduled clinical visits) Allergen level (dust mite, cockroach, cat) Sensitization to common allergens
Notes	Outcome not reported so that meta-analysis is possible

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Unclear risk	NS
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	High risk	Outcome not reported so that meta-analysis is possible
Free of other bias?	Low risk	

Carter 2001 *(Continued)*

Trial size > 49?	Low risk	N = 55
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Drop-out > 15% or NS

Carter 2003

Methods	Design: three group parallel trial Purpose: examine the effect of unguided self-help for bulimia nervosa
Participants	Patients: patients with bulimia nervosa Baseline comparability: yes (age, duration of bulimia nervosa)
Interventions	Placebo: cognitive behaviour self-help therapy Untreated: no self-help therapy Experimental: non-specific self-help therapy (manual on 'self-assertion for women' and hearing a plausible rationale) (Co-intervention: NS)
Outcomes	Frequency of binge eating Frequency of compensatory behaviours Eating disorder inventory scores Rosenberg self-esteem score Beck depression inventory score Inventory of interpersonal problems score
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	'Random numbers table'
Allocation concealment?	Low risk	'numbered opaque sealed envelopes'
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/self-guide)
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (binary outcome)

Carter 2003 *(Continued)*

Trial size > 49?	Low risk	N = 57
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Drop-out > 15% or NS

Cesarone 2001

Methods	Design: three group parallel trial Purpose: to evaluate the effect of local (foot) treatment with Essaven gel in subjects with diabetes mellitus and neuropathy without ulcers.
Participants	Patients: out-patients with diabetes mellitus and neuropathy without ulcers. Baseline comparability: NS
Interventions	Placebo: Placebo-gel Untreated: No-treatment Experimental: 1g of Essaven gel applied to foot (Co-intervention: Standard insulin management)
Outcomes	Laser Doppler flowmetry measuring flux PO_2/PCO_2 (Kontron analyzer with a Combi sensor)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Low risk	'the randomization process was controlled by an external statistical controller according to GCP rules'
Blinding? Treatment provider	Low risk	'The trial was a double-blind, placebo-controlled study'
Blinding? Outcome assessor	Low risk	Objective measurements of flux and PO_2/PCO_2
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
Trial size > 49?	High risk	N = 23
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Chenard 1991

Methods	Design: three group parallel trial Purpose: examine the effect of a back school treatment program and placebo intervention on chronic low back pain
Participants	Patients: out-patients with chronic low back pain Baseline comparability: yes
Interventions	Placebo: sessions of transcutaneous electrical nerve stimulation (TENS) with the TENS machine off Untreated: no sessions Experimental: sessions of the 'Interactional Back School' Program (Co-intervention: NS)
Outcomes	Pain (VAS)
Notes	Standard deviation of 10 cm visual analogue pain scales, pain means calculated from F-test statistic.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Unclear risk	NS
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	High risk	Either variance inequality (F-test statistically significant) or skewness (1.64 standard deviations exceeds the mean)
Trial size > 49?	High risk	N = 28
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Classen 1983

Methods	Design: two group, four period cross-over trial with a third untreated group assessed after the first period

Classen 1983 *(Continued)*

	Purpose: examine the relationship between sensory suggestibility and treatment effect
Participants	Patients: out-patients suffering from chronic intermittent headaches Baseline comparability: pretreatment headache scores
Interventions	Placebo: tablet without metamizole Untreated: no tablet Experimental: tablet with metamizole (Co-intervention: NS)
Outcomes	Pain (headache scores, 4-item 6-point scale) Sensitivity values (d')
Notes	The first period was considered a parallel trial. Results from later periods were disregarded.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	High risk	Either variance inequality (F-test statistically significant) or skewness (1.64 standard deviations exceeds the mean)
Trial size > 49?	High risk	N = 30
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Colker 1999

Methods	Design: three group parallel trial Purpose: examine the effect of a combination of Citrus aurantium extract, caffeine, and St. John's wort on obesity
Participants	Patients: overweight individuals (body mass index > 25 kg per square meter)

Colker 1999 *(Continued)*

	Baseline comparability: clinically relevant differences in age and body weight were not statistically significant
Interventions	Placebo: maltodextrin capsules Untreated: no capsules Experimental: capsules with a compound of Citrus aurantium extract, caffeine, and St. John's wort (Co-intervention: dietary and exercise program)
Outcomes	Weight Percent body fat Fat mass Basal metabolic rate Profile of Mood States questionnaire (POMS)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'Using a double-masked, randomized, placebo-controlled protocol...'
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	High risk	N = 11
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Conn 1986

Methods	Design: three group parallel trial Purpose: compare the efficacy of transcutaneous electrical nerve stimulation (TENS) with sham TENS on postoperative pain
Participants	Patients: postoperative in-patients (after appendicectomy)

Conn 1986 *(Continued)*

	Baseline comparability: operative course not compared.
Interventions	Placebo: TENS with machine off Untreated: no TENS Experimental: TENS with machine on (Co-intervention: analgesics on demand)
Outcomes	Pain (VAS)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Low risk	'sealed envelope'
Blinding? Treatment provider	Unclear risk	NS
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	High risk	N = 27
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Corver 2006

Methods	Design: three group parallel trial Purpose: study the effect of house dust mite impermeable mattress covers on the development of respiratory symptoms, atopic eczema, and mite-sensitization in children born to mothers with allergy
Participants	Patients: pregnant women in third trimester with allergy Baseline comparability: yes (several factors), no for gender of children
Interventions	Placebo: house dust mite permeable mattress (cotton) covers Untreated: no mattress covers Experimental: house dust mite impermeable mattress (polyester-cotton) covers

Corver 2006 *(Continued)*

	(Co-intervention: NS)
Outcomes	Wheezing at least once Recurrent wheezing Night cough without a cold Runny nose without a cold Atopic dermatitis House dust mite allergen level on bed Total IgE House dust mite specific IgE
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'...participants were randomly allocated... in a double blind fashion'
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (binary outcome)
Trial size > 49?	Low risk	N = 695
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Allocation not clearly concealed

Costello 2006

Methods	Design: three group parallel trial Purpose: study the effect of ethyl vinyl chloride spray on the pain associated with cannulation in children
Participants	Patients: children (9 to18 years) undergoing cannulation Baseline comparability: yes (age, gender ratio)
Interventions	Placebo: isopropyl alcohol spray

Costello 2006 *(Continued)*

	Untreated: no spray Experimental: ethyl vinyl chloride spray (Co-intervention: no)
Outcomes	Pain intensity VAS
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	'random number allocation'
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'The investigators and nursing staff performin IV cannulation were blinded to the cannister's contents...'
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	High risk	Either variance inequality (F-test statistically significant) or skewness (1.64 standard deviations exceeds the mean)
Trial size > 49?	Low risk	N = 90
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Not clearly concealed allocation

Coyne 1995

Methods	Design: three group parallel trial Purpose: examine the effect of transcutaneous electrical nerve stimulation (TENS) on pain
Participants	Patients: persons having a venepuncture to give blood Baseline comparability: yes
Interventions	Placebo: placebo TENS Untreated: no TENS or placebo TENS Experimental: TENS (Co-intervention: NS)
Outcomes	Pain (VAS)

Coyne 1995 *(Continued)*

Notes	Standard deviation of 10 cm visual analogue pain scale, means calculated from F-test statistic.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Unclear risk	NS
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	High risk	Either variance inequality (F-test statistically significant) or skewness (1.64 standard deviations exceeds the mean)
Trial size > 49?	High risk	N = 42
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Crosby 1994

Methods	Design: four group parallel trial Purpose: examine the effect of iron supplement on acute blood loss anaemia after surgery
Participants	Patients: postoperative out-patients Baseline comparability: yes for age and sex.
Interventions	Placebo: NS Untreated: no placebo or iron Experimental: iron supplement at two doses (Co-intervention: no)
Outcomes	Hb concentration (mg Hgl/dl) (59 days after surgery) Haematocrit Serum-iron Serum-ferritin
Notes	

Crosby 1994 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	'computer-generated table of random numbers'
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'Consenting patients were randomized into four groups in a double-blind fashion...'
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	Low risk	N = 59
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Allocation not clearly concealed

Cupal 2001

Methods	Design: three group parallel trial Purpose: examine the effect of relaxation + guided imagery (and attention-placebo) on physical and psychological aspects of rehabilitation following orthopedic surgery
Participants	Patients: patients having had performed anterior cruciate ligament reconstruction Baseline comparability: NS
Interventions	Placebo: over a period of 6 months, 10 sessions of 30 to 40 minutes of encouragement, support and reminders to visualise a peaceful scene daily Untreated: no sessions Experimental: sessions of structured relaxation and guided imagery (Co-intervention: physical therapy)
Outcomes	Pain (11 point scale, 0 to 10) Re-injury anxiety Knee strength (ratio of injured knee to the uninjured knee)
Notes	

Risk of bias

Cupal 2001 *(Continued)*

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	'random block'
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/relaxation)
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	High risk	N = 20
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Davidson 1980

Methods	Design: five group parallel trial Purpose: examine the effect of psychological treatments on compulsive nail biting
Participants	Patients: out-patients regarding nail biting a serious problem and a source of personal shame Baseline comparability: yes
Interventions	Placebo: factual information on nails, diseases of nails and of theories about pathological nail biting Untreated: waiting list Experimental: two types of psychological intervention separately, and one combined. (Co-intervention: NS)
Outcomes	Length of nails (mm) and estimated frequency of nail biting (per day) Estimated control over nail biting Cosmetic appearance rate
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Davidson 1980 *(Continued)*

Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/psychological intervention)
Blinding? Outcome assessor	Low risk	'Post-test and follow-up sessions were conducted by an experimenter who had no knowledge of the groups to which subjects had been assigned during treatment'
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	High risk	N = 20
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

De Sanctis 2001

Methods	Design: three group parallel trial Purpose: examine the effect of Essaven gel in patients with venous microangiopathy and venous ulceration
Participants	Patients: out-patients with microangiopathy and venous ulcers Baseline comparability: yes (age, gender ratio)
Interventions	Placebo: Gel not containing Essaven Untreated: no gel Experimental: Gel containing Essaven (Co-intervention: elastic stockings)
Outcomes	Ulcer healing rates Total symptom score (based on Pain, edema, alternation in social life and working handicaps, cost of care, deambulation) Microcirculatory parameters (flux, CO2, O2)
Notes	No patient in either group had healed ulcers. For computing reasons we have entered data as one patient in each group had a healed ulcer.

Risk of bias

Bias	Authors' judgement	Support for judgement

De Sanctis 2001 *(Continued)*

Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Low risk	'The randomization process was controlled by an external statistical controller according to GCP rules'
Blinding? Treatment provider	Low risk	'Operators were unaware of the contents of the tube, which was numbered'
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (binary outcome)
Trial size > 49?	High risk	N = 19
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Defrin 2005

Methods	Design: six group parallel trial Purpose: study the effect of segmental versus innocuous electrical stimulation for chronic pain relief
Participants	Patients: out-patients needing screening flexible endoscopy Baseline comparability: yes (age, gender)
Interventions	Placebo: stimulation with interferential current (IF) device off Untreated: no IF device treatment Experimental: stimulation with IF device on (Co-intervention: analgesic medication. Patients were asked not to change regime during the study)
Outcomes	Pain (VAS) Pain relief (%) Morning stiffness (VAS) Range of motion (Goniometry) Pain threshold
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Defrin 2005 *(Continued)*

Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/electrical stimulus device)
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	High risk	N = 17
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Dibble 2007

Methods	Design: three group parallel trial Purpose: study the effect of acupressure on chemo-therapy induced nausea
Participants	Patients: cancer patients receiving chemotherapy Baseline comparability: yes
Interventions	Placebo: needling in S13 point theoretically inert for nausea Untreated: no needling Experimental: needling in P6 (Co-intervention: antiemetic drugs)
Outcomes	Nausea intensity (NRS) Rhodes Index of Nausea (3 items) Rhodes index of nausea and vomiting (1 item) Functional status (NRS) State-Trait Anxiety Inventory
Notes	Data provided from authors: mean nausea NRS (0 to 10) evening after getting chemotherapy.

Risk of bias

Bias	Authors' judgement	Support for judgement

Dibble 2007 *(Continued)*

Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'The researchers endeavoured to keep the research assistant masked as to the active point'
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	High risk	No protocol available. Data provided from authors
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	High risk	Either variance inequality (F-test statistically significant) or skewness (1.64 standard deviations exceeds the mean)
Trial size > 49?	Low risk	N = 100
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Allocation not clearly concealed

Ditto 2003

Methods	Design: three group parallel trial Purpose: study the effect of applied muscle tension on blood donation reactions
Participants	Patients: English speaking blood donors Baseline comparability: yes (age, gender)
Interventions	Placebo: applied muscle tension training for 2 minutes Untreated: no training Experimental: applied muscle tension training for 15 minutes (Co-intervention: no)
Outcomes	Blood donations reactions inventory score Proportion of cases in which donation chairs were reclined Proportion of full blood portion donated Doner's estimate of the probability of giving blood again Pain Anxiety Heart rate Blood pressure
Notes	Trialists assumed that at least 5 minutes of applied muscle tension training was needed for an effect.
Risk of bias	

Ditto 2003 *(Continued)*

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/applied muscle tension)
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	High risk	Either variance inequality (F-test statistically significant) or skewness (1.64 standard deviations exceeds the mean)
Trial size > 49?	Low risk	N = 389
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Drop-out > 15% or NS

Ditto 2006

Methods	Same as Ditto 2003
Participants	Patients: french speaking blood donors Baseline comparability: yes (age, gender)
Interventions	Same as Ditto 2003
Outcomes	Same as Ditto 2003
Notes	Same trial as Ditto 2003 but results for French speaking donors reported separately

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/applied muscle tension)

Ditto 2006 *(Continued)*

Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	High risk	Either variance inequality (F-test statistically significant) or skewness (1.64 standard deviations exceeds the mean)
Trial size > 49?	Low risk	N = 295
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Drop-out > 15% or NS

Doty 1975

Methods	Design: five group parallel trial Purpose: to examine the effect of social skills training on the interpersonal interaction of chronic psychiatric patients
Participants	Patients: chronic psychiatric in-patients Baseline comparability: probably (stratified by level of daily interaction)
Interventions	Placebo: sessions with transactional game followed by lectures by the therapist Untreated: no sessions Experimental: -sessions with social skills training (role playing) -sessions with incentive condition (re-enforcement by reward) -combination (Co-intervention: yes, most patients received psychotropic drugs; type, dose and group distribution NS)
Outcomes	% alone: the % of the time the individual was observed more than 4 feet away from another person. % silent: the % of the time the person was silent in a group discussion
Notes	Relevant outcome data not accessible

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/social skills training)

Doty 1975 *(Continued)*

Blinding? Outcome assessor	Low risk	'The observers were blind to both the nature of the dependent variable to be extracted from their recordings and the group assignments...'
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	High risk	Relevant outcome data not accessible
Free of other bias?	Low risk	
Trial size > 49?	High risk	N = 20
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Double 1993

Methods	Design: three group, three period cross-over trial Purpose: to examine the effect of discontinuation of antiparkinsonian medication in patients maintained on neuroleptics
Participants	Patients: psychiatric in-patients on concomitant antiparkinsonian and neuroleptic medication for over one year Baseline comparability: not relevant
Interventions	Placebo: capsules with no antiparkinsonian medication Untreated: no capsules Experimental: capsules with antiparkinsonian medication (type and dose individual but fixed through trial) (Co-intervention: yes, neuroleptics, fixed dose through trial except for three patients)
Outcomes	Number of patients with relapse of parkinsonian symptoms (= need for escape medication) Extrapyramidal Symptom Rating Scale (ESRS)
Notes	The outcome data was not available from the first period only, and was calculated as deriving from a parallel group trial.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'The medication periods were assigned blindly...'
Blinding? Outcome assessor	Unclear risk	NS

Double 1993 *(Continued)*

Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Unclear risk	The outcome data from this cross-over trial was not available from the first period only, and was calculated as deriving from a parallel group trial.
No signs of variance inequality or skewness?	Unclear risk	Not relevant (binary outcome)
Trial size > 49?	High risk	N = 44
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Dundee 1986

Methods	Design: three group parallel trial Purpose: examine the prophylactic effect of acupuncture on perioperative nausea
Participants	Patients: surgical in-patients undergoing minor gynaecological procedures Baseline comparability: 'broadly comparable', but no data presented
Interventions	Placebo: needling on the lateral elbow crease, a point that is not on any recognized acupuncture line Untreated: no needling Experimental: needling at the P6 point (Neiguan) (Co-intervention: 10 mg nalbuphene as routine premedication)
Outcomes	Number of patients with nausea
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/acupuncture)
Blinding? Outcome assessor	Low risk	'These assessments were performed by an observer who was unaware of which patients had undergone acupuncture'
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS

Dundee 1986 *(Continued)*

Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (binary outcome)
Trial size > 49?	Low risk	N = 50
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Drop-out > 15% or NS

Elliott 1978

Methods	Design: four group parallel trial Purpose: examine the effect of a multiple-component treatment approach on smoking reduction
Participants	Patients: smokers Baseline comparability: yes
Interventions	Placebo: non-directive discussions Untreated: no discussions Experimental: -rapid smoking (smoked every 6 seconds until unable to continue) -package treatment (rapid smoking, applied relaxation, covert sensitization, systematic desensitization, self-reward and punishment etc) (Co-intervention: NS)
Outcomes	Number of abstinent smokers Mean number of cigarettes smoked / day
Notes	The trial consisted of a primary intervention phase and a secondary booster phase. Only the allocation to the booster treatment was explicitly described as random. Contact with authors clarified that allocation in the primary phase was also random.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/package treatment)
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS

Elliott 1978 *(Continued)*

Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (binary outcome)
Trial size > 49?	High risk	N = 24
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Erdogmus 2007

Methods	Design: three group parallel trial Purpose: study the effect of physiotherapy
Participants	Out-patients having had a disc herniation operation Baseline comparability: yes (except for body mass index)
Interventions	Placebo: sessions with neck massage Untreated: no sessions Experimental: sessions with physiotherapy-based rehabilitation (Co-intervention: yes)
Outcomes	Low Back Pain Rating Scale Overall satisfaction Socioeconomic parameters State Trait Anxiety Inventory
Notes	SDs were obtained from the reported CIs

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	'block randomization (SAS) was performed by the Department of Medical Statistics'
Allocation concealment?	Low risk	'sequentially numbered, sealed opaque envelopes'
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/physiotherapy)
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available

Erdogmus 2007 *(Continued)*

Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (not naturally positive continuous outcomes e.g. change)
Trial size > 49?	Low risk	N = 80
Clearly concealed allocation + trial size > 49 + drop-out max 15%	Low risk	All three categories fulfilled

Espie 1989

Methods	Design: six group parallel trial Purpose: examine the effect of psychological treatments on chronic insomnia
Participants	Patients: out-patients suffering from chronic sleep-onset insomnia Baseline comparability: yes (age, sex, duration of insomnia)
Interventions	Placebo: imaginary belief treatment: neutral images paired with bed time activities. Untreated: waiting list Experimental: -relaxation therapy -stimulus control -paradoxical intervention -tailored therapy condition (reported in another publication) (Co-intervention: hypnotics, fixed ordination and withdrawal scheme, compliance NS)
Outcomes	Sleep latency (min) Sleep quality
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	'predetermined list of random numbers'
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/psychological intervention)
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available

Espie 1989 *(Continued)*

Free of other bias?	Low risk	
No signs of variance inequality or skewness?	High risk	Either variance inequality (F-test statistically significant) or skewness (1.64 standard deviations exceeds the mean)
Trial size > 49?	High risk	N = 27
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Etringer 1982

Methods	Design: three group parallel trial Purpose: examine the effect of 'participant modelling' (snake handling) therapy on snake phobia
Participants	Patients: individuals who were unable to hold a snake for 10 sec Baseline comparability: yes
Interventions	Placebo: sessions of 'graduated subliminal modelling'. Patients were exposed to blank slides and told they were subliminal pictures of snakes. Untreated: no sessions Experimental: sessions of 'participant modelling' (Co-intervention: NS)
Outcomes	Behavioral avoidance test (18 successive steps of snake interaction tasks). Fear arousal accompanying approach. Anticipatory fear. Self-efficacy expectations
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/participant modelling)
Blinding? Outcome assessor	Low risk	'The assessors were kept blind as to each subject's particular treatment condition'
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	

Etringer 1982 *(Continued)*

No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	High risk	N = 25
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Etter 2002

Methods	Design: three group parallel trial Purpose: test the effect of nicotine replacement therapy, and placebo, in reducing cigarette consumption in smokers willing to intend to reduce number of smoked cigarettes but not to quit
Participants	Patients: cigarette smokers unwilling to quit, but intending to reduce smoking by half Baseline comparability: not for gender (54% male in nicotine group and 44% in no treatment group); yes for age, cigarette consumption, intention to reduce consumption (and several other variables)
Interventions	Placebo: transdermal patch, gum, or inhaler without nicotine (and information leaflet) mailed every other week at the choice of the patient for 6 months Untreated: no transdermal patch, gum, inhaler or leaflet Experimental: transdermal patch, gum, inhaler with nicotine (and information leaflet) (Co-intervention: information booklet after three months)
Outcomes	Mean number of cigarettes smoked per day after 6 months Score of smoking intensity (0 to 100) Score of total smoke inhalation per day (0 to 10) Mean number of reduction of smoked cigarettes per day Smoking cessation rate
Notes	Not 1:1 randomisation. The combination of baseline inequality for gender, and lack of clear description of concealment of allocation indicate possible selection bias. In the no treatment group 7% did not provide information on smoking habits; in the placebo group it was 3%. For these individuals the baseline values were computed as the end result. Because the dropout rate was higher in the no-treatment group this may have resulted in an inflated estimate of the mean number of smoked cigarettes, and thus a too optimistic estimate of the effect of placebo on smoking reduction.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	'computer generated list of random numbers'
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/drug)
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed?	Low risk	Drop-out < 15%

Etter 2002 *(Continued)*
All outcomes

Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	High risk	See notes
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	Low risk	N = 658
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Allocation not clearly concealed

Faas 1993

Methods	Design: three group parallel trial Purpose: examine the prophylactic effect of physical exercise and advice on daily living on recurrence of acute low back pain
Participants	Patients: out-patients visiting a GP with acute low back pain Baseline comparability: yes
Interventions	Placebo: sessions with ultrasound at lowest possible frequency Untreated: no sessions (standard therapy) Experimental: sessions with exercise and advice on daily living (Co-intervention: analgesics on demand, dose NS)
Outcomes	Number of patients with recurrent low back pain episodes Duration of recurrent low back pain episodes Functional health status Mobility problems Influence on daily life In-between consultation of the GP
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Low risk	'sealed envelope'
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/exercise)
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed?	Low risk	Drop-out < 15%

Faas 1993 *(Continued)*

All outcomes

Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (binary outcome)
Trial size > 49?	Low risk	N = 317
Clearly concealed allocation + trial size > 49 + dropout max 15%	Low risk	All three categories fulfilled

Fanti 2003

Methods	Design: three group parallel trial Purpose: study the effect of acupuncture on discomfort, pain and anxiety during colonoscopy
Participants	Patients: patients scheduled to undergo colonoscopy Baseline comparability: yes (age, pre-colonoscopy anxiety)
Interventions	Placebo: needling and electrical stimulation on sites not regarded analgesic acupuncture sites Untreated: no needling Experimental: needling and electrical stimulation on sites regarded analgesic acupuncture sites (L14, S36, SP6, SP9) (Co-intervention: midazolam 15 minutes before procedure and as required)
Outcomes	Escape medication (midazolam) Pain at 4 times during the procedure (5-point scale) Procedure acceptability (5-point scale) Patient satisfaction Technical difficulty of the procedure (physician and nurse) Satisfaction with sedation (physician and nurse) Total procedural time
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	'computer-generated sequence of numbers'
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Unclear risk	NS
Blinding? Outcome assessor	Unclear risk	NS

Fanti 2003 *(Continued)*

Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (binary outcome)
Trial size > 49?	High risk	N = 20
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Fiorellini 2005

Methods	Design: three group parallel trial Purpose: evaluate the efficacy of bone induction for the placement of dental implants using recombinant human bone morphogenetic protein-2.
Participants	Patients: patients requiring local alveolar ridge preservation/augmentation of buccal wall defects following extraction of maxillary teeth. Baseline comparability: NS
Interventions	Placebo: bioabsorbable collagen sponge (ACS) alone Untreated: No-treatment Experimental: recombinant human bone morphogenetic protein-2 delivered on a ACS. (Co-intervention: preoperative antibiotics and 0.12% chlohexidine rinse (15ml))
Outcomes	Alveolar bone height and bone width (CT scan) Alveolar bone volume (CT scan) Bone density (CT scan) Bone biopsy
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'Two sequential cohorts of 40 patients each were randomized in a double-masked manner...'
Blinding? Outcome assessor	Low risk	'... three independent masked CT scan reviewers...'

Fiorellini 2005 *(Continued)*

Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
Trial size > 49?	High risk	N = 37
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Fisher 2006

Methods	Design: three group parallel trial Purpose: study the feasibility of running a randomised trial aimed at evaluating specific and non-specific effects in homeopathy
Participants	Out-patients with dermatitis Baseline comparability: yes (age, gender)
Interventions	Placebo: lactose pills Untreated: no pills Experimental: homeopathic pills (Co-intervention: NS)
Outcomes	Overall symptoms Skin symptoms Itching Sleep DLQI (dermatology life quality index) Use of steroids
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	'randomisation list'
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'double-blind placebo'
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed?	High risk	Drop-out > 15% or NS

Fisher 2006 *(Continued)*

All outcomes		
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	High risk	N = 27
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Forster 1994

Methods	Design: three group parallel trial Purpose: examine the effect of transcutaneous nerve stimulation (TENS) on pain
Participants	Patients: postoperative in-patients (coronary artery bypass surgery) Baseline comparability: yes
Interventions	Placebo: TENS with machine turned off Untreated: no TENS Experimental: TENS with machine turned on (Co-intervention: analgesics as deemed appropriate by staff)
Outcomes	Pain (verbal numerical scale) Lung function parameters
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Unclear risk	NS
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available

Forster 1994 *(Continued)*

Free of other bias?	Low risk	
No signs of variance inequality or skewness?	High risk	Either variance inequality (F-test statistically significant) or skewness (1.64 standard deviations exceeds the mean)
Trial size > 49?	High risk	N = 30
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Foster 2004

Methods	Design: three group parallel trial Purpose: study the effect of the Trager approach on chronic headache
Participants	Patients: outpatients with chronic headache Baseline comparability: yes
Interventions	Placebo: attention treatment by physician including physical exam (15 to 20 minutes) Untreated: no treatment Experimental: Trager approach (movement based educational process to increase body awareness, learn relaxation skills, and practise pain-free, balanced movement) (Co-intervention: medication)
Outcomes	The headache quality of life instrument Headache frequency, duration, and intensity Medication use
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/Trager)
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	

Foster 2004 *(Continued)*

No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	High risk	N = 18
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Foster 2007

Methods	Design: three group parallel trial Purpose: study the effect of acupuncture on osteoarthrosis of the knee
Participants	Patients: older outpatients with osteoarthrosis of the knee Baseline comparability: yes
Interventions	Placebo: needling with a non-penetrating blunt needle Untreated: no needling Experimental: needling at with a proper acupuncture needle (Co-intervention: exercise and advice)
Outcomes	WOMAC pain sub-scale WOMAC scale Function and general improvement
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	'a computed generated randomisation'. We assume 'a computer generated randomisation'
Allocation concealment?	Low risk	After inclusion of patients into the trials the 'physiotherapist telephoned an administrator at the research centre to ... receive ... a computed generated randomisation group.'
Blinding? Treatment provider	High risk	Acupuncturist knew type of acupuncture
Blinding? Outcome assessor	Unclear risk	Not relevant as patient-reported outcome
Incomplete outcome data addressed? All outcomes	Low risk	Drop out <15%
Free of selective reporting?	Low risk	Protocol published. No sign of outcome selection bias for the primary outcome
Free of other bias?	Low risk	

Foster 2007 *(Continued)*

No signs of variance inequality or skewness?	High risk	SD x 1.67 >mean
Trial size > 49?	Low risk	N = 217
Clearly concealed allocation + trial size > 49 + drop-out max 15%	Low risk	All three criteria fulfilled

Frank 1990

Methods	Design: five group parallel trial Purpose: examine the effect of psychotherapy, imipramine and placebo on relapse of depression
Participants	Patients: stable out-patients with unipolar depression having improved markedly after imipramine medication and psychotherapy Baseline comparability: yes
Interventions	Placebo: continuous treatment with -tablets containing no imipramine (content NS) plus psychotherapy sessions -tablets containing no imipramine (content NS) plus visits to a medication clinic Untreated: continuous treatment with psychotherapy but without any tablets Experimental: continuous treatment with -imipramine tablets and psychotherapy sessions -imipramine tablets and visits to a medication clinic -continuous treatment with imipramine tablets without psychotherapy sessions (Co-intervention: NS)
Outcomes	Number of patients with relapse of depression Time to recurrence of depression
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'...both the patients and the members of their treatment team remained blind to whether they were receiving active medication or placebo'
Blinding? Outcome assessor	Low risk	Partly blinded
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available

Frank 1990 *(Continued)*

Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (binary outcome)
Trial size > 49?	Low risk	N = 52
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Allocation not clearly concealed

Frankel 1978

Methods	Design: three group parallel trial Purpose: examine the effect of biofeedback on arterial hypertension
Participants	Patients: out-patients with essential arterial hypertension Baseline comparability: yes
Interventions	Placebo: sessions of discussions of past and present problems with no behavioural techniques taught Untreated: no sessions Experimental: training sessions for behavioural techniques (Co-intervention: NS)
Outcomes	Diastolic blood pressure (mm Hg) Multiple personality, depression and activity tests
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	'random number table'
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/biofeedback)
Blinding? Outcome assessor	Low risk	'... nurses (who was blind to the patient's experimental status)...'
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)

Frankel 1978 *(Continued)*

Trial size > 49?	High risk	N = 15
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Frega 1994

Methods	Design: three group parallel trial Purpose: to evaluate the pain caused by laser vaporization of intraepithelial cervical neoplasia
Participants	Patients: women with intraepithelial cervical neoplasia Baseline comparability: NS
Interventions	Placebo: tablet without naproxen Untreated: no tablet Experimental: tablet with naproxen (Co-intervention: NS)
Outcomes	Pain (VAS)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Unclear risk	NS
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	High risk	Either variance inequality (F-test statistically significant) or skewness (1.64 standard deviations exceeds the mean)
Trial size > 49?	High risk	N = 42
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Fuchs 1977

Methods	Design: three group parallel trial Purpose: examine the effect of self-control behaviour therapy on depression
Participants	Patients: female out-patients with depression as defined by a multiple cut-off procedure of the Minnesota Multi phasic Personality Inventory (D more than 69) Baseline comparability: yes (depression scores)
Interventions	Placebo: sessions of discussion on past and present problems with no behavioural techniques taught Untreated: no sessions Experimental: sessions of behavioural techniques training (Co-intervention: NS)
Outcomes	Beck Depression inventory Minnesota Multi phasic Personality Inventory (depression scale and total evaluation) Group interaction activity and response elicitation Pleasant events activity and reinforcement potential Self-evaluation Common associates test Concepts test
Notes	The standard deviation (SD) on the improvement of the mean on Beck Depression Inventory was not reported. The SD was calculated from a F-test statistic.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/behaviour therapy)
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	High risk	N = 20

Fuchs 1977 *(Continued)*

Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Gluckman 1980

Methods	Design: three group parallel trial Purpose: study the effect of a remedial program on visual-motor perception in children with spina bifida
Participants	Patients: Children with spina bifida who were able to respond to verbal and paper-and-pencil task Baseline comparability: yes
Interventions	Placebo: sessions with stimulating environment (jig-saw puzzles, drawing, colouring, reading etc) Untreated: no sessions Experimental: sessions with a program of development of visual perception (Co-intervention: NS)
Outcomes	Development test of visual perception (five sub-tests)
Notes	Outcome not reported so that meta-analysis is possible.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Unclear risk	NS
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	High risk	Outcome not reported so that meta-analysis is possible.
Free of other bias?	Low risk	
Trial size > 49?	High risk	N = 24
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Godfrey 1973

Methods	Design: three group, three period cross-over trial Purpose: to examine the effect of placebo on exercise induced asthma
Participants	Patients: children with bronchial asthma Baseline comparability: not relevant
Interventions	Placebo (according to active drug): -injections of saline -inhalations of saline -inhalations of lactose with sodium sulphate Untreated: no injections or inhalations Experimental: -inhalations of salbutamol -injections of atropine -inhalation of cromoglycate (Co-intervention: NS)
Outcomes	Fall in % peak expiratory flow (PEF) rate Number of patients with a drop in PEF rate of at least 15%
Notes	Data originally came from three small cross-over trials. The outcome data was not available from the first period only, and was calculated as deriving from one parallel group trial.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Unclear risk	NS
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15 % or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	High risk	Data originally came from three small cross-over trials. The outcome data was not available from the first period only, and was calculated as deriving from one parallel group trial.
No signs of variance inequality or skewness?	Unclear risk	Not relevant (not naturally positive continuous outcomes e.g. change)
Trial size > 49?	Low risk	N = 88
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Drop-out > 15 % or NS

Goldstein 2000

Methods	Design: three group parallel trial Purpose: study the effect of eye movement desensitization and reprocessing (EMDR) on panic disorder with agoraphobia
Participants	Patients: out-patients with panic disorder with agoraphobia Baseline comparability: NS
Interventions	Placebo: sessions with a credible attention-placebo ('association and relaxation therapy') Untreated: no sessions Experimental: sessions with EMDR (Co-intervention: anxiolytic drugs in moderate doses)
Outcomes	Frequency of panic attacks Daily and weekly expectancy of panic attack Daily highest anxiety Daily average anxiety The agoraphobic cognitions questionnaire Body sensations questionnaire Brief body sensations interpretations Panic appraisal inventory The mobility inventory Beck depression inventory Beck anxiety inventory Brief symptom inventory Social adjustment scale (self-report) Distress questionnaire
Notes	After completion of waiting-list period the no treatment group was randomised to placebo and active treatment. Results from the placebo group also included patients who originally were in the no-treatment group. Contact with the authors made it clear that the data from the originally randomised patients had been lost.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/EMDR)
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	High risk	No protocol available. Contact to the authors made it clear that the data from the originally randomised patients had been lost.
Free of other bias?	Low risk	

Goldstein 2000 *(Continued)*

Trial size > 49?	High risk	N = 27
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Goodenough 1997

Methods	Design: three group parallel trial Purpose: examine the effect of placebo medication and suggestion on acute pain associated with venepuncture
Participants	Patients: children undergoing venepuncture in a hospital setting Baseline comparability: NS
Interventions	Placebo: cream with no analgesic component and no suggestion of analgesic effect Untreated: no cream Experimental: cream with no analgesic component but with the suggestion of analgesic effect (Co-intervention: NS)
Outcomes	Pain (facial pain scale) Anxiety
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/placebo+suggestion)
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	High risk	Either variance inequality (F-test statistically significant) or skewness (1.64 standard deviations exceeds the mean)
Trial size > 49?	Low risk	N = 78

Goodenough 1997 *(Continued)*

Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Drop-out > 15% or NS

Gracely 1979

Methods	Design: three group parallel trial Purpose: examine the effect of placebo medication and naloxone on acute pain
Participants	Patients: postoperative in-patients after extraction of molars Baseline comparability: NS
Interventions	Placebo: injection with naloxone vehicle Untreated: no injection Experimental: injection with naloxone (Co-intervention: NS)
Outcomes	Pain
Notes	Data reported in a way not extractable for meta-analysis. Original data lost (personal communication Gracely RH)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	'random table generated by a shuffle program'
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'Two groups of 12 subjects received double-blind intravenous injections of either 10mg naloxone or naloxone vehicle (placebo)...'
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	High risk	No protocol available. Data reported in a way not extractable for meta-analysis. Original data lost (personal communication Gracely RH)
Free of other bias?	Low risk	
Trial size > 49?	High risk	N = 24
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Gracely 1983

Methods	Design: three group parallel trial Purpose: examine the influence of hidden infusion of naloxone on the effect of fentanyl and placebo in acute pain
Participants	Patients: postoperative in-patients after extraction of molars Baseline comparability: NS
Interventions	Placebo: injection with saline Untreated: no injection Experimental: injection with fentanyl (Co-intervention: pre-treatment hidden infusion of either naloxone or naloxone vehicle)
Outcomes	Pain (McGill pain rating index)
Notes	The trial report does not explicitly state that allocation was random, however personal communication with authors established that this is likely to have been the case.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	'random table generated by a shuffle program'
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'Hidden infusions of naloxone (10 mg) or naloxone vehicle were administered double-blind...'
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available.
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (not naturally positive continuous outcomes e.g. change)
Trial size > 49?	High risk	N = 29
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Grammer 1984

Methods	Design: three group parallel trial Purpose: examine whether patients with allergic rhinitis would have lower or higher symptom scores depending upon the presence of asthma

Grammer 1984 *(Continued)*

Participants	Patients: out-patients with allergic, ragweed rhinitis Baseline comparability: NS
Interventions	Placebo: injections without ragweed (caramelised glucose) Untreated: no injections Experimental: injections with polymerised ragweed (Co-intervention: histamine, dosage part of composite outcome score)
Outcomes	Rhinitis symptom-medication scores (sneeze, nasal congestion, histamine medication)
Notes	Relevant outcome data not accessible

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Unclear risk	NS
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	High risk	Relevant outcome data not accessible
Free of other bias?	Low risk	
Trial size > 49?	High risk	N = 31
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

GRECHO 1989

Methods	Design: four group parallel trial Purpose: examine the effect of two homoeopathic preparations on postoperative ileus
Participants	Patients: postoperative in-patients (after abdominal surgery) Baseline comparability: yes (sex, age, type and duration of operation)
Interventions	Placebo: granule with no homoeopathic content Untreated: no granule Experimental: homoeopathic preparations 'opium' or 'raphanus' (Co-intervention: use of laxatives higher in placebo than untreated)

GRECHO 1989 *(Continued)*

Outcomes	Time from abdominal closure to first stool and first flatus (hours)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	'random numbers'
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'... in a controlled, double-blind therapeutic trial...'
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	High risk	Drop out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	High risk	Either variance inequality (F-test statistically significant) or skewness (1.64 standard deviations exceeds the mean)
Trial size > 49?	Low risk	N = 300
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Drop out > 15% or NS

Guglielmi 1982

Methods	Design: three group parallel trial Purpose: examine the effect of skin temperature biofeedback on Raynaud's disease
Participants	Patients: out-patients with primary Raynaud's disease Baseline comparability: yes (age and severity of attack)
Interventions	Placebo: biofeedback training focused at relaxing forehead muscles Untreated: no training Experimental: biofeedback training focused at increasing finger temperature (Co-intervention: no)
Outcomes	Number of patients with attacks Duration of attacks Severity of attacks Extent of hand involvement Number of symptoms experienced Pain

Guglielmi 1982 *(Continued)*

	Impairment Length of time spent in laboratory to relieve the attack Amount of relief obtained from laboratory training
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'... a double-blind design was adopted'
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (binary outcome)
Trial size > 49?	High risk	N = 24
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Hall 1974

Methods	Design: four group parallel trial Purpose: examine the effect of two self-management treatments on obese persons
Participants	Patients: overweight adults Baseline comparability: NS
Interventions	Placebo: sessions with relaxation training Untreated: no sessions Experimental: -sessions with combined self-management technique: based on re-enforcement principles -sessions with simple self-management technique: based on re-enforcement principles (Co-intervention: information booklet on nutrition)
Outcomes	Weight loss (percentage of initial body weight)

Hall 1974 *(Continued)*

Notes	33 out of 84 patients were college students. The standard deviation (SD) of the mean % reduction of body weight was not reported. The SD was calculated from the reported F-test statistic.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/self-management technique)
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (not naturally positive continuous outcomes e.g. change)
Trial size > 49?	High risk	N = 45
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Hallström 1988

Methods	Design: three group parallel trial Purpose: examine the effect of propranolol on tranquillizer dependence
Participants	Patients: out-patients who had not succeeded in stopping tranquilliser medication despite attempts Baseline comparability: yes for diazepam intake
Interventions	Placebo: tablets without propranolol Untreated: no tablets Experimental: tablets of propranolol (Co-intervention: NS)
Outcomes	Abstinence 50% reduction of medication Time to abstinence Pulse rates
Notes	Relevant outcome data not accessible

Hallström 1988 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'Patients were also treated... under double blind conditions'
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	High risk	Relevant outcome data not accessible
Free of other bias?	Low risk	
Trial size > 49?	High risk	N = 18
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Hanson 1976

Methods	Design: five group parallel trial Purpose: examine the effect of self-management behavioural therapy on weight loss
Participants	Patients: media-recruited obese persons Baseline comparability: yes (weight)
Interventions	Placebo: sessions of deep muscle relaxation therapy Untreated: no sessions (waiting list) Experimental: sessions with -behavioural training with standard therapist contact -behavioural therapy with low therapist contact -behavioural therapy with high therapist contact (Co-intervention: antihypertensive medication, fixed ordination scheme: NS)
Outcomes	Weight loss (percentage of initial body weight)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Hanson 1976 *(Continued)*

Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/behavioural therapy)
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (not naturally positive continuous outcomes e.g. change)
Trial size > 49?	High risk	N = 21
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Hargreaves 1989

Methods	Design: three group parallel trial Purpose: examine the effect of transcutaneous electrical nerve stimulation (TENS) on acute pain associated with wound dressing
Participants	Patients: postoperative patients needing surgical wound dressing. Baseline comparability: NS
Interventions	Placebo: TENS with no current passing to electrodes Untreated: no TENS Experimental: TENS with current passing to electrodes (Co-intervention: analgesics administered at the same rate for all groups)
Outcomes	Pain (VAS)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS

Hargreaves 1989 *(Continued)*

Blinding? Treatment provider	Low risk	'...the experimenter was unaware of the assigned intervention during the initial preparation of each subject for the study'
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	Low risk	N = 50
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Drop-out > 15% or NS

Harrison 1975

Methods	Design: three group parallel trial Purpose: examine the effect of doxycycline treatment on infertility
Participants	Patients: couples suffering from infertility of unknown origin Baseline comparability: yes (age, duration of infertility)
Interventions	Placebo: tablet without doxycycline Untreated: no tablet Experimental: tablet with doxycycline (Co-intervention: NS)
Outcomes	Number of women who got pregnant
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'Double-blind Trial with Doxycycline'
Blinding? Outcome assessor	Unclear risk	NS

Harrison 1975 *(Continued)*

Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (binary outcome)
Trial size > 49?	Low risk	N = 58
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Drop-out > 15% or NS

Hashish 1986

Methods	Design: five group parallel trial Purpose: examine the effect of ultrasound and placebo on pain and swelling
Participants	Patients: postoperative in-patients (after removal of impacted third molars) Baseline comparability: NS
Interventions	Placebo: ultrasound with machine off Untreated: no ultrasound Experimental: ultrasound at three levels of intensity (Co-intervention: analgesics, fixed ordination scheme)
Outcomes	Pain (VAS) and facial swelling (cubic cm) Trismus C-reactive protein
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'... in a double-blind controlled study...'
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS

Hashish 1986 *(Continued)*

Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	High risk	Either variance inequality (F-test statistically significant) or skewness (1.64 standard deviations exceeds the mean)
Trial size > 49?	Low risk	N = 75
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Drop-out > 15% or NS

Hashish 1988

Methods	Design: five group parallel trial Purpose: examine the mechanism of placebo effects in ultrasound treatment
Participants	Patients: postoperative in-patients (after removal of impacted third molars) Baseline comparability: NS
Interventions	Placebo a: ultrasound without massage and machine off Placebo b: ultrasound with massage and machine off Untreated: no ultrasound or massage Experimental a: ultrasound without massage and machine on Experimental b: ultrasound with massage and machine on (Co-intervention: analgesics on demand)
Outcomes	Pain (VAS) and facial swelling (cubic cm) C-reactive protein Trismus Plasma cortisol Anxiety
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	'random number tables'
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'In a placebo-controlled double-blind clinical trial...'
Blinding? Outcome assessor	Low risk	'All assessments and measurements were performed by an investigator (I.H.) who was unaware of the treatment group to which the patient has been allocated'
Incomplete outcome data addressed?	Low risk	Drop-out < 15%

Hashish 1988 *(Continued)*
All outcomes

Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	Low risk	N = 50
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Allocation not clearly concealed

Hawkins 1995

Methods	Design: three group parallel trial Purpose: examine the effect of hypnosis and placebo on nausea and vomiting in children receiving chemotherapy
Participants	Patients: in-patients with cancer in need of nausea-inducing chemotherapy Baseline comparability: chemotherapy type and dose NS
Interventions	Placebo: sessions with psychologists who talked with the children about what they liked Untreated: no sessions Experimental: sessions with hypnosis (Co-intervention: NS)
Outcomes	Nausea (VAS) Vomiting
Notes	The number of patients in each group was not reported. The number was estimated to n = 10 (total patient number 30 divided by 3 groups)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/hypnosis)
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%

Hawkins 1995 *(Continued)*

Free of selective reporting?	High risk	No protocol available. The number of patients in each group was not reported. The number was estimated to n=10 (total patient number 30 divided by 3 groups)
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	High risk	N = 20
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Heinzl 1981

Methods	Design: four group parallel trial Purpose: examine the effect of prostaglandin E2-alpha on cervical dilatation
Participants	Patients: in-patients undergoing first trimester abortion Baseline comparability: yes
Interventions	Placebo: intra-cervically placed gel without prostaglandin Untreated: no gel or tablet Experimental: -intra-cervically placed gel with prostaglandin E2-alpha -tablet with prostaglandin E2-alpha (Co-intervention: Valium on fixed scheme and analgesic on demand, distribution NS)
Outcomes	Successful cervical dilatation (number of patients with dilatation of cervical os > Hegar no. 6)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Unclear risk	NS
Blinding? Outcome assessor	Low risk	'The investigating doctor had no idea what treatment, if any, the patients had received'
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available

Heinzl 1981 *(Continued)*

Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (binary outcome)
Trial size > 49?	Low risk	N = 262
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Allocation not clearly concealed

Helms 1987

Methods	Design: four group parallel trial Purpose: examine the effect of acupuncture on dysmenorrhoea
Participants	Patients: out-patients with primary dysmenorrhoea Baseline comparability: yes, however somewhat lower pretreatment pain scores.
Interventions	Placebo: needling at points not recognized as acupuncture points (lateral thighs and arms) Untreated a): no needling, minimum contact (our control group) b): no needling, visit by investigator Experimental: needling in correct acupuncture points (Co-intervention: analgesics)
Outcomes	Pain (scores) Use of analgesic medication Proportion of improved patients
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	'random numbers table'
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/acupuncture)
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	

Helms 1987 *(Continued)*

No signs of variance inequality or skewness?	High risk	Either variance inequality (F-test statistically significant) or skewness (1.64 standard deviations exceeds the mean)
Trial size > 49?	High risk	N = 22
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Hong 1993

Methods	Design: six group parallel trial Purpose: examine the effect of different physical medicine modalities on pain threshold of a myofascial trigger point
Participants	Patients: out-patients with myofascial pain syndrome Baseline comparability: yes (sex, age, pain duration)
Interventions	Placebo: sham ultrasound Untreated: no ultrasound Experimental: -spray and stretch -hydrocollator -ultrasound -massage (Co-intervention: NS)
Outcomes	Pain (Index of threshold change (ITS), based on measurements with a pressure algometer)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Unclear risk	NS
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	

Hong 1993 *(Continued)*

No signs of variance inequality or skewness?	Unclear risk	Not relevant (not naturally positive continuous outcomes e.g. change)
Trial size > 49?	High risk	N = 37
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Hossmann 1981

Methods	Design: four period, four group, cross-over trial Purpose: examine the effect of hospitalisation (habituation to the medical environment and rest in hospital bed) and placebo on arterial hypertension
Participants	Patients: patients with untreated essential hypertension
Interventions	Placebo: oval pink tablet Untreated: no tablet Experimental: hospitalisation (Co-intervention: NS)
Outcomes	Diastolic arterial blood pressure (mm Hg) Systolic arterial blood pressure (mm Hg) Heart rate Plasma renin activity Plasma norepinephrine activity Anxiety scores Urinary catecholamines
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Unclear risk	NS
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	

Hossmann 1981 *(Continued)*

No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	High risk	N = 24
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Hovell 2003

Methods	Design: three group parallel trial Purpose: study the effect of adherence coaching to treatment adherence for TB
Participants	Patients: adolescents with TB Baseline comparability: yes
Interventions	Placebo: sessions with self-esteem counselling (12 sessions, 9 months) Untreated: no sessions Experimental: sessions with adherence counselling (Co-intervention: TB medication)
Outcomes	Cumulative number of pills Proportion of TB treatment completers (180 pills within 9 moths) Interaction of alcohol consumption and lack of treatment adherence
Notes	We have multiplied the results by negative 1 to change the direction of the summary statistics.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/coaching)
Blinding? Outcome assessor	Unclear risk	Not relevant as outcome was patient reported (number of pills)
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)

Hovell 2003 *(Continued)*

Trial size > 49?	Low risk	N = 194
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Allocation not clearly concealed

Hruby 2006

Methods	Design: three group parallel trial Purpose: study the effect TENS for pain associated with cystoscopy
Participants	Patients: outpatients needing flexible cystoscopy Baseline comparability: yes (age, gender)
Interventions	Placebo: sessions with TENS device not producing nerve stimulation Untreated: no sessions Experimental: sessions TENS device not producing nerve stimulation (Co-intervention: lidocaine gel)
Outcomes	Pain (VAS) Vital signs International prostate symptom score
Notes	It is unclear wether the spread of the mean VAS pain score refer to standard errors or standard deviations. We assume that they are standard deviations as their size (1.50 and 2.05) are comparable to the standard deviations for other mean VAS pain scores.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Unclear risk	NS
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	High risk	No protocol available. It is unclear wether the spread of the mean VAS pain score refer to standard errors or standard deviations. We assume that they are standard deviations as their size (1.50 and 2.05) are comparable to the standard deviations for other mean VAS pain scores.
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	High risk	Either variance inequality (F-test statistically significant) or skewness (1.64 standard deviations exceeds the mean)

Hruby 2006 *(Continued)*

Trial size > 49?	Low risk	N = 100
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Drop-out > 15% or NS

Hutton 1991

Methods	Design: three group parallel trial Purpose: examine the effect of antihistamine decongestant and placebo on common cold symptoms in children
Participants	Patients: paediatric primary care unit out-patients (0.5 to 5 years) with common cold symptoms Baseline comparability: NS
Interventions	Placebo: medication containing no antihistamines Untreated: no medication Experimental: medication containing antihistamines (brompheniramine, phenylephrine and phenylpropanolamine) (Co-intervention: instructions to avoid, however 9/30 in untreated group took NSAID, 0/24 in placebo group)
Outcomes	Number of children with improved rhinorrhoea (parental assessment) Individual cold symptoms (breathing problems, fever, cough, decreased appetite, crankiness, sleeping disturbance, vomiting) General assessment
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'Neither parents and guardians nor investigators were aware of the drug-placebo assignment'
Blinding? Outcome assessor	Unclear risk	Not relevant as patient (parents) reported outcome
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (binary outcome)

Hutton 1991 *(Continued)*

Trial size > 49?	Low risk	N = 54
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Allocation not clearly concealed

Hyland 2006

Methods	Design: three group parallel trial Purpose: study the effect of calcaneal taping on plantar heel pain
Participants	Patients: outpatients with plantar heel pain Baseline comparability: no (age, body mass)
Interventions	Placebo: Cover-Roll stretch bandage and leucotape that did not attempt to control the alignment/position of the calcaneus. The tape was 'simply being overlaid on the skin'. Untreated: no tape Experimental: calcaneal taping 'repositioning the calcaneal alignment closer to neutral'. (Co-intervention: NS)
Outcomes	Pain VAS (0 to 10) PSFS (patient-specific function scale)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	'random numbers table'
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/taping)
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	High risk	N = 20

Hyland 2006 *(Continued)*

Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Hyman 1986

Methods	Design: four group parallel trial Purpose: examine the effect of behaviour therapy, hypnosis and placebo on smoking cessation
Participants	Patients: smokers wanting to quit Baseline comparability: yes
Interventions	Placebo: sessions with general discussions of topics of concern to the participant Untreated: no sessions Experimental: -hypnosis sessions: negative aspects of smoking were repeated while patient was in trance -behavioural therapy sessions: focused smoking technique where participants were to concentrate on the aversive aspects of smoking (Co-intervention: NS)
Outcomes	Number of abstinent smokers (based on thiocyanate concentration) Number of abstinent smokers (based on self report) Mean smoking rate
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/behaviour therapy)
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (binary outcome)
Trial size > 49?	High risk	N = 30

Hyman 1986 *(Continued)*

Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Irjala 1993

Methods	Design: three group parallel trial Purpose: examine the relationship between quality of sleep the night before surgery and several biochemical cerebro-spinal fluid indicators
Participants	Patients: in-patients in need of surgery Baseline comparability: yes (age, sex, weight, height)
Interventions	Placebo: tablet with no midazolam or temazepam Untreated: no tablet Experimental: -tablet with midazolam -tablet with temazepam (Co-intervention: no)
Outcomes	Quality of sleep Concentrations of 3,4-dihydroxyphenylglycol, 3-methoxy-4-hydroxyphenylglycol, 3,4-dihydroxyphenylacetic acid, homovanillic acid, tryptophan, 5-hydroxyindoleacetic acid and cortisol
Notes	Relevant outcome data not accessible: data lost (personal communication Irjala J)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'... the anaesthetist (J.I.) was not aware of the groupings'
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	High risk	Relevant outcome data not accessible: data lost (personal communication Irjala J)
Free of other bias?	Low risk	
Trial size > 49?	High risk	N = 35

Irjala 1993 *(Continued)*

Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Irvin 1996

Methods	Design: three group parallel trial Purpose: examine the effect of relaxation therapy on postmenopausal symptoms
Participants	Patients: postmenopausal women attending an out-patient clinic Baseline comparability: yes
Interventions	Placebo: sessions of leisure reading Untreated: no sessions Experimental: sessions of video instructed relaxation therapy (Co-intervention: NS)
Outcomes	Hot flashes: intensity (numerical rating scale) Hot flashes: frequency Profile of Mood State (anxiety, depression, anger, vigour, fatigue, confusion) Spielberger State-Trait Anxiety Inventory
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	'random numbers table'
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/relaxation therapy)
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	High risk	N = 22

Irvin 1996 *(Continued)*

Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Jacobs 1971

Methods	Design: five group parallel trial Purpose: examine the effect of different drugs, in addition to a supportive treatment program, on cessation of smoking
Participants	Patients: male smokers wanting to quit Baseline comparability: yes (prognostic variables)
Interventions	Placebo: tablet with no drug Untreated: no tablet Experimental: tablet with lobeline, dextroamphetamine or imipramine Untreated: no tablet (Co-intervention: supportive treatment program, mostly group sessions)
Outcomes	Number of abstinent smokers (cessation or reduction to < 10% of baseline value)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'... administering five drug conditions in a random and double-blind fashion...'
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (binary outcome)
Trial size > 49?	Low risk	N = 54
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Drop-out > 15% or NS

Jacobson 1978

Methods	Design: four group parallel trial Purpose: examine the effect of behavioural therapy on marital discord
Participants	Patients: couples with marital discord Baseline comparability: yes
Interventions	Placebo: sessions of discussions with no behavioural elements or problem solving training Untreated: no sessions Experimental: -sessions of behavioural therapy + problem solving skills training based on good faith principles -sessions of behavioural therapy + problem solving skills training based on quid pro quo principles (Co-intervention: NS)
Outcomes	Marital happiness scale Marital adjustment scale Negative behaviour Positive behaviour
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/therapy)
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	High risk	N = 13
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Jakes 1992

Methods	Design: five group parallel trial Purpose: examine the effect of auditory masking and group cognitive therapy on tinnitus
Participants	Patients: out-patients suffering from tinnitus Baseline comparability: yes (outcome variables)
Interventions	Placebo: auditory masking with noise at hearing threshold Untreated: no masking Experimental: -auditory masking with variable noise level -group cognitive therapy -group cognitive therapy and auditory masking with variable noise level (Co-intervention: NS)
Outcomes	Tinnitus Effects Questionnaire (insomnia, emotional distress, auditory perceptional difficulties) Interference with daily activities Crown Crisp Experimental Index
Notes	Relevant outcome data not accessible: data lost (personal communication Jakes SC)

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Unclear risk	NS
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	High risk	Relevant outcome data not accessible: data lost (personal communication Jakes SC)
Free of other bias?	Low risk	
Trial size > 49?	High risk	N = 28
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Kaptchuk 2008

Methods	Design: three group parallel trial Purpose: study the effect of placebo treatment and patient-practioner relationship
Participants	Patients: outpatients with irritable bowel syndrome

Kaptchuk 2008 *(Continued)*

	Baseline comparability: yes
Interventions	Placebo: sessions of needling with a sham needle that does not penetrate the skin and limited patient-provider interaction ('placebo acupuncture alone') Untreated: no session Experimental: sessions of needling with a sham needle that does not penetrate the skin and extensive patient-provider interaction (placebo acupuncture augmented by warmth, attention and confidence') (Co-intervention: NS)
Outcomes	Global improvement scale scores (1 to 7 point) Proportion of patients with adequate relief Symptom severity scale Quality of life scale
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Low risk	'sequentially numbered opaque sealed envelopes'
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/acupuncture)
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No primary outcomes mentioned in the protocol.
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	Low risk	N = 175
Clearly concealed allocation + trial size > 49 + drop-out max 15%	Low risk	All three categories fulfilled

Karst 2007

Methods	Design: four group parallel trial Purpose: study the effect of auricular acupuncture on dental procedural anxiety
Participants	Patients: outpatients undergoing dental extraction Baseline comparability: yes

Karst 2007 *(Continued)*

Interventions	Placebo: needling with non penetrative needle at points not regarded having effect on anxiety (finger and liver points) Untreated: no needling Experimental: -needling at ' ... relaxation, tranquillizer, and master cerebral points in the external ear ...'. -midazolam, intranasal (average dose 4mg) (Co-intervention: NS)
Outcomes	Spielberger state-trait anxiety inventory VAS Sedation score Quality of dental condition Physiological status
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	'list of random numbers'
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/acupuncture)
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	High risk	N = 29
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Karunakaran 1997

Methods	Design: three group parallel trial Purpose: examine the effect of sulfonylurea therapy on patients with increased fasting plasma glucose

Karunakaran 1997 *(Continued)*

Participants	Patients: out-patients with increased but not diabetic fasting plasma glucose Baseline comparability: yes
Interventions	Placebo: tablets containing no sulfonylurea Untreated: no tablets Experimental: tablets containing sulfonylurea (Co-intervention: reinforced or basic health advice in a factorial design)
Outcomes	Fasting plasma glucose (mmol/l) Haemoglobin A1c Plasma insulin Beta-cell function Weight Blood lipids Arterial blood pressure
Notes	Data from placebo and no-treatment groups pooled in the original trial report. Contact with researchers provided unpooled data.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'... double-blind placebo...'
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	High risk	Data from placebo and no-treatment groups pooled in the original trial report. Contact with researchers provided unpooled data.
Free of other bias?	High risk	See notes
No signs of variance inequality or skewness?	High risk	Either variance inequality (F-test statistically significant) or skewness (1.64 standard deviations exceeds the mean)
Trial size > 49?	Low risk	N = 115
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Drop-out > 15% or NS

Kendall 1979

Methods	Design: four group parallel trial

Kendall 1979 *(Continued)*

	Purpose: examine the effect of cognitive-behavioural and patient education interventions on the anxiety related to cardiac catheterization
Participants	Patients: in-patients undergoing cardiac catheterization Baseline comparability: yes
Interventions	Placebo: pre-catheterization session where patients' feelings were discussed, avoiding coping skills, procedures or factual information Untreated: no sessions (observational group) Experimental: sessions with: -cognitive-behavioural training in anxiety coping strategies -patient education: factual information on heart diseases and the procedure of cardiac catherization (Co-intervention: NS)
Outcomes	Anxiety (Spielberger state trait anxiety inventory) Pain Anger
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/active)
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (not naturally positive continuous outcomes e.g. change)
Trial size > 49?	High risk	N = 22
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Kerr 2003

Methods	Design: three group parallel trial

Kerr 2003 *(Continued)*

	Purpose: study the effect of penicillin troches for recurrent aphthous ulcers
Participants	Patients: outpatients with recurrent aphthous ulcers Baseline comparability: yes (age, gender, ulcer age)
Interventions	Placebo: sessions with TENS device not producing nerve stimulation Untreated: no sessions Experimental: sessions TENS device producing nerve stimulation (Co-intervention: installation of 4% lidocaine gel)
Outcomes	Proportion of patients with healed ulcers Proportion of patients with no pain
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	urn randomisation '...the subject drawing a single envelope from a pool of sealed blank envelopes'
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'Both the investigators and treatment group subjects were blinded'
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (binary outcome)
Trial size > 49?	Low risk	N = 69
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Allocation not clearly concealed

Killeen 2004

Methods	Design: three group parallel trial Purpose: study the effect of naltrexone for alcohol dependence
Participants	Patients: outpatients with alcohol dependence Baseline comparability: yes (age, gender)

Killeen 2004 *(Continued)*

Interventions	Placebo: NS (12 weeks) Untreated: no placebo or naltrexone Experimental: naltrexone (Co-intervention: various individual or group programs)
Outcomes	Alcohol consumption (time line follow-back: average drinks per day, percent days drinking, drinks per drinking days, heavy drinking days) Percentage with at least one heavy drinking episode Craving (obsessive compulsive drinking scale) Various explorative analyses
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	urn randomisation
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Unclear risk	NS
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (not naturally positive continuous outcomes e.g. change)
Trial size > 49?	Low risk	N = 59
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Drop-out > 15% or NS

Killen 1990

Methods	Design: 4 x 3 group parallel trial (see notes) Purpose: examine the effect of behavioural intervention (3 types) and pharmacological intervention (4 types) in smoking relapse prevention
Participants	Patients: tobacco smokers abstinent for more than 48 hours and volunteering for a self-help program Baseline comparability: yes
Interventions	Placebo: gum with no nicotine

Killen 1990 *(Continued)*

	Untreated: no gum Experimental: -nicotine gum ad libitum -nicotine gum with fixed regimen (Co-intervention: NS)
Outcomes	Number of abstinent smokers
Notes	As the behavioural treatments showed no significant difference the 3 x 4 factorial design was collapsed into a four group parallel trial.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'Assignment to gum condition was double-blind...'
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (binary outcome)
Trial size > 49?	Low risk	N = 618
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Allocation not clearly concealed

Kilmann 1987

Methods	Design: five group parallel trial Purpose: study the effect of three different psychological interventions on secondary erectile dysfunction
Participants	Patients: men with secondary erectile dysfunction Baseline comparability: yes
Interventions	Placebo: sessions with factual information on sexual education and relationship enhancement Untreated: no sessions Experimental:

Kilmann 1987 *(Continued)*

	-sessions with communication technique training -sessions with sexual technique training -sessions with combination treatment (Co-intervention: NS)
Outcomes	Coital success in % Marital adjustment test Sexual interaction inventory Sexual anxiety inventory Sexual pleasure rating
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/psychological interventions)
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	High risk	Either variance inequality (F-test statistically significant) or skewness (1.64 standard deviations exceeds the mean)
Trial size > 49?	High risk	N = 8
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Klerman 1974

Methods	Design: 2 x 3 factorial design (high and low personal interaction versus amitriptyline, placebo, no treatment) Purpose: examine the effect of amitriptyline, placebo and psychotherapy treatment on relapse of depression
Participants	Patients: out-patients with neurotic depression having improved markedly after 1 to 2 months amitriptyline medication Baseline comparability: yes

Klerman 1974 *(Continued)*

Interventions	Placebo: -continuous treatment with tablets containing no amitriptyline (content NS) Untreated: -tablet treatment discontinued (observational group) Experimental: -continuous treatment with amitriptyline tablets (Co-intervention: no)
Outcomes	Number of patients with relapse of depression Residual symptoms of depression Social adjustment
Notes	As the high and low personal interaction treatments showed no significant difference the 2 x 3 factorial design was collapsed into a three group parallel trial.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'... in a double-blind controlled manner..'
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (binary outcome)
Trial size > 49?	Low risk	N = 50
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Drop-out > 15% or NS

Kober 2002

Methods	Design: three group parallel trial Purpose: study the analgesic effect of accupressure
Participants	Patients: victims of minor trauma under transport to hospital

Kober 2002 *(Continued)*

	Baseline comparability: yes (age, gender)
Interventions	Placebo: stimulation on sites not regarded analgesic acupressure sites Untreated: no stimulation Experimental: stimulation on sites regarded analgesic acupressure sites (Di4, KS9, KS6, BL60, LG20) (Co-intervention: no)
Outcomes	Pain (100 mm VAS) Anxiety (100 VAS) Heart frequency
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	'opened an envelope'
Blinding? Treatment provider	Low risk	'... we conducted a prospective, randomized, double-blinded study...'
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	High risk	N = 41
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Kokol 2005

Methods	Design: three group parallel trial Purpose: study the effect of 685 nm laser and placebo on venous leg ulcers
Participants	Patients: out-patients with venous leg ulcers Baseline comparability: yes
Interventions	Placebo: polychromatic red light Untreated: no light

Kokol 2005 *(Continued)*

	Experimental: 685 nm laser light (red) (Co-intervention: standard venous leg ulcers treatments)
Outcomes	Area of leg ulcers (photographs)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'... weder vom Arzt noch vom Patienten unterschieden werden kann'
Blinding? Outcome assessor	Low risk	'Erst nach Ende der Nachbeobachtungensphase (Tag 90) wurden die verwendeten als A und B be zeichneten Geräte decodiert (entblindet), um die Ergebnisse nicht zu beeinflussen'
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	High risk	Either variance inequality (F-test statistically significant) or skewness (1.64 standard deviations exceeds the mean)
Trial size > 49?	High risk	N = 26
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Kotani 2001

Methods	Design: three group parallel trial Purpose: study the effect of insertion of intradermal needles into painful points on intractable scar pain
Participants	Patients: out-patients with intractable abdominal scar pain Baseline comparability: yes
Interventions	Placebo: intradermal needling into nonpainful points Untreated: no needling Experimental: intradermal needling into painful points (Co-intervention: diclofenac until 24 hours before pain evaluation)
Outcomes	Number of analgesic tablets per week

Kotani 2001 *(Continued)*

	Proportion of patients with global pain relief (50% reduction or more) Pain, continuous (VAS) Pain, lancinating (VAS) Pain area (square cm) Threshold pressure
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	'random number table'
Allocation concealment?	Low risk	'sequentially sealed opaque envelopes'
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/needling into painful points)
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	High risk	N = 47
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Lamazza 1986

Methods	Design: three group parallel trial Purpose: examine the effect of pinaverium bromide (antispasmodic and analgesic drug) in the premedication of endoscopic retrograde cholangio-pancreaticography (ERCP) and on the motor activity of the sphincter of Oddi
Participants	Patients: with biliary and pancreatic disease and in need of a ERCP Baseline comparability: NS
Interventions	Placebo: tablet with no pinaverium bromide Untreated: no tablet Experimental: tablet with pinaverium bromide (Co-intervention: diazepam injection, 10 to 20 mg)

Lamazza 1986 *(Continued)*

Outcomes	Patient's tolerance of procedure Time for procedure Sphincter of Oddi pressure and wave pattern
Notes	Relevant outcome data not accessible

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'A double-blind study was carried out...'
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	High risk	Relevant outcome data not accessible
Free of other bias?	Low risk	
Trial size > 49?	High risk	N = 12
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Lander 1993

Methods	Design: three group parallel trial Purpose: examine the effect of transcutaneous electrical nerve stimulation (TENS) for children's pain on blood sampling
Participants	Patients: children attending out-patient clinics undergoing venepuncture Baseline comparability: yes (age, sex, expected pain, anxiety)
Interventions	Placebo: TENS with machine off Untreated: no TENS Experimental: TENS with machine on (Co-intervention: NS)
Outcomes	Pain (VAS, Faces Affective Pain Scale)
Notes	

Risk of bias

Lander 1993 *(Continued)*

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Low risk	'sealed envelopes'
Blinding? Treatment provider	High risk	Not
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	High risk	Either variance inequality (F-test statistically significant) or skewness (1.64 standard deviations exceeds the mean)
Trial size > 49?	Low risk	N = 340
Clearly concealed allocation + trial size > 49 + drop-out max 15%	Low risk	All three categories fulfilled

Larson 2005

Methods	Design: three group parallel trial Purpose: study the risk of vomiting and regurgitation in children with diarrhoea treated with Zink or placebo
Participants	Patients: children with diarrhoea (short stay ward or outpatient clinic) Baseline comparability: yes
Interventions	Placebo: dispersible tablet without Zink Untreated: no tablet Experimental: dispersible tablet with Zink (Co-intervention: standard treatment for diarrhoea)
Outcomes	Proportion of patients that vomit Proportion of patients that regurgitatee
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Larson 2005 *(Continued)*

Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Low risk	'numbered' and 'opaque envelopes'
Blinding? Treatment provider	Low risk	'This randomized, double-blind, placebo-controlled clinical trial...'
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
Trial size > 49?	Low risk	N =1066
Clearly concealed allocation + trial size > 49 + drop-out max 15%	Low risk	All three categories fulfilled

Lee 2005

Methods	Design: two group parallel trial Purpose: study the effect of placebo on cough
Participants	Patients: out-patients with cough and signs of upper respiratory infection Baseline comparability: NS
Interventions	Placebo: capsule with vitamin E Untreated: no capsule (Co-intervention: no)
Outcomes	Changes in cough frequency per 15 minutes Cough suppression time
Notes	Mean changes in cough frequency per 15 minutes calculated from individual patient data in Figure 1

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Unclear risk	NS

Lee 2005 *(Continued)*

Blinding? Outcome assessor	Low risk	'microphone connected to a pen recorder'
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	High risk	Either variance inequality (F-test statistically significant) or skewness (1.64 standard deviations exceeds the mean)
Trial size > 49?	Low risk	N = 54
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Allocation not clearly concealed

Leibing 2002

Methods	Design: three group parallel trial Purpose: study the analgesic effect of acupuncture for low-back pain
Participants	Patients: out-patients with non-radiating low-back pain of more than 6 months duration Baseline comparability: yes
Interventions	Placebo: needling on sites not regarded analgesic acupuncture sites Untreated: no needling Experimental: needling on sites regarded analgesic acupressure sites (Co-intervention: active physiotherapy)
Outcomes	Pain (100 mm VAS) Pain disability (pain disability index) Psychological distress Spine flexion
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/acupuncture)
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome

Leibing 2002 *(Continued)*

Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	Low risk	N = 79
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Allocation not clearly concealed

Levine 1984

Methods	Design: 8 group parallel trial (incomplete 3 x 3 factorial design) Purpose: examine the effect of open and hidden infusion of placebo on pain
Participants	Patients: postoperative in-patients (after removal of impacted third molars) Baseline comparability: NS
Interventions	Placebo: open infusion of vehicle by bedside investigator Untreated: patient unaware of infusion of vehicle (either by machine or hidden investigator) Experimental: infusions of naloxone and morphine (8 and 12 mg) (Co-intervention: NS)
Outcomes	Pain (VAS)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'Each patient was randomly assigned to receive, after surgery, a double-blind injection...'
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS

Levine 1984 *(Continued)*

Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (not naturally positive continuous outcomes e.g. change)
Trial size > 49?	High risk	N = 36
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Levitt 1981

Methods	Design: three group parallel trial Purpose: examine the effect of investigating cardiovascular parameters in cancer patients receiving antiemetic cannabis treatment
Participants	Patients: cancer patients receiving nausea inducing chemotherapy Baseline comparability: NS
Interventions	Placebo: NS Untreated: no placebo or cannabis Experimental: -cannabis (three doses) -prochlorperazine (Co-intervention: yes, chemotherapy)
Outcomes	Emetic events Psychological events Heart rate Blood pressure Intraocular pressure
Notes	Relevant outcome data not accessible

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Unclear risk	NS
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed?	High risk	Drop-out > 15% or NS

Levitt 1981 *(Continued)*
All outcomes

Free of selective reporting?	High risk	Relevant outcome data not accessible
Free of other bias?	Low risk	
Trial size > 49?	High risk	N = 48
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Licciardone 2003

Methods	Design: three group parallel trial Purpose: study the effect of osteopathic manipulative treatment techniques for chronic low-back pain
Participants	Patients: out-patients with chronic low-back pain Baseline comparability: yes
Interventions	Placebo: simulated osteopathic manipulative treatment techniques Untreated: no simulated osteopathic manipulative treatment techniques Experimental: osteopathic manipulative treatment techniques (Co-intervention: 'usual or other low back care')
Outcomes	Back pain (VAS) SF-36 health survey (physical functioning subscale) SF-36 health survey (all subscales) Roland-Morris disability questionnaire Lost work or school days Satisfaction with back care
Notes	We selected back pain as the relevant outcome (and not the SF-36 which was the basis for the power calculation), because also back pain was described as a 'main outcome', and because pain (and not quality of life) is mentioned in the aims section and the title. We extracted pain data (at six months) from Figure 3

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Low risk	'sequentially sealed envelopes'
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/manipulation)
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS

Licciardone 2003 *(Continued)*

Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	High risk	Either variance inequality (F-test statistically significant) or skewness (1.64 standard deviations exceeds the mean)
Trial size > 49?	High risk	N = 34
Clearly concealed allocation + trial size > 49 + dropout max 15%	High risk	Trial size < 49

Lick 1975

Methods	Design: four group parallel trial Purpose: examine the effect of behavioural therapy and placebo on snake and spider phobia
Participants	Patients: out-patients suffering from phobia against snakes and spiders Baseline comparability: yes
Interventions	Placebo: -with feedback: patients told that pictures with phobic stimulus would be flickered too rapidly for the conscious mind to register and phobic responses would be detected by a 'polygraph' that would deliver a mild but uncomfortable electrical shock. In fact only light was shown and no machine detected any phobias. The rate of shocks associated with lights was programmed to be reduced from 90% in the first session to 10% in the last session. The patients were shown outprints and explained that treatment was 'going well'. - without feedback: similar procedure, but no outprints were shown and patients told that the machine reduced the number of shocks independently of their response. Patients were also 'assured throughout treatment that things were going well' Untreated: no behavioural or placebo procedure (waiting-list) Experimental: systematic desensitization procedure (Co-intervention: NS)
Outcomes	Percentage of fear remaining (index) and pulse rate at confrontation with snake or spider Behavioural approach test Behavioural inhibition test Reaction to picture test Global behavioural improvement Therapy expectancy Warmth and competence of therapist
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding?	High risk	Not described as double-blind (placebo/behavioural therapy)

Lick 1975 *(Continued)*
Treatment provider

Blinding? Outcome assessor	Low risk	'... experimenter who was blind to the conditions that the subjects had been assigned'
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (not naturally positive continuous outcomes e.g. change)
Trial size > 49?	High risk	N = 18
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Lick 1977

Methods	Design: four group parallel trial Purpose: examine the effect of relaxation therapy and placebo on insomnia
Participants	Patients: out-patients suffering from chronic insomnia Baseline comparability: yes (time to fall asleep)
Interventions	Placebo: 'T-scope therapy', a sham procedure designed to induce expectancy Untreated: no relaxation or placebo therapy (waiting list) Experimental: relaxation therapy (Co-intervention: sleep inducing drugs, no difference in % days in which patients took drugs in placebo and untreated groups)
Outcomes	Sleep latency (min) Hours slept Quality of sleep Feelings on awakening Minnesota Multi phasic Personality Inventory Number of awakenings % days taking a sleeping pill
Notes	5 out of 40 participants were replaced by others approximately equivalent in age, sex and time to falling asleep.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS

Lick 1977 *(Continued)*

Blinding? Treatment provider	High risk	Not described as double-blind (placebo/relaxation therapy)
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	High risk	See notes
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	High risk	N = 20
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Limoges 2004

Methods	Design: three group parallel trial Purpose: study the effect of TENS during sigmoidoscopy
Participants	Patients: out-patients needing screening endoscopy Baseline comparability: yes
Interventions	Placebo: session with TENS machine off Untreated: no session Experimental: session with TENS machine turned on (Co-intervention: NS)
Outcomes	Pain intensity (1-5) Bloating Nausea Pain or burning or tingling at electrode site Pain compared with previous sigmoidoscopy
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding?	High risk	(but endoscopist and patients were blinded)

Limoges 2004 *(Continued)*

Treatment provider		
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	Low risk	N = 60
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Unclear allocation concealment

Lin 2002

Methods	Design: three group parallel trial Purpose: study the analgesic effect of electroacupuncture
Participants	Patients: postoperative patients (hysterectomy) Baseline comparability: yes
Interventions	Placebo: needling without electrical stimulation at ST-36 Untreated: no needling Experiemental: needling with electrical stimulation at ST-36 (Co-intervention: pethidine and morphine at request)
Outcomes	Use of morphine (mg at 8, 16 and 24 hours) Pain Time to first pethidine dose Heart rate Blood pressure Oxygen saturation
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	'computer-generated'
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/acupuncture)

Lin 2002 *(Continued)*

Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	Low risk	N = 50
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Allocation not clearly concealed

Lincoln 2003

Methods	Design: three group parallel trial Purpose: study the effect of cognitive behavioral psychotherapy for post-stroke depression
Participants	Patients: out-patients with a recent stroke and depression Baseline comparability: yes
Interventions	Placebo: sessions with conversations focusing on daily events and physical effects of stroke and life changes Untreated: no sessions Experimental: sessions with cognitive behavioural psychotherapy (Co-intervention: NS)
Outcomes	Beck depression inventory Wakefield self-assessment of depression inventory Extended activities of daily living scale London handicap scale Satisfaction with care rating
Notes	Standard deviation for the mean scores on the Beck depression inventory were not reported. We took the standard deviation from another trial (Verduyn C 2003).

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	'computer generated'
Allocation concealment?	Low risk	'sealed in opaque, consecutively numbered envelopes'
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/cognitive behavioral psychotherapy)

Lincoln 2003 *(Continued)*

Blinding? Outcome assessor	Low risk	'Outcome assessments were administered by an assistant psychologist, who was blind to the group allocation...'
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	High risk	No protocol available. Standard deviation for the mean scores on the Beck depression inventory were not reported. We took the standard deviation from another trial (Verduyn C 2003).
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	High risk	Either variance inequality (F-test statistically significant) or skewness (1.64 standard deviations exceeds the mean)
Trial size > 49?	Low risk	N = 80
Clearly concealed allocation + trial size > 49 + drop-out max 15%	Low risk	All three categories fulfilled

Linde 2005

Methods	Design: three group parallel trial Purpose: study the effect of acupuncture on migraine
Participants	Patients: out-patients with migraine headache Baseline comparability: yes
Interventions	Placebo: needling at places not regarded true acupuncture sites Untreated: no needling Experimental: needling at places regarded true acupuncture sites (Co-intervention: standard headache treatment according to the guideline of the German Migraine and Headache Society)
Outcomes	Number of headache days of moderate or severe intensity until week 9-12 Number of migraine headaches Total number of headache days Proportion of treatment responders Number of days with medication Pain disability index Scale for assessing the emotional aspects of pain Algemeine Depressionskalla SF-36
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	'random list generated with Sample Size 2.0'

Linde 2005 *(Continued)*

Allocation concealment?	Low risk	'centralized telephone randomization procedure'
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/acupuncture)
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Low risk	Primary outcome specified in protocol
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (not naturally positive continuous outcomes e.g. change)
Trial size > 49?	Low risk	N = 157
Clearly concealed allocation + trial size > 49 + drop-out max 15%	Low risk	All three categories fulfilled

Lindholm 1996

Methods	Design: multi centre 2 x 3 factorial design (normal or intensive advice x pravastatin, placebo or no drug) Purpose: examine the effect of pharmacological and non-pharmacological strategies on cardiovascular risk
Participants	Patients: out-patients with increased risk of cardiovascular disease and moderately increased serum-cholesterol Baseline comparability: yes
Interventions	Placebo: tablet with no pravastatin (with usual or intense advice) Untreated: no pharmacological intervention (with usual or intense advice) Experimental: pravastatin (with usual or intense advice) (Co-intervention: usual health care advice on diet conducted by a GP or intense health care advice where usual advice is supplemented by group sessions)
Outcomes	Serum-cholesterol (mmol/l) Serum-cholesterol: high and low density lipoprotein Serum-triglycerides Blood-glycose Blood pressure Framingham risk score
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Lindholm 1996 *(Continued)*

Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'A prospective, double-blind, randomized, controlled trial...'
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	Low risk	N = 453
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Allocation not clearly stated

Liossi 2003

Methods	Design: four group parallel trial Purpose: study the effect of hypnosis on procedure-related pain
Participants	Patients: children (6 to 16 years) with cancer Baseline comparability: yes
Interventions	Placebo: attention control treatment ('development of rapport, nonmedical play, nonmedical verbal interaction'. Therapist was 'supportive, warm, encouraged the child to express freely their interests, and formed a close relationship with the child.' Untreated: no hypnosis Experimental: -direct hypnosis (hypnotic indiction by reference to request for numbness and imagining 'numbing medicine', etc) -indirect hypnosis (hypnotic induction by reference to 'the setting sun metaphor' and the 'Mexican food metaphor') (Co-intervention: standard medical care)
Outcomes	Pain (6 point scale) Anxiety Observed distress
Notes	
Risk of bias	

Liossi 2003 *(Continued)*

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Unclear risk	NS
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	High risk	N = 40
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Longo 1988

Methods	Design: three group parallel trial Purpose: examine the effect of psycho-social intervention on recurrence of genital herpes simplex
Participants	Patients: media and healthcare-referred persons with recurrent genital herpes simplex with 4 or more attacks a year Baseline comparability: yes
Interventions	Placebo: -sessions of social support consisting of discussions of interpersonal conflicts without any relaxation techniques or stress management. Untreated: no sessions (waiting-list) Experimental: sessions of relaxation techniques and stress management + playing a relaxation tape during herpes attacks (Co-intervention: NS)
Outcomes	Herpes attack: severity (index) Herpes attack: frequency and duration Zung Depression Scale Profile of Mood States UCLA Loneliness Scale Multidimensional Health Locus of Control Scales

Longo 1988 *(Continued)*

Notes

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/psycho-social intervention)
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	High risk	N = 19
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Lorr 1961

Methods	Design: five group parallel trial Purpose: examine the effect of pharmacological treatment in addition to psychotherapy in patients with anxiety and hostility
Participants	Patients: out-patients with anxiety and hostility admitted to a veteran's Mental Hygiene Clinic for psychotherapy Baseline comparability: NS
Interventions	Placebo: tablet containing lactose but not chlorpromazine, meprebomate or phenobarbital Untreated: no tablet (observational group) Experimental: -tablets with chlorpromazine -tablet with meprobamate -tablet with phenobarbital (Co-intervention: sessions of individual psychotherapy)
Outcomes	Anxiety (index) Hostility

Lorr 1961 *(Continued)*

	Discomfort
Notes	42% drop-outs. The standard deviation (SD) of the anxiety score was not reported. The SD was calculated from the reported F-test statistic.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'...12-week double-blind study'
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	Low risk	N = 80
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Drop-out > 15% or NS

Macaluso 1995

Methods	Design: three group parallel trial Purpose: examine the effect of fentanyl as premedication
Participants	Patients: in-patients undergoing same day surgery Baseline comparability: yes
Interventions	Placebo: oralet without fentanyl Untreated: no oralet Experimental: oralet with fentanyl (Co-intervention: NS)
Outcomes	Anxiety (Spielberger state trait anxiety inventory) Heart rate Volume and pH of gastric contents Arterial pressure Respiratory frequency

Macaluso 1995 *(Continued)*

	Oxygen saturation
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	'by computer program'
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'All investigators were blinded to the type of oralet patients in Groups I and II consumed...'
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (not naturally positive continuous outcomes e.g. change)
Trial size > 49?	Low risk	N = 60
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Drop-out > 15% or NS

Malcolm 1980

Methods	Design: three group parallel trial Purpose: examine the effect of nicotine chewing gum treatment on smoking
Participants	Patients: smokers Baseline comparability: yes
Interventions	Placebo: chewing gum without nicotine Untreated: no chewing gum Experimental: chewing gum with nicotine (Co-intervention: NS)
Outcomes	Number of abstinent smokers (based on carboxyhaemoglobin levels) Number of abstinent smokers (based on self report)
Notes	

Malcolm 1980 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'The trial was double blind between the gum groups'
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (binary outcome)
Trial size > 49?	Low risk	N = 121
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Drop-out > 15% or NS

Markland 1993

Methods	Design: three group parallel trial Purpose: examine the effect of a relaxation tape session on preoperative anxiety
Participants	Patients: in-patients undergoing day-case surgery Baseline comparability: yes, except for diastolic blood pressure
Interventions	Placebo: session where patients listen to a recorded short story Untreated: no session Experimental: session where patients listen to a recorded relaxation procedure (Co-intervention: NS)
Outcomes	Anxiety (Spielberger state trait anxiety inventory) Heart rate Blood pressure Anaesthesia measures (dose of sedative, time to settle the patient, mean concentration per min of isoflurane, anaesthetist's score)
Notes	

Risk of bias

Markland 1993 *(Continued)*

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/relaxation procedure)
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (not naturally positive continuous outcomes e.g. change)
Trial size > 49?	High risk	N = 14
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Matros 2006

Methods	Design: three group parallel trial Purpose: study the effect of gum chewing on postoperative ileus
Participants	Patients: in-patients having had performed abdominal surgery Baseline comparability: yes (age, gender)
Interventions	Placebo: Acupressure bracelet used on an inert location Untreated: no chewing gum or bracelet Experimental: chewing gum (Co-intervention: standard postoperative care)
Outcomes	Time to first flatus Time to first bowel movement Time to ready for discharge Time to actual discharge
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Matros 2006 *(Continued)*

Adequate sequence generation?	Unclear risk	'computer-generated'
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/chewing gum)
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	High risk	N = 44
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Mattarei 1985

Methods	Design: two period, two group, cross-over trial Purpose: examine the effect of placebo on arterial hypertension
Participants	Patients: out-patients with untreated mild essential hypertension Baseline comparability: NS
Interventions	Placebo: capsule Untreated: no capsule (Co-intervention: no)
Outcomes	Diastolic blood pressure in mm Hg after 4 weeks Systolic blood pressure in mm Hg
Notes	The outcome data was not available.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS

Mattarei 1985 *(Continued)*

Blinding? Treatment provider	Unclear risk	NS
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	High risk	The outcome data was not available.
Free of other bias?	Low risk	
Trial size > 49?	High risk	N = 24
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

May 1988

Methods	Design: four group, four period cross-over trial Purpose: examine the effect of terbutaline, isotonic saline, ambient air and no-treatment on chronic airway obstruction in asthmatics
Participants	Patients: asthmatic out-patients with reversible chronic airway obstruction Baseline comparability: no carry-over effect
Interventions	Placebo: -inhalation of air from a noisy nebulizer -inhalation of isotonic saline from a noisy nebulizer Untreated: inhalation of air through a mouthpiece disconnected from the nebulizer Experimental: inhalation of terbutaline from a noisy nebulizer (Co-intervention: use of corticosteroids or bronchodilator drugs prohibited)
Outcomes	Change in forced expiratory volume in 1 second (FEV1) Change in forced vital capacity (FVC)
Notes	The outcome data was not available from the first period only, and was calculated as deriving from a parallel group trial.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'The treatment was given double-blind...'

May 1988 *(Continued)*

Blinding? Outcome assessor	Low risk	'... but the nurse in charge of spirometry did not know whether or not the patient was receiving treatment'
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Unclear risk	The outcome data from this cross-over trial was not available from the first period only, and was calculated as deriving from a parallel group trial.
No signs of variance inequality or skewness?	Unclear risk	Not relevant (not naturally positive continuous outcomes e.g. change)
Trial size > 49?	High risk	N = 48
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

McLachlan 1991

Methods	Design: three group parallel trial Purpose: examine the effect of the aluminium chelator desferrioxamine on progression of Alzheimer's disease
Participants	Patients: out-patients with probable Alzheimer's disease (memory problems, cerebral atrophy, no cerebral infarcts) Baseline comparability: NS
Interventions	Placebo: tablets containing lecithin and no desferrioxamine Untreated: no tablets or injections (observational group) Experimental: injections with desferrioxamine (Co-intervention: NS)
Outcomes	Activities of daily living (ADL, rate of decline of video recorder home-behavioural assessment)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	'table of random numbers'
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/desferrioxamine)
Blinding? Outcome assessor	Low risk	'... trained raters who were not told about the nature of the study'

McLachlan 1991 *(Continued)*

Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	High risk	Either variance inequality (F-test statistically significant) or skewness (1.64 standard deviations exceeds the mean)
Trial size > 49?	High risk	N = 20
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

McMillan 1994

Methods	Design: four group parallel trial Purpose: examine the prophylactic antiemetic effect of transcutaneous electrical stimulation (TENS) of the P6 (Neiguan) acupuncture point
Participants	Patients: in-patients in need of major surgery and at risk of opoid analgesic-induced nausea Baseline comparability: yes (type of analgesic)
Interventions	Placebo: TENS with machine turned off Untreated: no TENS Experimental: TENS with machine turned on (Co-intervention: pharmacological analgesic and anti-emetic medication)
Outcomes	Number of patients with nausea Number of patients with vomiting
Notes	Inconsistent data reporting in original trial report clarified by contact with author. Not 1:1 randomisation.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/acupuncture)
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed?	Low risk	Drop-out < 15%

McMillan 1994 *(Continued)*

All outcomes

Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (binary outcome)
Trial size > 49?	Low risk	N = 72
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Allocation not clearly concealed

Medici 2002

Methods	Design: three group parallel trial Purpose: examine the effect of real and sham acupuncture on bronchial asthma
Participants	Patients: out-patients with chronic asthma Baseline comparability: yes
Interventions	Placebo: needling at 11 sites not regarded true acupuncture sites Untreated: no needling Experimental: needling at 11 sites 'believed to have an anti-asthmatic effect'. (Co-intervention: standard pharmacological inhalation therapy)
Outcomes	Proportion of patients scoring 1 to 4 on a VAS for nausea Proportion of patients scoring 1 to 4 on a VAS for difficulty of swallowing gastroscopy Proportion of patients scored 1 to 4 by gastrocopist on a VAS for nausea/retching Proportion of patient who accept re-gastroscopy
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Unclear risk	NS
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%

Medici 2002 *(Continued)*

Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (not naturally positive continuous outcomes e.g. change)
Trial size > 49?	High risk	N = 41
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Mehl-Madrona 2007

Methods	Design: Five group parallel trial Purpose: To study the effect of acupuncture, craniosacral therapy, acupuncture and craniosacral therapy, attention control and waiting list control on asthma.
Participants	Patients: out-patients with chronic asthma Baseline comparability: NS
Interventions	Placebo: Attention control Untreated: waiting list control Experimental: Acupuncture, craniosacral, acupuncture and craniosacral. (Co-intervention: Standard medical management)
Outcomes	Pulmonary function Asthma quality of life questionnaire. Profile of mood states. Beck depression inventory. Beck anxiety inventory. Medication form.
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	'random number generating program'
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/acupuncture)
Blinding? Outcome assessor	Low risk	'The respiratory therapist performing pulmonary function testing was blind to the assignments of the subjects'
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available

Mehl-Madrona 2007 *(Continued)*

Free of other bias?	Low risk	
Trial size > 49?	High risk	N = ?
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Melchart 2005

Methods	Design: three group parallel trial Purpose: study the effect of acupuncture on tension type headache
Participants	Patients: out-patients with tension type headache Baseline comparability: yes for most aspects, however 'some differences in previous use of acupuncture and in parts of the pain questionnaire'.
Interventions	Placebo: needling at places not regarded true acupuncture sites Untreated: no needling Experimental: needling at places regarded true acupuncture sites (Co-intervention: standard headache treatment)
Outcomes	Days with headache Hours with headache Headache scores Days with more than mild headache Days with analgesic drugs Number of days with medication Pain disability index SF-36 Algemeine Depressionskala Scale for assessing the emotional aspects of pain Average pain (1 to 10 scale)
Notes	Average days with analgesic drugs in placebo group was 2.6 (SD: 2.6), and in the no-treatment group 4.4 (SD: 4.1) at week 12.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	'random list generated with sample size 2.0 by the statistician'
Allocation concealment?	Low risk	'centralized telephone randomization procedure'
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/acupuncture)
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%

Melchart 2005 *(Continued)*

Free of selective reporting?	Low risk	Primary outcome specified in protocol
Free of other bias?	Unclear risk	Average days with analgesic drugs in placebo group was 2.6 (SD: 2.6), and in the no-treatment group 4.4 (SD:4.1).
No signs of variance inequality or skewness?	High risk	Either variance inequality (F-test statistically significant) or skewness (1.64 standard deviations exceeds the mean)
Trial size > 49?	Low risk	N = 120
Clearly concealed allocation + trial size > 49 + drop-out max 15%	Low risk	All three categories fulfilled

Moffet 1996

Methods	Design: three group parallel trial Purpose: examine the effect of pulsed short wave therapy (PSW) on chronic pain
Participants	Patients: out-patients with chronic pain associated with osteoarthritis of hip or knee Baseline comparability: yes
Interventions	Placebo: PSW with machine off Untreated: no PSW Experimental: PSW with machine on (Co-intervention: NS)
Outcomes	Pain (numerical/verbal rating scale)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	'minimisation method'
Allocation concealment?	Low risk	'minimisation method'
Blinding? Treatment provider	Low risk	'... double blind randomised controlled trial'
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	

Moffet 1996 *(Continued)*

No signs of variance inequality or skewness?	High risk	Either variance inequality (F-test statistically significant) or skewness (1.64 standard deviations exceeds the mean)
Trial size > 49?	High risk	N = 49
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size is not 50 or more

Molsberger 2002

Methods	Design: three group parallel trial Purpose: examine the effect of acupuncture on chronic low back pain
Participants	Patients: patients with low back pain of more than 6 weeks duration Baseline comparability: yes (age, pain)
Interventions	Placebo: superficial needling at sites not regarded acupuncture sites (12 sessions over 4 weeks) Untreated: no needling Experimental: needling at acupuncture sites (Co-intervention: conservative orthopaedic treatment (physiotherapy, exercise, back school, mud packs, infrared heat therapy, and diclofenac on demand))
Outcomes	Proportion of patients with 50% reduction of 100 mm pain VAS at one month Proportion of patients with 50% reduction of 100 mm pain VAS at follow-up Proportion of patients with excellent or good ratings on a four-point box scale
Notes	According to protocol we extracted the post treatment outcome data at one month, overruling a secondary principle of extracting the primary outcome of a trial (follow up data at three months). The effect of placebo was neutral at post treatment (RR = 1.16, 0.86 to 1.56), but positive at follow-up (RR = 0.64, 0.43 to 0.95). The drop out rate in the two groups was (3+7)/121 = 8% at one month, and (19+23)/121 = 35% at three months.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	'computer generated randomisation list'
Allocation concealment?	Low risk	'central telephone randomisation'
Blinding? Treatment provider	Unclear risk	NS
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available

Molsberger 2002 *(Continued)*

Free of other bias?	High risk	See notes
No signs of variance inequality or skewness?	Unclear risk	Not relevant (binary outcome)
Trial size > 49?	Low risk	N = 111
Clearly concealed allocation + trial size > 49 + drop-out max 15%	Low risk	All three categories fulfilled

Moreland 2006

Methods	Design: three group parallel trial Purpose: examine the effect of a blood glucose monitoring manual in adults with diabetes
Participants	Patients: out-patients with diabetes Baseline comparability: yes
Interventions	Placebo: session of diabetes education and a blood glucose meter ('attention control') Untreated: no session Experimental: session of diabetes education based on a blood glucose manual and a blood glucose meter (Co-intervention: standard diabetes care)
Outcomes	Frequency of blood glucose measurements Glycaemic control Knowledge of HbA1c Affect regarding blood glucoses results
Notes	We have multiplied the results by negative 1 to change the direction of the effect in the analyses.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/manual)
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	

Moreland 2006 *(Continued)*

No signs of variance inequality or skewness?	Unclear risk	Not relevant (not naturally positive continuous outcomes e.g. change)
Trial size > 49?	Low risk	N = 149
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Drop-out > 15% or NS and unclear allocation concealment

Morey 2006

Methods	Design: three group parallel trial Purpose: examine the effect of exercise health counselling
Participants	Patients: elderly out-patients with chronic illnesses Baseline comparability: yes
Interventions	Placebo: sessions of disease management or prevention unrelated to physical activity and with no efforts made to modify behaviour ('attention control') Untreated: no sessions Experimental: sessions aiming at providing patient centred motivational, behavioural, and cognitive techniques to increase physical activity (Co-intervention: NS)
Outcomes	Physical activity (CHAMPS questionnaire) -weekly frequency -caloric expenditure -estimated total minutes (estimated moderate minutes + estimated walk/bike minutes)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	'computer-generated'
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (attention control placebo/exercise health counselling)
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	

Morey 2006 *(Continued)*

No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	Low risk	N = 80
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Allocation not clearly concealed

Morton 1993

Methods	Design: four group, four period cross-over trial Purpose: examine the prophylactic effect of acupuncture on exercise induced asthma
Participants	Patients: female out-patients suffering from exercise induced asthma Baseline comparability: not relevant
Interventions	Placebo: acupuncture with laser beam off Untreated: no acupuncture Experimental: -acupuncture with laser beam on -salbutamol inhalation (Co-intervention: corticosteroids in 3 participants)
Outcomes	Forced expiratory volume after 1 second (FEV1) as % of pretreatment value Proportion with bronchoconstriction (15% reduction in FEV1)
Notes	The outcome data was treated as if coming from a parallel trial

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/acupuncture)
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Unclear risk	The outcome data from this cross-over trial was treated as if coming from a parallel trial

Morton 1993 *(Continued)*

No signs of variance inequality or skewness?	Unclear risk	Not relevant (not naturally positive continuous outcomes e.g. change)
Trial size > 49?	High risk	N = 26
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Murphy 1982

Methods	Design: 2 x 2 factorial design with two additional control groups Purpose: examine the effect of behavioural therapy with spouse involvement on weight loss
Participants	Patients: self-referred couples with at least one obese person Baseline comparability: yes (weight, sex, age)
Interventions	Placebo: sessions with supportive group discussions about different weight loss programs Untreated: no sessions Experimental: sessions of behavioural therapy where the -person is alone and without spouse involvement by contract -person is alone in therapy and with spouse involvement by contract -couple is in therapy but without spouse involvement by contract -couple is in therapy and with spouse involvement by contract (Co-intervention: corticosteroids in 3 subjects)
Outcomes	Weight loss (pounds)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/behavioural therapy)
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	

Murphy 1982 *(Continued)*

No signs of variance inequality or skewness?	Unclear risk	Not relevant (not naturally positive continuous outcomes e.g. change)
Trial size > 49?	High risk	N = 17
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Mussell 1988

Methods	Design: five period cross-over trial Purpose: examine the effect of trachea-noise biofeedback in asthma
Participants	Patients: 'asthmatics were recruited with informed consent' Baseline comparability: not relevant
Interventions	Placebo: inhaled saline Type of untreated: no inhalation or biofeedback Type of experimental: -salbutamol inhalation -biofeedback wrong information -biofeedback correct information (Co-intervention: no asthma medication)
Outcomes	Forced expiratory volume after 1 second (FEV1)
Notes	Relevant outcome data not accessible

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'...the active and placebo bronchodilator inhaler given double blind..'
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	High risk	Relevant outcome data not accessible
Free of other bias?	Low risk	
Trial size > 49?	High risk	N = 16

Mussell 1988 *(Continued)*

Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Najnigier 1997

Methods	Design: three group parallel trial Purpose: examine the preventive effect of ondansetron on postoperative nausea
Participants	Patients: in-patients undergoing laparoscopic cholecystectomy Baseline comparability: NS
Interventions	Placebo: tablets without ondansetron Untreated: no tablets Experimental: tablets with ondansetron (Co-intervention: NS)
Outcomes	Number of patients with nausea Number of patients with vomiting
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	Very likely a double-blind study
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (binary outcome)
Trial size > 49?	Low risk	N = 60
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Allocation not clearly concealed

Nandi 1976

Methods	Design: three group parallel trial Purpose: examine the effect of imipramine on depression in patients not spontaneously seeking treatment
Participants	Patients: out-patients with clinical depression identified through a door to door survey in a rural community Baseline comparability: yes (score on Hamilton's depressive rating scale)
Interventions	Placebo: tablets without imipramine (lactose) Untreated: no tablets (observational group) Experimental: tablets with imipramine (Co-intervention: NS)
Outcomes	Score on Hamilton's rating scale
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Unclear risk	NS
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	High risk	N = 18
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Naumann 1989

Methods	Design: three group parallel trial

Naumann 1989 *(Continued)*

	Purpose: examine the effect of transcutaneous electrical nerve stimulation (TENS) and placebo on postoperative pain
Participants	Patients: postoperative patients Baseline comparability: NS
Interventions	Placebo: TENS with no current Untreated: no TENS Experimental: TENS with current (Co-intervention: standard pharmacological analgesic care)
Outcomes	Number of analgesic injections
Notes	Outcome not reported so that meta-analysis is possible.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'Der Versuchsaufbau entsprach Doppelblindbedingungen'
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	High risk	Outcome not reported so that meta-analysis is possible.
Free of other bias?	Low risk	
Trial size > 49?	Low risk	N = 117
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Drop-out > 15% or NS

Nawrocki 1997

Methods	Design: three group parallel trial Purpose: examine the effect of transurethral microwave thermotherapy (TUMT) on benign prostatic hyperplasia
Participants	Patients: out-patients suffering from benign prostatic hyperplasia Baseline comparability: NS
Interventions	Placebo: TUMT with no microwave emission Untreated: no TUMT

Nawrocki 1997 *(Continued)*

	Experimental: TUMT with machine on (Co-intervention: NS)
Outcomes	American Urologist Association's symptom score and Minimum urethral opening pressure (mm H20) Maximum urinary flow rate Post-void residual urine volume Maximum detrusor pressure
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	'selecting ... numbered ... balls from a sealed bag'
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'The treatment of the first two groups was 'double-blind'...'
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	High risk	Either variance inequality (F-test statistically significant) or skewness (1.64 standard deviations exceeds the mean)
Trial size > 49?	Low risk	N = 82
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Drop-out > 15% or NS

Nicassio 1974

Methods	Design: four group parallel trial Purpose: examine the effect of two different relaxation techniques on insomnia
Participants	Patients: media recruited out-patients suffering from insomnia Baseline comparability: yes (time to fall asleep)
Interventions	Placebo: sessions of self relaxation without any technique being taught Untreated: no sessions Experimental: sessions of taught techniques of relaxation: -autogenic training (focusing on heaviness and warmth of legs and arms) -progressive relaxation (muscle tension-release cycles)

Nicassio 1974 *(Continued)*

	(Co-intervention: no)
Outcomes	Sleep latency (minutes) Hours slept Number of awakenings Overall quality of the night's sleep (fatigue, depression, ability to relax, feeling of anxiety, ability to function at work and irritability during day) Pupillography
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/relaxation techniques)
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	High risk	Either variance inequality (F-test statistically significant) or skewness (1.64 standard deviations exceeds the mean)
Trial size > 49?	High risk	N = 16
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Nocella 1982

Methods	Design: three group parallel trial Purpose: examine the effect of cognitive-behavior modification on coping with dental procedure stress
Participants	Patients: children attending a dental clinic for a painful procedure Baseline comparability: yes (sex, procedure)
Interventions	Placebo: one session where a child received the full attention of the experimenter without implementing strategies for stress coping Untreated: no session Experimental: one session where stress coping strategies of a cognitive-behavioral nature were given

Nocella 1982 *(Continued)*

	(co-intervention: NS)
Outcomes	Frequency (per min) of behaviour expressing stress (facial grimaces, restlessness, moving legs and arms, sitting up, gripping chair and verbalizations)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/cognitive-behavior intervention)
Blinding? Outcome assessor	Low risk	'... each child's behavior was categorized by a judge who was blind to treatment conditions'
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	High risk	Either variance inequality (F-test statistically significant) or skewness (1.64 standard deviations exceeds the mean)
Trial size > 49?	High risk	N = 20
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

O'Brien 1996

Methods	Design: three group parallel trial Purpose: examine the effect of acupressure on nausea associated with pregnancy
Participants	Patients: pregnant women with nausea Baseline comparability: yes for baseline nausea
Interventions	Placebo: acupressure on a neutral point (not P6) Untreated: no acupressure Experimental: acupressure on the point P6 (Co-intervention: antiemetic medication, dietary and activity recommendations. The acupressure group used less antiemetic medication than the two other groups).
Outcomes	Nausea (Rhodes inventory of nausea and vomiting)

O'Brien 1996 *(Continued)*

	Vomiting
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	'group assignments were computer generated'
Allocation concealment?	Low risk	'numbered sealed envelopes'
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/acupressure)
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	High risk	Either variance inequality (F-test statistically significant) or skewness (1.64 standard deviations exceeds the mean)
Trial size > 49?	Low risk	N = 107
Clearly concealed allocation + trial size > 49 + drop-out max 15%	Low risk	All three categories fulfilled

Parker 1995

Methods	Design: three group parallel trial Purpose: examine the effect of stress management on clinical outcomes of rheumatoid arthritis (RA)
Participants	Patients: out-patients with RA Baseline comparability: yes
Interventions	Placebo: sessions where a education programme was discussed with each patient Untreated: no sessions Experimental: sessions with stress management (Co-intervention: standard RA treatment, 74% of patients in placebo and 77% in untreated group continued on stable medication).
Outcomes	Pain (VAS) McGill Pain Questionnaire Hassles scale Daily Stress Inventory Arthritis Helplessness Index

Parker 1995 *(Continued)*

	Center for Epidemiologic Studies Depression Scale State-Trait Anxiety inventory Arthritis Self-Efficacy Scale Coping Strategy Questionnaire Arthritis impact Measurement Scale Disease Activity
Notes	Relevant outcome data not accessible in trial report but retrieved by contact with authors.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/stress-management)
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out <15%
Free of selective reporting?	High risk	Relevant outcome data not accessible in trial report but retrieved by contact with authors.
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	High risk	Either variance inequality (F-test statistically significant) or skewness (1.64 standard deviations exceeds the mean)
Trial size > 49?	Low risk	N = 94
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Allocation not clearly concealed

Parker 2003

Methods	Design: three group parallel trial Purpose: examine the effect of cognitive-behavioural therapy on depression associated with rheumatoid arthritis
Participants	Patients: in-patients with rheumatoid arthritis Baseline comparability: no (age)
Interventions	Placebo: general patient education program Untreated: no program Experimental: cognitive behavioural program (10 weekly visits) (Co-intervention: standard medical care and anti-depressive medication)

Parker 2003 *(Continued)*

Outcomes	Center for epidemiological studies-depression scale (CES-D) Hamilton rating scale for depression Geriatric depression scale Symptom checklist 90-R Coping strategies questionnaire Daily stress inventory Hassles scale State-trait anxiety inventory Arthritis helplessness index Arthritis self-efficiency scale Arthritis impact measurement scale 2 multidimensional assessment of fatigue Pain (VAS) McGill pain questionnaire Rapid assessment of disease activity in rheumatology Erythrocyte sedimentation rate
Notes	Standard deviation for mean CES-D scores not reported. Standard deviation taken from another study (Kozora 2006): 7.5.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/cognitive behavioural therapy)
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	High risk	No protocol available. Standard deviation for mean CES-D scores not reported. Standard deviation taken from another study (Kozora 2006): 7.5.
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	High risk	N = 27
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Pearl 1956

Methods	Design: three group parallel trial

Pearl 1956 *(Continued)*

	Purpose: examine the effect of reserpine on schizophrenic patients
Participants	Patients: in-patients with schizophrenia Baseline comparability: NS
Interventions	Placebo: NS Untreated: no reserpine or placebo Experimental: reserpine (Co-intervention: institutionalised patients, beside that NS)
Outcomes	Multidimensional Scale for Rating Psychiatric Patients
Notes	Relevant outcome data not accessible

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'Except for the ward psychiatrist and nurse, no personnel involved were aware of patient's treatment. Persons dispensing the placebo were told it was a variant of reserpine'
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	High risk	Relevant outcome data not accessible
Free of other bias?	Low risk	
Trial size > 49?	Low risk	N = 100
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Drop-out > 15% or NS

Pelham 1992

Methods	Design: three group, multi-period cross-over trial (number of periods NS) Purpose: examine the perception of what influenced mood and behaviour (causal attribution) in boys treated for attention deficit hyperactivity disorder by methylphenidate or placebo
Participants	Patients: boys with attention deficit hyperactivity disorder attending a summer camp Baseline comparability: not relevant
Interventions	Placebo: tablet with no methylphenidate Untreated: no tablet

Pelham 1992 *(Continued)*

	Experimental: tablet with methylphenidate (Co-intervention: -summer camp treatment program (behavioural therapy principles) -same boys also participated in trials with other drugs on days not included in the present study)
Outcomes	Behaviour rating scales, including ratings of "Did you have a good day?" Attribution rating scales (what the children themselves thought influenced behaviour or mood) Mood/self-esteem rating scales Forced-Choice Questions
Notes	The outcome data was not available from the first period only, and was calculated as deriving from a parallel group trial.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'... designed to examine ADHD boys' causal attributions in a double-blind, within-subject, placebo-controlled medication trial'
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	Low risk	N = 76
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Drop-out > 15% or NS

Quahagen 1995

Methods	Design: three group parallel trial Purpose: examine the effect of cognitive training program for patients with dementia
Participants	Patients: out-patients with possible or confirmed diagnosis of Alzheimer's disease Baseline comparability: yes
Interventions	Placebo: passive cognitive stimulation where patients did not engage in training activities Untreated: no training

Quahagen 1995 *(Continued)*

	Experimental: active cognitive stimulation where patients did engage in training activities (Co-intervention: NS)
Outcomes	Cognitive functioning (Mattis dementia rating scale) Behavioural functioning (Memory and behaviour problems checklist, part A)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/cognitive training program)
Blinding? Outcome assessor	Low risk	'... research assistants who, with rare exception, were blinded to the condition to which the family had been assigned'
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	Low risk	N = 53
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Drop-out > 15% or NS

Rabkin 1990

Methods	Design: two group parallel trial Purpose: examine the effect of continuous placebo treatment on relapse of chronic mild depression
Participants	Patients: out-patients with chronic, mild depression having improved markedly after a 10 day placebo medication Baseline comparability: yes
Interventions	Placebo: continuous treatment with a tablet (content NS) Untreated: discontinued treatment with tablet (Co-intervention: NS)

Rabkin 1990 *(Continued)*

Outcomes	Number of patients with relapse of depression
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Treatment provider was not blinded
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (binary outcome)
Trial size > 49?	Low risk	N = 50
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Allocation not clearly concealed

Rawling 2001

Methods	Design: three group parallel trial Purpose: examine the effect of fentanyl and placebo on the pain related to abortion
Participants	Patients: women undergoing abortion Baseline comparability: yes
Interventions	Placebo: saline injections Untreated: no injections Experimental: fentanyl injections (Co-intervention: ibuprofen or acetaminophen, and lorazepam)
Outcomes	Pain (11 point numerical pain scale, 0 to 10) after removal of speculum
Notes	

Risk of bias

Rawling 2001 *(Continued)*

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Low risk	'sequentially numbered, opaque envelopes'
Blinding? Treatment provider	Low risk	'Physicians, clinic staff, and women in the study did not know the contents of the syringes'
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	High risk	Either variance inequality (F-test statistically significant) or skewness (1.64 standard deviations exceeds the mean)
Trial size > 49?	Low risk	N = 185
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Drop-out > 15% or NS

Reading 1982

Methods	Design: three group parallel trial Purpose: examine the effect of preoperative interview and placebo interview on postoperative pain and recovery
Participants	Patients: women undergoing elective laparoscopy Baseline comparability: yes (age)
Interventions	Placebo: preparation interview with neutral questions about hospitalisation in general Untreated: no preparation interview Experimental: preparation interview presenting 'information in a reassuring /supportive way' (Co-intervention: analgesics on demand, type and dose NS, 7 from placebo and 9 from untreated group required pain medication)
Outcomes	Pain (numerical/verbal rating scale) Time to return to health and work
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Reading 1982 *(Continued)*

Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/interview)
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	High risk	Either variance inequality (F-test statistically significant) or skewness (1.64 standard deviations exceeds the mean)
Trial size > 49?	High risk	N = 38
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Ristikankare 1999

Methods	Design: three group parallel trial Purpose: examine the tolerance and technical difficulty (and cardiorespiratory adverse effects) of sedative premedication during colonoscopy
Participants	Patients: out-patients undergoing colonoscopy Baseline comparability: yes (age, gender)
Interventions	Placebo: saline injections Untreated: no injections Experimental: midazolam injections (Co-intervention: NS)
Outcomes	Overall difficulty of colonoscopy, patient's report post procedure and after 2 weeks (100 mm VAS) Abdominal pain, patient's report (100 mm VAS) Discomfort, patient's report (100 mm VAS) Overall difficulty of colonoscopy, observer's report (100 mm VAS) Abdominal pain, observer's report (100 mm VAS) Discomfort, observer's report (100 mm VAS) Oxygen saturation in % Arterial blood pressure R-R intervals on continuous ECG readings
Notes	

Ristikankare 1999 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'An injection was administered for 30 to 60 seconds in a double-blind manner...'
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	Low risk	N = 122
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Drop-out > 15% or NS

Ristikankare 2006

Methods	Design: three group parallel group trial Purpose: study the effect of sedation and topical pharyngeal anaesthesia on cardiorespiratory safety during gastroscopy
Participants	Patients: patients undergoing gastroscopy Baseline comparability: yes
Interventions	Placebo: spray (NS) and injection (saline) Untreated: no spray or sedation injection Experimental: topical lidocaine spray or midazolam injection) (Co-intervention: NS)
Outcomes	Heart rate Blood pressure (diastolic and systolic) Saturation of Oxygen
Notes	

Risk of bias

Ristikankare 2006 *(Continued)*

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'The patient, the endoscopist, and the endoscopy nurse were all blinded as to whether the patient received effective drug or placebo'
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
Trial size > 49?	Low risk	N = 128
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Allocation not clearly concealed

Robinson 2001

Methods	Design: three group parallel trial Purpose: examine the analgesic effect of transcutaneous electrical nerve stimulation (TENS) during colonoscopy
Participants	Patients: out-patients undergoing colonoscopy Baseline comparability: yes
Interventions	Placebo: TENS without current Untreated: no TENS Experimental: TENS with current (Co-intervention: midazoalam, and escape analgesic drugs)
Outcomes	Breakthrough analgesia (mg nalbuphrine) Patient reported pain (100 point scale) Endoscopist rated pain (100 point scale) Post-procedure evaluation questionnaire (physical discomfort, psychological distress, satisfaction)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	'envelopes shuffled'

Robinson 2001 *(Continued)*

Allocation concealment?	Low risk	'sealed envelopes'
Blinding? Treatment provider	Unclear risk	NS
Blinding? Outcome assessor	Low risk	'Assesments were conducted by an assistant psychologist (CW) who did not attend the colonoscopy and was blind to study group'
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	High risk	Either variance inequality (F-test statistically significant) or skewness (1.64 standard deviations exceeds the mean)
Trial size > 49?	High risk	N = 23
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Roongpisuthip 1999

Methods	Design: three group parallel trial Purpose: examine the effect of dexfenfluramine on weight loss and thermogenesis in obese individuals
Participants	Patients: out-patients with body mass index > 25 kilograms per square meter Baseline comparability: yes
Interventions	Placebo: capsules for three months Untreated: no capsules Experimental: capsules with dexfenfluramine (Co-intervention: 8 week behavioural weight loss program)
Outcomes	Weight loss Other weight outcomes (waist/hip ratio, biceps fold, subscapular fold, arm circumference, etc) Daily activity and changes in behaviour Side effects
Notes	13 of 32 patients in the no treatment group dropped out.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS

Roongpisuthip 1999 *(Continued)*

Blinding? Treatment provider	Low risk	'Patients in group I were randomly stratified into 2 subgroups... in a double-blind, placebo-controlled manner'
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (not naturally positive continuous outcomes e.g. change)
Trial size > 49?	High risk	N = 37
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Roscoe 2002

Methods	Design: three period, Latin square, cross-over trial Purpose: examine the effect of acustimulation on chemotherapy-induced nausea
Participants	Patients: cancer patients receiving chemotherapy who previously have experienced moderate or severe chemotherapy-induced nausea
Interventions	Placebo: acustimulation wrist-band without stimulation of point PC-6 Untreated: no acustimulation write band Experimental: acustimulation wrist band with stimulation on point PC-6 (Co-intervention: 'antiemetic pills')
Outcomes	Antiemetic use (pills per day) Nausea Acute nausea Delayed nausea
Notes	The outcome data was not available from the first period only, and was calculated as deriving from a parallel group trial.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding?	Unclear risk	NS

Roscoe 2002 *(Continued)*

Treatment provider		
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Unclear risk	The outcome data from this cross-over trial was not available from the first period only, and was calculated as deriving from a parallel group trial.
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	Low risk	N = 54
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Drop-out > 15% or NS

Roscoe 2005

Methods	Design: three group parallel trial Purpose: examine the effect of acustimulation on chemotherapy-induced nausea in women with breast cancer
Participants	Patients: patients about to receive their second chemotherapy treatment who experienced nausea or vomiting after the first treatment
Interventions	Placebo: acustimulation wrist-band without stimulation Untreated: no acustimulation wrist band Experimental: acustimulation wrist band with stimulation (Co-intervention: standard clinical antiemetic prophylaxis, including a 5-HT_3 receptor antagonist)
Outcomes	Acute nausea (7-point scale) Delayed nausea Vomiting Quality of life Antiemetic medication
Notes	SE values were provided in the original publication and these values were converted to SDs.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding?	Unclear risk	NS

Roscoe 2005 *(Continued)*

Treatment provider		
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	Low risk	N = 64
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Allocation not clearly concealed

Rosen 1976

Methods	Design: five group parallel trial Purpose: examine the effect of three types of behavioural therapy on snake phobia
Participants	Patients: out-patients suffering from snake phobia Baseline comparability: yes
Interventions	Placebo: -posted instructions of factual information about snakes ('systematic re-learning') Untreated: no behavioural or placebo procedure (waiting-list) Experimental: -systematic desensitization procedure by posted instructions -systematic desensitization procedure by therapist -systematic desensitization procedure by minimal therapist contact through telephone (Co-intervention: No)
Outcomes	Anxiety score and heart rate and at slide provocation test Snake Attitude Questionnaire (SNAQ) Behavioural Approach test Fear Survey Schedule Rate of fear change
Notes	38% drop-outs

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS

Rosen 1976 *(Continued)*

Blinding? Treatment provider	Low risk	'.... a self-administered double-blind placebo control...'
Blinding? Outcome assessor	Low risk	'... follow-up assessments... were conducted by assistants blind to subjects' group assignment'
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	High risk	N = 14
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Rossi 1982

Methods	Design: three group, three period cross-over trial Purpose: examine the effect of labetalol on hypertension
Participants	Patients: in-patients with essential hypertension Baseline comparability: yes
Interventions	Placebo: tablet without labetalol Untreated: no tablet Experimental: tablet with labetalol (Co-intervention: No)
Outcomes	Diastolic blood pressure (mm Hg)
Notes	The outcome data was not available from the first period only, and was calculated as deriving from a parallel group trial.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Unclear risk	NS
Blinding?	Unclear risk	NS

Rossi 1982 *(Continued)*

Outcome assessor		
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Unclear risk	The outcome data from this cross-over trial was not available from the first period only, and was calculated as deriving from a parallel group trial.
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	High risk	N = 12
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Roughan 1981

Methods	Design: three group parallel trial Purpose: examine the effect of pelvic floor exercises on orgasmic potential
Participants	Patients: female out-patients not having had an orgasm for two years Baseline comparability: NS
Interventions	Placebo: instruction to do relaxation exercises Untreated: no exercises (waiting-list) Experimental: instructions to do pelvic floor exercises (Co-intervention: no psychological counselling)
Outcomes	Number of women having had orgasm
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/exercise instructions)
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed?	High risk	Drop-out > 15% or NS

Roughan 1981 *(Continued)*
All outcomes

Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (binary outcome)
Trial size > 49?	High risk	N = 26
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Rowbotham 1996

Methods	Design: three group, four period cross-over trial Purpose: examine the effect of lidocaine patches on post-herpetic neuralgia
Participants	Patients: out-patients with post-herpetic neuralgia Baseline comparability: not relevant
Interventions	Placebo: patch with vehicle but no lidocaine Untreated: no patch (observational group) Experimental: patch with vehicle and lidocaine (two periods) (Co-intervention: oral analgesics as prescribed before entering the trial, including escape medication, dose NS)
Outcomes	Pain (VAS) Side effects Blood lidocaine
Notes	The outcome data was not available from the first period only, and was calculated as deriving from a parallel group trial.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'... double-blind controlled study...'
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%

Rowbotham 1996 *(Continued)*

Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Unclear risk	The outcome data from this cross-over trial was not available from the first period only, and was calculated as deriving from a parallel group trial.
No signs of variance inequality or skewness?	Unclear risk	Not relevant (not naturally positive continuous outcomes e.g. change)
Trial size > 49?	Low risk	N = 70
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Allocation not clearly concealed

Rupert 1978

Methods	Design: factorial design, 3 (biofeedback, placebo, no biofeedback) x 2 (instructions to increase or decrease heart rate) + 1 (no treatment) Purpose: examine the effect of biofeedback on anxiety and heart rate
Participants	Patients: psychiatric in-patients deemed to have a high degree of anxiety problems by their physician Baseline comparability: yes (anxiety scores, heart rate)
Interventions	Placebo: biofeedback sessions with false positive feedback Untreated: no sessions (observational) Experimental: biofeedback sessions with correct feedback (Co-intervention: anxiolytics, fixed dosage.)
Outcomes	Anxiety Heart rate
Notes	Relevant outcome data not accessible

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Unclear risk	NS
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	High risk	Relevant outcome data not accessible

Rupert 1978 *(Continued)*

Free of other bias?	Low risk	
Trial size > 49?	High risk	N = 16
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Rybarczyk 1990

Methods	Design: four group parallel trial Purpose: examine the effect of stress management interventions on preoperative anxiety
Participants	Patients: older male in-patients undergoing major surgery Baseline comparability: yes (anxiety scores)
Interventions	Placebo: session of present focus interview prompting discussions on positive activities in the patient's present life Untreated: no session Experimental: -session of general reminiscence interview prompting patient to recall positive events from the first half of their life -session of challenge reminiscence interview prompting the patient to recall successfully met challenges (Co-intervention: NS)
Outcomes	Anxiety (Spielberger State-trait Anxiety Inventory) Coping self-efficacy inventory Physiological and postoperative adjustment measures
Notes	Relevant outcome data not accessible in trial report but retrieved by contact with authors.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/stress management interventions)
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15 % or NS
Free of selective reporting?	High risk	Relevant outcome data not accessible in trial report but retrieved by contact with authors.
Free of other bias?	Low risk	

Rybarczyk 1990 *(Continued)*

No signs of variance inequality or skewness?	Unclear risk	Not relevant (not naturally positive continuous outcomes e.g. change)
Trial size > 49?	High risk	N = 49
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Drop-out > 15 % or NS

Röschke 2000

Methods	Design: three group parallel trial Purpose: examine the effect of acupuncture on major depression
Participants	Patients: inpatients with depression (score > 17 on 21 item Hamilton depression scale) Baseline comparability: yes for age and score on Hamilton depression scale; no for gender
Interventions	Placebo: whole body needling in sites not regarded true acupuncture points for 30 minutes 3 times weekly for 4 weeks Untreated: no acupuncture Experimental: whole body acupuncture sessions (Co-intervention: mianserin at fixed doses; diazepam 'if required' but actual medication the first four weeks was roughly comparable between groups)
Outcomes	Self-rating scale (Bf-S) Global assessment scale (GAS) Bech-Rafaelsen melancholia Scale (BRMS) Clinical global impressions scale (CGI) Need of diazepam medication
Notes	SD for GAS and Self-rating scale not reported. Authors were contacted and provided the data.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/acupuncture)
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	High risk	SD for GAS and Self-rating scale not reported. Authors were contacted and provided the data.
Free of other bias?	Low risk	

Röschke 2000 *(Continued)*

No signs of variance inequality or skewness?	High risk	Either variance inequality (F-test statistically significant) or skewness (1.64 standard deviations exceeds the mean)
Trial size > 49?	High risk	N = 48
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Rösler 2003

Methods	Design: three group parallel trial Purpose: examine the effect of single needle acupuncture in suppressing gag-reflex during trans-esophageal echocardiography (TEE)
Participants	Patients: acupuncture naive patients with presumed cardioembolic stroke or transient ischemic attack Baseline comparability: yes
Interventions	Placebo: needling in the Chengjiang point (CV24) during TEE Untreated: no needling Experimental: needling 'at a sham point' (tip of the chin (Co-intervention: 0.5% tetracaine spray)
Outcomes	Gag-reflex (10 point VAS)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	'computer-evoked'
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Unclear risk	NS
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	High risk	N = 27

Rösler 2003 *(Continued)*

Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Sanders 1990

Methods	Design: three group parallel trial Purpose: examine the effect of chiropractic spinal manipulation on acute low back pain
Participants	Patients: out-patients with acute low back pain Baseline comparability: no, stratified for sex
Interventions	Placebo: light physical touch by investigator at L4/L5-S1 region Untreated: no touch or manipulation Experimental: low amplitude high velocity manipulation of L4/L5-S1 region (Co-intervention: no)
Outcomes	Pain (5-point NRS) Plasma B-endorphin concentration
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	'table of random numbers'
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/ manipulation)
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	High risk	N = 12
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Schallreuter 2002

Methods	Design: three group parallel trial Purpose: examine the effect of pseudocatalase cream and placebo on repigmentation in vitiligo
Participants	Patients: out-patients with vitiligo Baseline comparability: NS
Interventions	Placebo: cream with no pseudocatalase Untreated: no cream Experimental: cream with pseudocatalase (Co-intervention: climatotherapy)
Outcomes	No or minimal repigmentation (photographs graded 0 to 3)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Unclear risk	NS
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (binary outcome)
Trial size > 49?	High risk	N = 20
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Scharf 2006

Methods	Design: three group parallel trial Purpose: examine the effect of acupuncture in patients with osteoarthritis

Scharf 2006 *(Continued)*

Participants	Patients: patients with symptomatic osteoarthritis of the knee Baseline comparability: yes (age, gender, pain duration)
Interventions	Placebo: acupuncture on sites not regarded acupuncture sites Untreated: no acupuncture Experimental: acupuncture on sites regarded acupuncture sites (Co-intervention: standard medical care (physiotherapy and NSAIDs)).
Outcomes	Success rate (at least 36% change from baseline WOMAC scores) WOMAC (Western Ontario and McMaster Universities osteoarthritis) index Physical and mental health (SF-36) Global patient assessment
Notes	Patients in the no-treatment group took more medication, and received more sessions of physiotherapy (median 10) than the other groups (median 6).

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	'block randomization with block size of 6, stratified by center, was computer-generated by an independent statistician'
Allocation concealment?	Low risk	'Centralised telephone procedure'
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/acupressure)
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Low risk	Primary outcome specified in protocol
Free of other bias?	Unclear risk	See notes
No signs of variance inequality or skewness?	Unclear risk	Not relevant (binary outcome)
Trial size > 49?	Low risk	N = 681
Clearly concealed allocation + trial size > 49 + drop-out max 15%	Low risk	All three criteria fulfilled

Scharff 2002

Methods	Design: three group parallel trial Purpose: examine the effect of minimal-contact thermal biofeedback and attention-placebo on children's migraine

Scharff 2002 *(Continued)*

Participants	Patients: children 7 to 17 years with migraine (minimum average 5 attacks a month) referred by neurologists Baseline comparability: yes (age, gender, headache index, days with headache, etc)
Interventions	Placebo: four 1-hour sessions within a period of 6 weeks with 'handcooling' sham biofeedback and general discussion about 'their lives and headache' Untreated: no sessions Experimental: sessions of thermal biofeedback ('hand warming') (Co-intervention: ibuprofen and acetaminophen for headache. Instruction of 'not to change' medication habits)
Outcomes	Incidence of patients with decrease in headache index of 50% or more Pain (Headache Index, 4-point Likert scale) Temperature change Treatment credibility Child depression index (CDI) State-trait anxiety inventory for children (STAIC)
Notes	We have presented the outcome as no improvement for consistency of direction of outcomes. We excluded one patient from the numerators of both the placebo and no-treatment groups to be able to compute the result, as relative risk cannot be calculated when all patients in a group have a negative outcome.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	'randomization table stratified by two age groups'
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/biofeedback)
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (binary outcome)
Trial size > 49?	High risk	N = 23
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49, unclear allocation concealment

Seer 1980

Methods	Design: three group parallel trial Purpose: examine the effect of meditation on hypertension
Participants	Patients: out-patients with essential arterial hypertension Baseline comparability: NS
Interventions	Placebo: relaxation sessions Untreated: no relaxation or meditation sessions Experimental: meditation sessions (Co-intervention: no)
Outcomes	Diastolic blood pressure (mm Hg) Heart rate
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Unclear risk	NS
Blinding? Outcome assessor	Low risk	'... trained psychologist who was blind to all experimental conditions'
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	High risk	N = 27
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Senediak 1985

Methods	Design: four group parallel trial Purpose: examine the effect of rapid versus gradual scheduling of behavioural weight reduction programme

Senediak 1985 *(Continued)*

Participants	Patients: obese children Baseline comparability: yes
Interventions	Placebo: discussion and relaxation sessions Untreated: no sessions (waiting list) Experimental: sessions with rapid versus gradual scheduling of a behavioural weight reduction programme (Co-intervention: NS)
Outcomes	Weight (kg) % overweight Subcapsular skin fold thickness Normal % skin fold thickness Caloric intake Activity output Expectancy and programme evaluation ratings
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/behavioural programme)
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	High risk	N = 21
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Shen 2000

Methods	Design: three group parallel trial

Shen 2000 *(Continued)*

	Purpose: examine the effect of electroacupuncture for chemotherapy-induced emesis
Participants	Patients: female patients receiving chemotherapy Baseline comparability: yes for age, no for emesis with prior chemotherapy
Interventions	Placebo: superficial needling at a location different from PC6 or ST36, no 'de Qi', or electrical stimulation ('minimal needling') Untreated: no needling Experimental: needling at PC6 or ST36, de Qi -sensation, and electrical stimulation (Co-intervention: standard antiemetic regime and escape medication)
Outcomes	Use of antiemetic medication Total number of emesis episodes Proportion of emesis free days
Notes	Overall antiemetic escape medication was not reported. We report the use of prochlorperazine as outcome, which we consider the relevant drug.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	'random number table'
Allocation concealment?	Low risk	'serially numbered, sealed, opaque envelopes'
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/electroacupuncture)
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	High risk	No protocol available. Overall antiemetic escape medication was not reported. We report the use of prochlorperazine as outcome, which we consider the relevant drug.
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	Low risk	N = 67
Clearly concealed allocation + trial size > 49 + drop-out max 15%	Low risk	All three categories fulfilled

Sibilio 1957

Methods	Design: three group parallel trial Purpose: examine the effect of promazine on the behaviour of chronic schizophrenics

Sibilio 1957 *(Continued)*

Participants	Patients: woman chronic schizophrenic in-patients Baseline comparability: yes
Interventions	Placebo: capsule with no promazine Untreated: no capsule Experimental: capsule with promazine (Co-intervention: no)
Outcomes	Behaviour change on Gardner Behavior Chart
Notes	Relevant outcome data not accessible

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'The double-blind technique was employed throughout the study'
Blinding? Outcome assessor	Low risk	'Those attendants who rated the patients' behavioral adjustment did not dispense medication and were unaware of the experimental group to which a patient was assigned'
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	High risk	Relevant outcome data not accessible
Free of other bias?	Low risk	
Trial size > 49?	Low risk	N = 62
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Allocation not clearly concealed

Sinaiko 1991

Methods	Design: four group parallel trial Purpose: examine the effect of low sodium diet or potassium supplementation on adolescent blood pressure
Participants	Patients: adolescents with systolic blood pressure above 109 mm Hg (boys) and 108 mm Hg (girls) Baseline comparability: yes
Interventions	Placebo: capsules Untreated: no capsules Experimental: - capsules with potassium

Sinaiko 1991 *(Continued)*

	-low sodium diet (Co-intervention: NS)
Outcomes	Diastolic blood pressure (mm Hg) at three years Systolic blood pressure
Notes	Data from the no-treatment group not published. Additional data received from the authors. Randomisation not 1:1.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'The capsule treatment is a double-masked design...'
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	High risk	Data from the no-treatment group not published. Additional data received from the authors. Randomisation not 1:1.
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	Low risk	N = 87
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Drop-out > 15% or NS

Sipich 1974

Methods	Design: five group parallel trial Purpose: examine the effect of 'covert sensitization' on smoking behaviour
Participants	Patients: smokers Baseline comparability: yes (number of smoked cigarettes)
Interventions	Placebo: sessions of listening to illusory subliminal messages Untreated: -no sessions with continuous monitoring of smoking rates -no sessions with pre-post monitoring of smoking rates Experimental:

Sipich 1974 *(Continued)*

	-covert sensitization sessions (visualization of feelings of nausea and vomiting as imagining themselves smoking) -self control suggestion sessions (told to quit by their own effort) (Co-intervention: NS)
Outcomes	Mean number of cigarettes smoked per day
Notes	Standard deviation of untreated and placebo means estimated from t-test of baseline-post intervention change in the placebo group

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/covert sensitization)
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	High risk	No protocol available. Standard deviation of untreated and placebo means estimated from t-test of baseline-post intervention change in the placebo group
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	High risk	Either variance inequality (F-test statistically significant) or skewness (1.64 standard deviations exceeds the mean)
Trial size > 49?	High risk	N = 20
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Sommerness 1955

Methods	Design: three group parallel trial Purpose: examine the effect of reserpine on the behaviour of chronic mentally ill patients
Participants	Patients: chronic mentally ill men Baseline comparability: yes
Interventions	Placebo: pill with no reserpine Untreated: no pill Experimental: pill with reserpine (Co-intervention: yes, no group difference)

Sommerness 1955 *(Continued)*

Outcomes	Behaviour change Blood pressure Weight
Notes	Relevant outcome data not accessible

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	'random numbers table'
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'The hospital pharmacist alone knew which group received reserpine or placebo'
Blinding? Outcome assessor	Unclear risk	NS
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	High risk	Relevant outcome data not accessible
Free of other bias?	Low risk	
Trial size > 49?	Low risk	N = 60
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Drop-out > 15% or NS

Spanos 1995

Methods	Design: four group parallel trial Purpose: examine the effect of hypnosis on smoking reduction
Participants	Patients: smokers Baseline comparability: yes (number of cigarettes smoked)
Interventions	Placebo: sessions of listening to illusory subliminal messages Untreated: no sessions Experimental: -sessions of hypnosis -sessions called 'cognitive restructuring' with procedures identical to the hypnosis group but with no mention of hypnosis and no hypnotic induction (Co-intervention: NS)
Outcomes	Mean number of cigarettes smoked per day
Notes	

Spanos 1995 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/hypnosis)
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	High risk	N = 25
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Sprott 1993

Methods	Design: three group parallel trial Purpose: examine the effect of acupuncture on fibromyalgia
Participants	Patients: in-patients suffering from fibromyalgia Baseline comparability: NS
Interventions	Placebo: laser acupuncture with laser off Untreated: no acupuncture Experimental: laser acupuncture with laser on (Co-intervention: physio-, thermo- and electrotherapy. Fixed scheme at start of treatment. Paracetamol on demand, intake NS)
Outcomes	Pain (VAS and pain threshold) Number of positive tender points
Notes	Standard deviations (SD) on 10 cm pain visual analogue scale data not reported. SD estimated from another pain RCT (Lander 1993: SD ~ 3 cm)

Risk of bias

Sprott 1993 *(Continued)*

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	'random numbers'
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/acupuncture)
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	High risk	No protocol available. Standard deviations (SD) on 10 cm pain visual analogue scale data not reported. SD estimated from another pain RCT (Lander 1993: SD ~ 3 cm)
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (not naturally positive continuous outcomes e.g. change)
Trial size > 49?	High risk	N = 20
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Stabholz 1991

Methods	Design: three group parallel trial Purpose: examine the effect of sustained release delivery system of chlorhexidine on oral hygiene of patients with Down's syndrome
Participants	Patients: institutionalised with Down's syndrome Baseline comparability: NS
Interventions	Placebo: teeth coating without chlorhexidine Untreated: no teeth coating Experimental: teeth coating with chlorhexidine (Co-intervention: penicillin before scaling and polishing teeth, normal oral hygiene)
Outcomes	Plaque index Gingival index Papillary bleeding Plaque bacterial counts
Notes	
Risk of bias	

Stabholz 1991 *(Continued)*

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'The study was double-blind...'
Blinding? Outcome assessor	Low risk	'... the examiner was not aware which treatment was given'
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	High risk	N = 20
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Steinsbekk 2004

Methods	Design: four group parallel trial Purpose: examine the effect of homeopathy for upper respiratory infections (URTI) in children
Participants	Patients: children with upper respiratory infection Baseline comparability: yes (age, gender)
Interventions	Placebo: lactose pill Untreated: no pill Experimental: -Self-selected ultramolecular homeopathic pill -treatment by homeopath (Co-intervention: no)
Outcomes	Total URTI score Days with URTI Days with antibiotics Days with analgesic/antipyretic Visits to medical doctor Days with other illness, noises from the chest, or work absence due to ill child (all outcomes also as binary: proportion of children with days of ...)
Notes	

Steinsbekk 2004 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	'computer'
Allocation concealment?	Low risk	'central'
Blinding? Treatment provider	Low risk	'This trial was of double-blind, randomized parallel group placebo controlled design'
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	High risk	Either variance inequality (F-test statistically significant) or skewness (1.64 standard deviations exceeds the mean)
Trial size > 49?	Low risk	N = 176
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Drop-out > 15% or NS

Stewart 1991

Methods	Design: four group parallel trial Purpose: examine the effect of cognitive-behavioural therapy on oral hygiene
Participants	Patients: veteran out-patients with normal oral hygiene Baseline comparability: yes
Interventions	Placebo: sessions of lectures on non-disease aspects of dentistry Untreated: no sessions Experimental: sessions of cognitive-behavioural therapy (Co-intervention: NS)
Outcomes	Brushing frequency (per week) and Plaque Index Flossing frequency
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Stewart 1991 *(Continued)*

Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/cognitive-behavioural therapy)
Blinding? Outcome assessor	Low risk	'The dentist that rated plaque levels was blind to each subject's assigned experimental group'
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	Low risk	N = 50
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Drop-out > 15% or NS

Stransky 1989

Methods	Design: three group parallel trial Purpose: examine the effect of vitamin B6 on carpal tunnel syndrome
Participants	Patients: out-patients suffering from carpal tunnel syndrome Baseline comparability: NS
Interventions	Placebo: tablet without vitamin B6 (content: dextrose) Untreated: no tablet Experimental: tablet with vitamin B6 (Co-intervention: NS)
Outcomes	Number of patients who improved in symptoms Improvement in median and ulnar nerve conduction latency
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS

Stransky 1989 *(Continued)*

Blinding? Treatment provider	Low risk	'We undertook a randomized, double-blind, placebo-controlled study...'
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (binary outcome)
Trial size > 49?	High risk	N = 9
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Straub 2001

Methods	Design: three group parallel trial Purpose: examine the effect of chiropractic care on jet lag
Participants	Patients: junior elite athletes Baseline comparability: NS
Interventions	Placebo: sham chiropractic manipulations for 19 days Untreated: no chiropractic sessions Experimental: chiropractic sessions (Co-intervention: NS)
Outcomes	Sleep disturbance (duration of sleep in hours, sleep onset in minutes, numbers of sleep bouts, movement and fragmentation index) Jet lag rating Mood (Profile of Mood States questionnaire)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	'table of random numbers'
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (chiropractic manipulation/placebo manipulation)

Straub 2001 *(Continued)*

Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	High risk	N = 10
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Sumaya 2001

Methods	Design: three group, three period, cross-over trial Purpose: examine the effect of bright light treatment on depression in institutionalised older adults
Participants	Patients: institutionalised older adults with moderate to severe depression (baseline scores on the Geriatric Depression Scale 11 to 20) Baseline comparability: not relevant
Interventions	Placebo: sessions with light treatment with 300 Lux for 30 minutes per day for 1 week Untreated: no light treatment Experimental: light treatment with 10,000 Lux (Co-intervention: NS)
Outcomes	Geriatric Depression Scale at day 5 of each treatment period
Notes	The outcome data was not available from the first period only, and was calculated as deriving from a parallel group trial.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Unclear risk	NS
Blinding? Outcome assessor	Unclear risk	NS

Sumaya 2001 *(Continued)*

Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Unclear risk	The outcome data from this cross-over trial was not available from the first period only, and was calculated as deriving from a parallel group trial.
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	High risk	N = 20
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Tan 1982

Methods	Design: three group parallel trial Purpose: examine the effect of prophylactic behavioural-cognitive training on procedural acute pain
Participants	Patients: out-patients having to undergo a painful diagnostic procedure (knee arthrogram) Baseline comparability: yes
Interventions	Placebo: procedural information and pain experience discussion without any pain control skills training Untreated: no information or training Experimental: behavioural-cognitive skills training for pain control (Co-intervention: NS)
Outcomes	Pain: McGill pain questionnaire Pain: radiologist's rating and videotaped pain behaviour Fear (self report and radiologist's rating) Discomfort (self report and radiologist's rating)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Unclear risk	NS
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome

Tan 1982 *(Continued)*

Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	High risk	N = 24
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Tan 1986

Methods	Design: three group parallel trial Purpose: examine the effect of cognitive-behaviour therapy on psycho-social problems and seizure control in epileptic patients
Participants	Patients: epileptic out-patients with psycho-social problems (anxiety, depression) and inadequate seizure control Baseline comparability: yes
Interventions	Placebo: sessions of supportive group counselling or discussion with no specific cognitive-behaviour therapy Untreated: no sessions Experimental: sessions of behavioural-cognitive therapy (Co-intervention: -'professional counselling or psychiatric treatment' to all but 6 patients -anticonvulsant medication. The difference in serum-level between the groups was not significant.)
Outcomes	Number of patients with improvement in seizure frequency (frequency diary) Seizure rating by blinded observer Global rating of psycho-social adjustment
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/behavioural cognitive training)
Blinding?	Unclear risk	Not relevant as patient reported outcome

Tan 1986 *(Continued)*

Outcome assessor		
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (binary outcome)
Trial size > 49?	High risk	N = 19
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trials size < 49

Tarcin 2004

Methods	Design: three group parallel trial Purpose: examine the effect of acustimulation in patients undergoing gastroscopy
Participants	Patients: out-patients undergoing gastroscopy Baseline comparability: yes (age, gender)
Interventions	Placebo: -electrical device attached to electrodes and acustimulation performed on a site not regarded acupuncture site -electrical device attached to electrodes but no acustimulatiuon performed Untreated: no electrical device attached nor acustimulation performed Experimental: acustimulation on point P6 (Co-intervention: no)
Outcomes	Proportion of patients scoring 1 to 4 on a VAS for nausea Proportion of patients scoring 1 to 4 on a VAS for difficulty of swallowing gastroscopy Proportion of patients scored 1 to 4 by gastrocopist on a VAS for nausea/retching Proportion of patient who accept re-gastroscopy
Notes	The results from the two placebo groups were combined

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/acustimulation)
Blinding?	Unclear risk	Not relevant as patient reported outcome

Tarcin 2004 *(Continued)*

Outcome assessor		
Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (binary outcome)
Trial size > 49?	Low risk	N = 235
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Allocation not clearly concealed

Tarrier 1998

Methods	Design: three group parallel trial Purpose: examine the effect of cognitive behaviour therapy on positive symptoms in patients with chronic schizophrenia
Participants	Patients: people with chronic schizophrenia Baseline comparability: yes
Interventions	Placebo: sessions of supportive counselling Untreated: no sessions Experimental: sessions of behavioural cognitive therapy (Co-intervention: standard care including medication, fixed dose)
Outcomes	Number of patients with improvement of positive symptoms by 50% or more Mean number and intensity of positive psychotic symptoms on Present state examination and Brief psychiatric rating scale
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	'stratified block randomised procedure'
Allocation concealment?	Low risk	'sealed envelopes' ... ' carried out by a third party'
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/behavioural cognitive therapy)
Blinding? Outcome assessor	Low risk	'Effort was made to blind the independent assessors...' ... '... suggesting that blinding was satisfactory'

Tarrier 1998 *(Continued)*

Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (binary outcome)
Trial size > 49?	Low risk	N = 54
Clearly concealed allocation + trial size > 49 + drop-out max 15%	Low risk	All three categories fulfilled

Tashjian 2006

Methods	Design: three group parallel trial Purpose: examine the effect of zolpidem on postoperative pain
Participants	Patients: out-patients undergoing knee arthroscopy Baseline comparability: yes (age, gender, preoperative pain score)
Interventions	Placebo: gelatin pills with no zolpidem Untreated: no pills Experimental: pills with zolpidem (Co-intervention: yes (ibuprofen + hydrocodone/acetaminophen))
Outcomes	Pain (0 to 10 VAS; mean daily postoperative) Pain (mean morning and evening postoperative) Fatigue (0 to 10 VAS; mean daily postoperative) Fatigue (mean morning and evening postoperative)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'... the surgeon was unaware if the patient was given zolpidem or placebo'
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed?	High risk	Drop-out > 15% or NS

Tashjian 2006 *(Continued)*

All outcomes

Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	High risk	Either variance inequality (F-test statistically significant) or skewness (1.64 standard deviations exceeds the mean)
Trial size > 49?	High risk	N = 43
Clearly concealed allocation + trial size > 49 + dropout max 15%	High risk	Trial size < 49

Theroux 1993

Methods	Design: three group parallel trial Purpose: examine the effect of intranasal midazolam in facilitating suturing of lacerations in children
Participants	Patients: preschool children with lacerations visiting an emergency department Baseline comparability: yes
Interventions	Placebo: nasal spray without midazolam Untreated: no nasal spray Experimental: nasal spray with midazolam (Co-intervention: NS)
Outcomes	Anxiety (cry score) Parent satisfaction Heart rate Blood pressure Respiratory rate Pulse oximetry Cry score Motion score Struggle score
Notes	Data from placebo and no-treatment groups pooled. Contact with researchers provided unpooled data

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Unclear risk	NS
Allocation concealment?	Unclear risk	NS
Blinding? Treatment provider	Low risk	'Blinding was maintained for the physician by having them leave the bedside for a short interval...'
Blinding? Outcome assessor	Low risk	'Cry... was assessed by the physician...' (See above)

Theroux 1993 *(Continued)*

Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15% or NS
Free of selective reporting?	High risk	Data from placebo and no-treatment groups pooled. Contact with researchers provided unpooled data
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	High risk	N = 32
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Thomas 1987

Methods	Design: 2 x 2 factorial design (positive or negative consultation x placebo tablet or no tablet) Purpose: examine the effect of positive consultation style and placebo tablet
Participants	Patients: out-patients attending a GP clinic with symptoms but without any physical signs and in whom no definite diagnosis could be made Baseline comparability: yes
Interventions	Placebo: tablet containing thiamine Untreated: no tablet Experimental: -positive consultation: firm diagnosis + good prognosis -negative consultation: no diagnosis and uncertain prognosis (Co-intervention: NS)
Outcomes	Number of patients who improved Doctor-patient contact Degree of communication Number of days before improvement Need for further treatment
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Unclear risk	NS
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	

Thomas 1987 *(Continued)*

Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (binary outcome)
Trial size > 49?	Low risk	N = 200
Clearly concealed allocation + trial size > 49 + dropout max 15%	High risk	

Thomas 1999

Methods	Design: three group parallel trial Purpose: examine the effect of cognitive-behavioural intervention, and placebo, on pain associated with sickle cell disease
Participants	Patients: out-patients with sickle cell disease (type HbSS) Baseline comparability: yes (age, gender, hospital admissions for painful crises, etc)
Interventions	Placebo: one hourly session per week for two months of general discussions of the problems of living with sickle cell disease (attention-placebo) Untreated: no sessions Experimental: sessions of cognitive-behavioural therapy (Co-intervention: NS)
Outcomes	Pain (Short form of McGill pain questionnaire) General health questionnaire Coping strategies questionnaire Pain self-efficacy questionnaire Beliefs about pain control questionnaire Number of hospital and emergency admissions Duration of hospital stay
Notes	The result is probably unreliable because 38 of 97 patients dropped out (39%). In addition, 23 of 56 patients treated with placebo or active sessions were excluded because of failure to attend sessions or to complete assessments, no such exclusions described for no-treatment group.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	'random number table and was restricted to blocks of four ...'
Allocation concealment?	Unclear risk	'a sequence of labeled cards contained in sealed numbered envelopes'
Blinding? Treatment provider	High risk	Not described as double-blind (cognitive-behavioural intervention/placebo)
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome

Thomas 1999 *(Continued)*

Incomplete outcome data addressed? All outcomes	High risk	Drop-out > 15%. The result is probably unreliable because 38 of 97 patients dropped out (39%). In addition, 23 of 56 patients treated with placebo or active sessions were excluded because of failure to attend sessions or to complete assessments, no such exclusions described for no-treatment group.
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	High risk	Either variance inequality (F-test statistically significant) or skewness (1.64 standard deviations exceeds the mean)
Trial size > 49?	High risk	N = 40
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Thomas 2002a

Methods	Design: 2x2 factorial design with an additional randomisation for one arm Purpose: examine the effect of a home based exercise programme on knee pain, and to determine the contribution of the contact with a therapist in explaining the outcome
Participants	Patients: out-patients with knee pain recruited through a postal questionnaire Baseline comparability: yes (age, gender, pain, weight, etc)
Interventions	Placebo: tablet with dolomite (calcium and magnesium) twice weekly for two years Untreated: no tablets Experimental: -exercise (20-30 minutes daily, initiated by four 30 minutes' instruction sessions within the first two months in the patients' home, and follow up visits every six months). -telephone (monthly telephone contact) (Co-intervention: no information on use of analgesic drugs)
Outcomes	Pain (WOMAC osteoarthritis index, 0 to 20) Knee stiffness Disability General physical function (SF-36) Hospital anxiety and depression scale Isometric quadriceps muscle strength
Notes	Not 1:1 randomisation. Dropout rate: 23.7%. Results not presented for placebo and no-treatment, but authors provided additional data.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	'computer generated lists in permuted blocks of 10, stratified by sex and age'
Blinding? Treatment provider	High risk	Not described as double-blind (home based exercise/placebo)

Thomas 2002a *(Continued)*

Blinding? Outcome assessor	Unclear risk	Patient reported outcome (interviewer was blinded)
Incomplete outcome data addressed? All outcomes	High risk	
Free of selective reporting?	High risk	No protocol available. Results not presented for placebo and no-treatment, but authors provided additional data.
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (not naturally positive continuous outcomes e.g. change)
Trial size > 49?	Low risk	N = 156
Clearly concealed allocation + trial size > 49 + dropout max 15%	High risk	

Thomas 2002b

Methods	Same trial as Thomas 2002a, but results are presented as two subanalyses because there was one group of patients randomised to placebo or no treatment (see above), and another group randomised to telephone contact, exercise and placebo versus telephone contact and exercise.
Participants	See Thomas 2002a
Interventions	Placebo: dolomite (calcium and magnesium) twice weekly for two years Untreated: no tablets Experimental: see Thomas 2002a (Co-intervention: exercise and telephone contact)
Outcomes	See Thomas 2002a
Notes	See Thomas 2002a

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	'computer generated lists in permuted blocks of 10, stratified by sex and age'
Blinding? Treatment provider	High risk	Not described as double-blind (home based exercise/placebo)
Blinding? Outcome assessor	Unclear risk	Patient reported outcome (interviewer was blinded)
Incomplete outcome data addressed? All outcomes	High risk	

Thomas 2002b *(Continued)*

Free of selective reporting?	High risk	No protocol available. Results not presented for placebo and no-treatment, but authors provided additional data.
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (not naturally positive continuous outcomes e.g. change)
Trial size > 49?	Low risk	N = 233
Clearly concealed allocation + trial size > 49 + dropout max 15%	High risk	

Tremeau 1992

Methods	Design: three group parallel trial Purpose: examine the effect of acupuncture on cervical maturation
Participants	Patients: women in 37th to 38th week of pregnancy and a Bishop score < 4 Baseline comparability: yes (Bishop score)
Interventions	Placebo: acupuncture in relevant sites Untreated: no acupuncture (observational) Experimental: acupuncture 1 cm from relevant sites (Co-intervention: standard care)
Outcomes	Bishop score
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/acupuncture)
Blinding? Outcome assessor	Low risk	'... par un obstétricien ou une sage-femme, ne connaissant ni l'un, ni l'autre, le groupe de tirage au sort de la patiente'
Incomplete outcome data addressed? All outcomes	High risk	
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (not naturally positive continuous outcomes e.g. change)
Trial size > 49?	Low risk	N = 64

Tremeau 1992 *(Continued)*

Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk

Tritrakarn 2000

Methods	Design: five group parallel trial Purpose: examine the analgesic effect of EMLA cream (lidocaine and prilocaine) on pain associated with extracorporeal lithotripsy, and if effective, to examine which component (the cutaneous anaesthesia, the cream or the occlusive dressing) contributes to the analgesia
Participants	Patients: out-patients undergoing pain inducing extracorporeal lithotripsy because of renal stones Baseline comparability: yes
Interventions	Placebo: no occlusive dressing -occlusive dressing without cream Untreated: no dressing or cream Experimental: 3 groups received occlusive dressing with and without cream (Co-intervention: no)
Outcomes	Pain (numerical verbal pain scale, 0 to 100)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Blinding? Treatment provider	Low risk	' A randomized, double-blind, crossover study...'
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	Low risk	N = 82
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	

Tsay 2003

Methods	Design: three group parallel trial Purpose: examine the effect of acupressure on quality of sleep
Participants	Patients: in-patients with end stage renal disease Baseline comparability: yes
Interventions	Placebo: acupressure on sites not regarded acupressure sites Untreated: no acupressure Experimental: acupressure on sites regarded acupressure sites (Co-intervention: standard medical care)
Outcomes	Pittsburgh sleep quality index Sleep log
Notes	The trial report does not state the number of patients allocated to each group. We assumed that out of 98 patients in the three-armed trial 32 patients entered the placebo group and 32 patients the no-treatment group

Risk of bias

Bias	Authors' judgement	Support for judgement
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	High risk	No protocol available. The trial report does not state the number of patients allocated to each group. We assumed that out of 98 patients in the three-armed trial 32 patients entered the placebo group and 32 patients the no-treatment group
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (not naturally positive continuous outcomes e.g. change)
Trial size > 49?	Low risk	N = 64
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Allocation not clearly concealed

Tsay 2004

Methods	Design: three group parallel trial Purpose: examine the effect of acupressure on fatigue in patients with end-stage renal disease
Participants	Patients: patients with end-stage renal disease Baseline comparability: yes
Interventions	Placebo: acupressure on sites not regarded acupressure sites Untreated: no acupressure Experimental: acupressure on sites regarded acupressure sites

Tsay 2004 *(Continued)*

	(Co-intervention: standard medical care)
Outcomes	Revised Piper fatigue Scale Fatigue (100 mm VAS) Pittsburgh Sleep Quality Index Beck Depression Inventory
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	Low risk	N = 71
Clearly concealed allocation + trial size > 49 + dropout max 15%	High risk	

Tuomilehto 1980

Methods	Design: three group parallel trial Purpose: examine the effect of high fibre intervention (guar gum) on serum lipoproteins and body weight
Participants	Patients: out-patients with hypercholesterolaemia Baseline comparability: NS
Interventions	Placebo: granule with no guar gum (wheat flower) Untreated: no granule Experimental: granule with guar gum (Co-intervention: diet instructions: decrease alcohol and fat, increase complex carbohydrates)
Outcomes	Serum-cholesterol: total (mmol/l) Serum-cholesterol: high density lipoprotein Serum-triglyceride Weight Blood pressure
Notes	

Tuomilehto 1980 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Blinding? Treatment provider	Low risk	'... studied in a double-blind controlled trial'
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	High risk	N = 22
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Turner 1979

Methods	Design: five group parallel trial Purpose: examine the effect of paradoxical intention therapy on insomnia
Participants	Patients: out-patients suffering from insomnia Baseline comparability: yes (sleep parameters)
Interventions	Placebo: sessions of 'quasi-desensitization' (neutral images paired with bedtime activity) Untreated: no sessions (waiting list) Experimental: sessions of -paradoxical intention therapy: instructions to remain awake as long as possible and presented with the true theoretical background -stimulus control: practical advice on bed time activities -progressive relaxation: training in relaxation techniques (Co-intervention: hypnotics, comparable doses between groups)
Outcomes	Sleep latency (min) Returning to sleep difficulty Restedness rating Falling asleep difficulty Hours of sleep Drug usage per week
Notes	

Risk of bias

Turner 1979 *(Continued)*

Bias	Authors' judgement	Support for judgement
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/paradoxical intention)
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	High risk	Either variance inequality (F-test statistically significant) or skewness (1.64 standard deviations exceeds the mean)
Trial size > 49?	High risk	N = 20
Clearly concealed allocation + trial size > 49 + dropout max 15%	High risk	Trial size < 49

Tyler 1946

Methods	Design: three group parallel trial Purpose: examine the prophylactic effect of placebo and various drugs on seasickness
Participants	Patients: soldiers undergoing amphibious training Baseline comparability: NS
Interventions	Placebo: lactose capsules Untreated: no capsules Experimental: various belladonna alkaloid and barbiturate preparations (Co-intervention: NS)
Outcomes	Number of patients with seasickness
Notes	The randomisation procedure was in principle open to selection bias, however, the allocation took place openly under full military discipline so we do not think selection bias was likely.

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	'cards from deck so stacked as to ensure a random distribution'
Allocation concealment?	Unclear risk	See notes
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome

Tyler 1946 *(Continued)*

Incomplete outcome data addressed? All outcomes	High risk	
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (binary outcome)
Trial size > 49?	Low risk	N = 563
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	

Vlaeyen 1996

Methods	Design: three group parallel trial Purpose: examine the effect of cognitive therapy on fibromyalgia
Participants	Patients: out-patients with fibromyalgia Baseline comparability: yes
Interventions	Placebo: sessions of group discussions on pain experience + educational programme on pain Untreated: no sessions Experimental: sessions of cognitive therapy + educational programme on pain (Co-intervention: NS)
Outcomes	Pain (McGill pain questionnaire) Pain: coping, control, behaviour % positive responders Relaxation Tension Catastrophing Activity Obsessive-compulsive Fear Depression
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/cognitive therapy)
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed?	Low risk	Drop-out < 15%

Vlaeyen 1996 *(Continued)*

All outcomes		
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (not naturally positive continuous outcomes e.g. change)
Trial size > 49?	Low risk	N = 79
Clearly concealed allocation + trial size > 49 + dropout max 15%	High risk	Allocation not clearly concealed

Walton 1993

Methods	Design: three group parallel trial Purpose: examine the prophylactic effect of penicillin on post treatment symptoms following root canal treatment for asymptomatic periapical pathosis
Participants	Patients: out-patients undergoing root canal treatment Baseline comparability: NS
Interventions	Placebo: tablets without penicillin Untreated: no tablets Experimental: tablets with penicillin (Co-intervention: NS)
Outcomes	Number of patients in pain Swelling Side effects
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Blinding? Treatment provider	High risk	Not described as double-blind
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	

Walton 1993 *(Continued)*

No signs of variance inequality or skewness?	Unclear risk	Not relevant (binary outcome)
Trial size > 49?	Low risk	N = 54
Clearly concealed allocation + trial size > 49 + dropout max 15%	High risk	

Wang 1997

Methods	Design: four group parallel trial Purpose: examine the effect of transcutaneous acupoint electrical stimulation (TAES) on postoperative analgesic requirement
Participants	Patients: patients having undergone lower abdominal surgical procedures Baseline comparability: yes
Interventions	Placebo: TAES without electrical stimulation Untreated: no TAES Experimental: TAES with electrical stimulation (low and high) (Co-intervention: standard operational procedures)
Outcomes	Total opoid requirement (in equivalents of mg hydromorphone) in 24 hours Morphine (mg) delivered by PCA (patient controlled analgesia) device Number of times patients used PCA device (patient controlled analgesia) Supplemental opioid analgesics (i.m.) Supplemental oral analgesics Duration of PCA Duration of use of TAES Duration of stay in postanaesthesia care unit Duration of hospital stay Pain, 100 mm VAS Fatigue, 100 mm VAS Discomfort, 100 mm VAS Follow-up questionnaire
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	‘computer-generated randomization sequence'
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/TAES)
Incomplete outcome data addressed? All outcomes	High risk	
Free of selective reporting?	Unclear risk	No protocol available

Wang 1997 *(Continued)*

Free of other bias?	Low risk	
No signs of variance inequality or skewness?	High risk	Either variance inequality (F-test statistically significant) or skewness (1.64 standard deviations exceeds the mean)
Trial size > 49?	Low risk	N = 51
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	

Watzl 1986

Methods	Design: 2 x 2 factorial design Purpose: examine the effect of strict control and placebo on relapse rate of abstinent alcoholics
Participants	Patients: woman in-patients attending an alcoholism clinic Baseline comparability: yes
Interventions	Placebo: injections with saline Untreated: no injections Experimental: -strict external control of alcohol abstinence -no strict external control of alcohol abstinence (Co-intervention: stay at a clinic with unspecified 'complex and extensive treatment program', e.g. in a few cases patients received 'liver preparation')
Outcomes	Number of abstinent drinkers
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/experimental)
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (binary outcome)
Trial size > 49?	Low risk	N = 70
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Allocation not clearly concealed

Weingaertner 1971

Methods	Design: three group parallel trial Purpose: examine the effect of aversive stimulation (self-administered electric shocks) on hallucinatious schizophrenic patients
Participants	Patients: schizophrenic in-patients (men) with auditory hallucinations Baseline comparability: yes
Interventions	Placebo: patients equipped with a device that did not produce an electric shock and instructed to activate it when hallucinating (told that some people could not feel the shock) Untreated: not equipped with a device to induce electric shock Experimental: equipped with a device that did produce an electric shock and instructed to activate it when hallucinating (Co-intervention: -medication (type and dose NS, four patients changed) -other experimental intervention (type NS, interference deemed implausible by authors) -group and milieu therapy (type, frequency NS))
Outcomes	Brief Psychiatric Rating Scale: hallucination scale Patient Data Sheet Symptom checklist Ward personnel comments
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/electric shock)
Incomplete outcome data addressed? All outcomes	High risk	
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (not naturally positive continuous outcomes e.g. change)
Trial size > 49?	High risk	N = 30
Clearly concealed allocation + trial size > 49 + dropout max 15%	High risk	Trial size < 49

Werntoft 2001

Methods	Design: three group parallel trial Purpose: examine the effect of acupressure on nausea and vomiting during pregnancy

Werntoft 2001 *(Continued)*

Participants	Patients: pregnant women with nausea without treatment Baseline comparability: not for week of pregnancy (yes for age, week of pregnancy at start of nausea)
Interventions	Placebo: acupressure waistband at the upper side of the wrist (not P6) for two weeks Untreated: no acupressure Experimental: acupressure waistband at P6 (Co-intervention: no)
Outcomes	Nausea (100 mm VAS) after 2 weeks Vomiting
Notes	The drop-out rate was 25% (20 out of 80). Trial probably stopped prematurely before inclusion of the planned 300 women

Risk of bias

Bias	Authors' judgement	Support for judgement
Adequate sequence generation?	Low risk	each woman ‘drew an envelope from a box'
Allocation concealment?	Low risk	The drawn envelopes had 'the same appearance but different content', and 'The women were asked not to open the envelope until returning home'
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/acupressure)
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	High risk	N = 40
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Whittaker 1963

Methods	Design: three group parallel trial Purpose: examine the effect of discontinuing medication with perphenazine in schizophrenia
Participants	Patients: chronic schizophrenic in-patients on perphenazine Baseline comparability: for age and length of hospital stay

Whittaker 1963 *(Continued)*

Interventions	Placebo: liquid solution with no perphenazine (content NS) Untreated: no liquid solution (observational group) Experimental: liquid solution with perphenazine (Co-intervention: no other psychotropic drugs allowed)
Outcomes	Number of patients with major relapse: need for known active medication Minor relapse: deterioration on symptom scales (psychiatric rating scale & Fergus Falls Behaviour Rating Scale)
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Blinding? Treatment provider	Low risk	'...the trial was blind in that only the pharmacist knew which bottles were active'
Incomplete outcome data addressed? All outcomes	High risk	
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (binary outcome)
Trial size > 49?	High risk	N = 26
Clearly concealed allocation + trial size > 49 + dropout max 15%	High risk	Trial size < 49

Wilcock 2008

Methods	Design: three group cross-over trial Purpose: examine the effect of nebulised furosemide and placebo on breathlessness
Participants	Patients: patients with cancer and breathlessness Baseline comparability: cross-over trial
Interventions	Placebo: inhalation of saline Untreated: no inhalation Experimental: inhalation of furosemide (Co-intervention: standard cancer treatment
Outcomes	Number reading test (number read per breath) Number reading test (total number) Arm exercise test Duration of arm test Borg Score at maximum equivalent work load Change in spirometric values

Wilcock 2008 *(Continued)*

Notes	Cross-over trial. data from 1 period not available.

Risk of bias

Bias	Authors' judgement	Support for judgement
Blinding? Treatment provider	Low risk	'The object of the current randomised, double-blind, placebo-controlled, cross-over study...'
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Unclear risk	Cross-over trial. Data from 1 period not available.
No signs of variance inequality or skewness?	High risk	Either variance inequality (F-test statistically significant) or skewness (1.64 standard deviations exceeds the mean)
Trial size > 49?	High risk	N = 30
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Williams 1988

Methods	Design: three group parallel trial Purpose: examine the effect of hypnosis on smoking cessation
Participants	Patients: smokers that had attended one smoking program before Baseline comparability: NS
Interventions	Placebo: one session in which the reason for smoking and attempts to stop were discussed Untreated: no session Experimental: single hypnosis session (Co-intervention: NS)
Outcomes	Number of abstinent smokers Mean number of cigarettes smoked per week
Notes	All 20 patients in the placebo and 20 patients in the no-treatment group smoked at post intervention. Data extracted as if one patient in each group did not smoke. This was done due to overcome software incapacity in computing data with no successes.

Risk of bias

Bias	Authors' judgement	Support for judgement
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/hypnosis)

Williams 1988 *(Continued)*

Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (binary outcome)
Trial size > 49?	High risk	N = 40
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Wilson 1980

Methods	Design: three group parallel trial Purpose: examine the effect of disulfiram and placebo implants on alcoholism
Participants	Patients: alcoholics Baseline comparability: NS
Interventions	Placebo: implants without disulfiram Untreated: no implants Experimental: implants with disulfiram (Co-intervention: NS)
Outcomes	Number of abstinent drinkers Mean time to first alcoholic consumption
Notes	Patients were randomised to placebo and no treatment in a 4:1 ratio

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Blinding? Treatment provider	Low risk	'Assignment to the disulfiram and placebo conditions was double-blind'
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	

Wilson 1980 *(Continued)*

No signs of variance inequality or skewness?	Unclear risk	Not relevant (binary outcome)
Trial size > 49?	Low risk	N = 50
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	

Witt 2005

Methods	Design: three group parallel trial Purpose: examine the effect of acupuncture for osteoarthritis of the knee
Participants	Patients: patients with symptomatic osteoarthritis of the knee Baseline comparability: yes (WOMAC score)
Interventions	Placebo: acupuncture on sites not regarded acupuncture sites Untreated: no acupuncture Experimental: acupuncture on sites regarded acupuncture sites (Co-intervention: standard medical care. All patients were allowed to take non-steroid anti-inflammatory drugs if necessary)
Outcomes	WOMAC (Western Ontario and McMaster Universities osteoarthritis) index Disability (Pain disability index) Physical and mental health (SF-36) Pain (questionnaire for assessing the emotional aspects of pain) Depression (ADS depression scale) Days with limited function Days in pain (patient diary) Days with medication in weeks 5-8 (patient diary)
Notes	Patients in the no-treatment group took medication on 5.8 days whereas the placebo group did so on 4.6 days (weeks 5 to 8). SE values were provided in the original publication and these values were converted to SD for analysis in the review.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	‘random list generated with Samp Size 2.0’
Allocation concealment?	Low risk	'centralised telephone randomisation procedure'
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/acupuncture)
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%

Witt 2005 *(Continued)*

Free of selective reporting?	Low risk	Primary outcome specified in protocol
Free of other bias?	Unclear risk	Patients in the no-treatment group took medication on 5.6 days whereas the placebo group did so on 4.6 days (weeks 5 to 8).
No signs of variance inequality or skewness?	Low risk	No variance inequality (F-test not statistically significant) and no skewness (1.64 standard deviations does not exceed the mean)
Trial size > 49?	Low risk	N = 140
Clearly concealed allocation + trial size > 49 + dropout max 15%	Low risk	All three categories fulfilled

Wojciechowski 1984

Methods	Design: five group parallel trial Purpose: to demonstrate a) therapist bias and b) that a double blind design is feasible in psychotherapy
Participants	Patients: women out-patients with tension headache Baseline comparability: no (pre treatment headache index score)
Interventions	Placebo: sessions with 'concentration therapy' and -positive therapist expectations -negative therapist expectations Untreated: no sessions Experimental: sessions with muscular relaxation therapy and -positive therapist expectations -negative therapist expectations (Co-intervention: NS)
Outcomes	Pain (Headache index score) Global therapist judgement of improvement Global patient judgement of improvement
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Blinding? Treatment provider	Low risk	'...the double blind design...'
Blinding? Outcome assessor	Unclear risk	Not relevant as patient reported outcome
Incomplete outcome data addressed? All outcomes	High risk	
Free of selective reporting?	Unclear risk	No protocol available

Wojciechowski 1984 *(Continued)*

Free of other bias?	Low risk	
No signs of variance inequality or skewness?	High risk	Either variance inequality (F-test statistically significant) or skewness (1.64 standard deviations exceeds the mean)
Trial size > 49?	High risk	N = 21
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Woods 2005

Methods	Design: three group parallel trial Purpose: examine the effect of therapeutic touch on patients with dementia
Participants	Patients: patients with Alzheimer's disease Baseline comparability: yes (age, gender, degree of dementia)
Interventions	Placebo: mimic treatment that resembled therapeutic touch to the naive observer (no attempt to enter 'a quiet meditative state ... instead the practitioner did mental calculations). Untreated: no therapeutic touch Experimental: therapeutic touch (Co-intervention: standard medical care).
Outcomes	Modified Agitated Behavior Rating Scale (ABRS) Revised Memory and Behavior checklist
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	'random numbers table'
Allocation concealment?	Unclear risk	‘Envelopes containing group assignments were opened just prior to the intervention to ensure blinding of all concerned during the pre-test measurement’
Blinding? Treatment provider	Low risk	'Using a double-blind (masked), three-group experimental pre-test/post-test design...'
Blinding? Outcome assessor	Low risk	'Six blind observers collected all of the data on a Behavior Monitoring Chart (BMC)'
Incomplete outcome data addressed? All outcomes	High risk	
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	

Woods 2005 *(Continued)*

No signs of variance inequality or skewness?	High risk	Either variance inequality (F-test statistically significant) or skewness (1.64 standard deviations exceeds the mean)
Trial size > 49?	High risk	N = 38
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Yan 2005

Methods	Design: three group parallel trial Purpose: study the effect of segmental vs. innocuous electrical stimulation for chronic pain relief
Participants	Patients: patients with first acute stroke Baseline comparability: NS
Interventions	Placebo: stimulation from electrical stimulation device with disconnected circuit and standard rehabilitation Untreated: standard rehabilitation only Experimental: functional electrical stimulation and standard rehabilitation (Co-intervention: standard rehabilitation program)
Outcomes	Composite spasticity scale (CSS) Maximum isometric voluntary contraction (MIVC) Walking ability (Up and Go (TUG) test)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Adequate sequence generation?	Low risk	'random number produced by Jensen's computerized method of minimization'
Blinding? Treatment provider	High risk	Described as single-blind (placebo/electrical stimulus device)
Blinding? Outcome assessor	Low risk	'... the assessor was blinded to the nature of intervention'
Incomplete outcome data addressed? All outcomes	Low risk	Drop-out < 15%
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
Trial size > 49?	High risk	N = 28

Yan 2005 *(Continued)*

Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Yates 1988

Methods	Design: three group parallel trial Purpose: examine the effect of chiropractic treatment on blood pressure
Participants	Patients: out-patients with hypertension and thoracic subluxation Baseline comparability: NS
Interventions	Placebo: session with a 'chiropractic adjusting device' without it performing the essential manipulative procedure Untreated: no session Experimental: session with a 'chiropractic adjusting device' performing the essential manipulative procedure (Co-intervention: 5 patients in the placebo and untreated group received hypertensive medication, dose NS)
Outcomes	Diastolic blood pressure reduction (mm Hg) Anxiety
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Blinding? Treatment provider	High risk	Not described as double-blind (placebo/chiropractic procedure)
Incomplete outcome data addressed? All outcomes	High risk	
Free of selective reporting?	Unclear risk	No protocol available
Free of other bias?	Low risk	
No signs of variance inequality or skewness?	Unclear risk	Not relevant (not naturally positive continuous outcomes e.g. change)
Trial size > 49?	High risk	N = 14
Clearly concealed allocation + trial size > 49 + drop-out max 15%	High risk	Trial size < 49

Outcomes: The first outcome listed is the one extracted for the review (all major outcomes for each trial are listed).
NS: not stated.
VAS: visual analogue scale.
EMG: electromyography.
GP: general practitioner.

Hb: haemoglobin

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abbot 1995	The 'placebo intervention' was 'compressed air with freon' which, sprayed on skin, lowers temperature: impure placebo.
Abikoff 1985	All patients underwent a placebo run-in period and only those not responding were included: not relevant participants.
Allen 1987	Dropout was > 50%.
Allen 1996	Randomisation was not described in the original paper. In a subsequent correspondence the authors described the method of randomisation: 'put three pieces of paper into a hat, each with the number 1, 2 or 3 and then drew a number each time a subject arrived and then assigned them accordingly '. There was no concealment of allocation. The number of patients in the placebo group was 105, in the no-treatment group 75.
Amanzio 1999	Pain was induced experimentally.
Amanzio 2001	Not explicitly a randomised trial.
Archer 1992	Not a randomised study.
Arnett 1990	Inclusion of patients to no-treatment groups started later than inclusion to active/placebo.
Avis 2008	Patients received payment.
Babizhayev 2001	No explicit randomisation between placebo and no-treatment.
Barrett 1999	Low self-esteem is not regarded a clinical problem.
Beck 2002	Male nursing home residents were not randomised, but 'assigned to the groups'. The proportion of males differed between the compared groups from 10% to 24%.
Benedetti 1998	Allocation to placebo and no-treatment was not explicitly random.
Benedetti 1999b	Pain was induced experimentally.
Benedict 1989	The outcome in this study of chronic schizophrenia was reaction-time which we regard not clinically relevant.
Bennet 2001	The outcome was not clinical.
Benton 1988	The trial studied the impact of vitamin supplements on the intelligence of normal schoolchildren, not regarded a clinical study.
Bergmann 1994	No untreated group.
Beutler 1988	The 'placebo' intervention consisted in 'paranormal healing at a distance', directed at a patient behind a screen, however the patients in the no treatment group also sat behind a screen, so the patient in both groups experienced the same: unacceptable no treatment group.
Bierman 1997	The outcome in this alcohol addiction trial was 'sleep quality': regarded not clinically relevant.

Study	Reason for exclusion
Björkstén 1986	Randomisation not mentioned.
Blackwell 1972	Participants were 'medical students': not a clinical study.
Blanchard 1978	6/30 patients were reallocated after randomisation.
Borden 1989	The clinically relevant outcomes (parents' and teachers' ratings) were not blinded.
Borkovec 1975	The participants were college students screened by group test program and receiving research credit for participation: not a clinical setting.
Bornstein 1973	The accumulated weight loss of the patients in the placebo group was 'positively reinforced': impure placebo.
Bouchet 1996	The participants were normal subjects.
Brown 1999	Pain was induced experimentally.
Buckalew 1972	The participants were normal subjects.
Bullock 1999	Drop out rate > 50%.
Bush 1985	Allocation of participants to the different groups of the trial was not concealed.
Butler 1984	The placebo intervention consisted in ordering difficult tasks for social phobics and practicing these tasks in ascending order: impure placebo.
Carlson 1993	The outcomes were 1) a questionnaire assessing the boys' attributions and 2) performance at an experimental word puzzle test: regarded not clinically relevant.
Carpenter 1994	Subjects were paid for participation.
Chambless 1984	Drop-out rate > 50%.
Chen 1999	Unclear wether the trial was randomised. Authors contacted by e-mail for clarification but did not respond.
Cole 1983	Randomisation not stated.
Corletto 1999	Placebo group got active treatment after 40 days.
Corson 1994	The placebo intervention implied pain inducing needle sticks: not a pure placebo intervention.
Cottraux 1986	Placebo group received not only a placebo intervention but also advice to reduce alcohol intake which is associated with smoking: impure placebo.
Cram 1980	The no treatment group sessions ('chart headaches only') also included discussions of 'situational themes': unacceptable no treatment group.
Cristofalo 1999	Normal subjects (athletes with no diagnosis of asthma).
Cullhed 1961	Allocation by day of admission.
Dahlquist 1986	Placebo group children were removed from parents. This was probably in itself anxiety inducing: impure placebo.

Study	Reason for exclusion
Daley 2007	According to the protocol patients received money for entering the trial.
Diamond 1995	The placebo used was saline. It is likely that saline has a physiological effect on congested nose, and is sold 'over the counter' in Denmark for this purpose: impure placebo.
Disney 1988	Not explicitly a randomised trial.
Dobia 1985	The 'placebo intervention' was relaxation therapy which was an integrated part of the experimental intervention: not a relevant placebo procedure.
Dundee 1988	Patients allocated by day of admittance.
Egbert 1964	The 'placebo' intervention in post-operative patients having had intra-abdominal surgery included instructions concerning pain modulating behaviour, e.g. how actively to relax abdominal muscles: impure placebo.
Eickholz 2002	Split mouth design. Teeth were randomised, not patients or treatment periods.
Elkin 1985	No untreated group.
Feather 1972	A non-clinical experimental setting where pain was induced by heat.
Fevery 1990	The trial was designed to measure outcome after 6, 12 and 24 months. The placebo intervention was only comparable to the no treatment group the first 8 weeks: not a relevant comparison.
Fillmore 1992	A non-clinical experimental setting with normal subjects.
Fillmore 1994	A non-clinical experimental setting with normal subjects.
Fillmore 1994b	A non-clinical experimental setting with normal subjects.
Flor 1983	Untreated group received co-intervention not given to the placebo group.
Fuller 1986	No untreated group.
Gam 1998	The placebo group received massage and exercise, the no treatment group did not: differential co-intervention.
Gelfand 1963	The subjects in this non-clinical experimental pain trial were nursing students.
Goodale 1990	No clear indication in the trial report that 'the reading group' constituted a placebo group.
Gowdey 1967	'Normal subjects': not a clinical problem.
Gregorio 1996	The trial was designed to measure outcome after 6, 12 and 18 months. The placebo intervention was only comparable to the no treatment group the first 6 weeks: not a relevant comparison.
Gregory 1983	The study was 'designed to investigate whether elderly hospitalized people can improve their performance if they are permitted a second attempt at the Set Test, a verbal fluency task': not a therapeutical clinical study.
Gryll 1978	The allocation of participants was not explicitly stated to be random.
Haake 2007	No no-treatment group. The group receiving acupuncture was not treated with conventional treatment given to the no-acupuncture group.

Study	Reason for exclusion
Hale 1986	Allocation of participants was done in 'orderly sequence' following randomisation of the first patient.
Hall 1994	'Subjects reimbursed $20 at weeks 3 and 8 and $35 at week 12': participants paid.
Hargreaves 1983	This laboratory study was an uncontrolled trial.
Hayden 1996	The placebo used was saline. It is likely that saline has a physiological effect on congested nose, and is sold 'over the counter' in Denmark for this purpose: impure placebo.
Herth 2000	Placebo not explicitly mentioned.
Hogarty 1973	No untreated group.
Huber 1986	The clinician who decided to remove the placenta knew which patients were in the untreated group: not blindly assessed.
Jensen 1991	The trial was a 'laboratory study' with normal subjects: not a clinical study.
Kalman 1998	The placebo group received dietary advice which was withheld from the no-treatment group.
Kanner 1999	The placebo treatment included 'intensive smoking-cessation sessions' which was withheld from the the no-treatment group.
Kelley 1976	Subjects were normal children: not a clinical study.
Khandwala 1997	According to personal communication with trial report authors, the vehicle was under suspicion of having an effect that was not only due to placebo and is actually sold 'over the counter' in the USA: impure placebo.
Klosko 1990	Patients in the untreated group continued on anxiolytic medication. Patients in the placebo group discontinued their medication. The groups in this anxiety trial are not comparable.
Korner 1982	No randomisation to placebo and untreated.
Lasagna 1954	The study was not randomised.
Levine 1980	The outcome was test anxiety which is not considered a clinically relevant outcome.
Liberman 1964	Not a randomised study.
Lopez 1999	Randomisation was conducted 'with due precaution to avoid differences among the subgroups in the children's mean ages and IQs'.
Lorr 1962	Drop-out rate > 50%.
Lujan 1992	The headache was induced: an experimental setting.
Lynn 1983	The placebo procedure is described as being of 'an active nature': impure placebo.
Manner 1987	7/20 placebo treated patients receive sedative anticholinergic premedication (glycopyrrolate) compared to 0/18 untreated patients. Also unclear whether the untreated patients were part of the randomization: differential co-intervention.

Study	Reason for exclusion
Marchand 1993	Patients were allocated through 'pseudo-random assignment'. Contact to the authors clarified that this meant that randomisation was based on drawing pieces of paper with group assignments from a hat. There was no concealment of allocation.
McGrath 1988	Suggestions to reduce impact of possible triggers in 'untreated group': unacceptable no treatment group.
Meehan 1985	The no treatment group took prescribed and escape analgesics, the placebo group only escape analgesics.
Montgomery 1996	A non-clinical experimental study with normal subjects.
Nikolaou 1998	Not a randomised trial.
Peart 1977	No randomisation to untreated and placebo.
Penman 1956	Post-randomisation reallocations took place.
Pollo 2001	Allocation to placebo and no-treatment was not explicitly random.
Price 1999	Healthy volunteers. Pain was induced experimentally.
Rampes 1997	Drop-out rate 33/58=56% [> 50%].
Reich 1990	The participants were normal older subjects: not a clinical study.
Robertson 1991	'All subjects were paid'.
Rodriguez 1997	Post randomisation patient re-allocation took place: 69 patients were randomised to the untreated group and but results were collected from 78 patients.
Roehrich 1993	This alcohol study had neuropsychological and psychological test variables as outcomes: regarded not clinically relevant.
Roelofs 2000	Paid healthy volunteers. Pain was induced experimentally.
Roos 1969	The placebo intervention was designed to include active components: not a pure placebo.
Roth 1986	Normal subjects.
Rustøen 1998	Placebo not explicitly mentioned.
Sarles 1977	Not a randomised trial.
Sartor 1980	Not properly randomised.
Shaw 1974	The placebo intervention consisted of listening to 'audiotapes designed to help persons cope with everyday fears and anxieties': not a pure placebo.
Sheikh 1986	The participants were older 'normal' volunteers with 'age associated memory impairment' : not a clinical study.
Silvestri 1977	Anxiety is the only outcome considered clinically relevant in this trial of the effect of implosive therapy for emotionally disturbed retardates, however, anxiety was not recorded in the no treatment group.

Study	Reason for exclusion
Skovlund 1991	No untreated group.
Smith 2002	The so-called 'no treatment' group (but not the placebo group) received advice about changes in diet and the use of vitamin B6.
Spanos 1988	'All were paid $15 for their participation'.
Staats 1998	Pain induced by 'hand exposure to ice water': not a clinical study.
Stanley 1989	Not blindly assessed.
Suchman 1992	Not blindly assessed.
Tashkin 1977	Not a randomised trial.
Taylor 1977	Anti-hypertensive drugs were given at variable dose as co-intervention. More patients in the placebo group than in the untreated group were increased in dose: differential co-intervention.
Vacc 1980	The investigation studied the effect of various interventions on maladaptive behaviour of otherwise normal children: not regarded a clinical study.
Van Damme 1998	Healthy volunteers.
Volweider 1981	Placebo procedure included physical exercise: not a pure placebo.
Weber 1975	Averaged Electroencephalic audiometry (AEA) thresholds was the outcome in this study of CNS stimulant medication on children with minimal brain damage: outcome regarded not clinically relevant.
Weintraub 1992	The placebo period (week 160 to 190) was followed by the untreated period (week 190 to 210), (no randomisation).
Windle 2001	Allocation of patients by alternation.
Winnan 1982	The Bernstein test is a diagnostic test. Pain was induced by infusion of acid: not a therapeutic clinical study.
Worner 1992	Drop out rate > 50%.
Zeisset 1968	The outcome was 'interview anxiety' which was not considered clinically relevant as a measure for general anxiety.

Impure placebos: interventions with clearly specified contents or procedures that have an effect which, with considerable likelihood, goes beyond the effect of the treatment ritual. Such interventions are mostly 1) physical or pharmacological vehicles (see, e.g., Khandwala 1997), or 2) psychological 'placebos' with clear behavioural-cognitive therapeutical elements (see, e.g., Bornstein 1973) or direct health related advice (see, e.g., Cottraux 1986).

Characteristics of studies awaiting assessment *[ordered by study ID]*

Shin 2005

Methods	Randomised trial
Participants	Women with hyperemesis gravidarum

Shin 2005 *(Continued)*

Interventions	P6 acupuncture; placebo acupuncture; no acupuncture
Outcomes	Unclear
Notes	Reported in Korean

Characteristics of ongoing studies *[ordered by study ID]*

Barret 2007

Trial name or title	PEP trial
Methods	Randomised trial
Participants	Out-patients with common cold
Interventions	Placebo Standard and enhanced patient-provider interaction Echinacea
Outcomes	Area under time severity curve based on the Wisconsin Upper Respiratory Symptom Survey
Starting date	NS
Contact information	bruce.barret@fammed.wisc.edu
Notes	

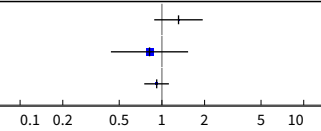
DATA AND ANALYSES

Comparison 1. Main analysis: overall pooled analyses

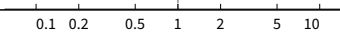
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Binary outcomes	44	6041	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.88, 0.99]
2 Continuous outcomes	158	10525	Std. Mean Difference (IV, Random, 95% CI)	-0.23 [-0.28, -0.17]

Analysis 1.1. Comparison 1 Main analysis: overall pooled analyses, Outcome 1 Binary outcomes.

Study or subgroup	Placebo n/N	No-treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Adriaanse 1995	50/328	38/326		1.66%	1.31[0.88,1.94]
Alkaissi 1999	9/20	11/20		0.76%	0.82[0.44,1.53]
Alkaissi 2002	77/139	82/136		3.81%	0.92[0.75,1.12]



Study or subgroup	Placebo n/N	No-treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Aune 1998	11/26	9/14		0.84%	0.66[0.36,1.19]
Berg 1983	9/11	9/15		1.14%	1.36[0.83,2.24]
Blackman 1964	6/12	6/12		0.49%	1[0.45,2.23]
Carter 2003	13/28	20/29		1.27%	0.67[0.42,1.07]
Corver 2006	227/279	360/416		6.48%	0.94[0.88,1.01]
De Sanctis 2001	9/10	8/9		2.34%	1.01[0.74,1.38]
Double 1993	3/22	3/22		0.15%	1[0.23,4.42]
Dundee 1986	17/25	17/25		1.75%	1[0.68,1.46]
Elliott 1978	6/18	6/6		0.7%	0.37[0.19,0.71]
Faas 1993	107/162	108/155		4.78%	0.95[0.81,1.1]
Fanti 2003	8/10	9/10		1.8%	0.89[0.61,1.29]
Frank 1990	14/26	14/26		1.12%	1[0.6,1.65]
Guglielmi 1982	12/12	11/12		3.44%	1.09[0.87,1.36]
Harrison 1975	24/28	25/30		3.51%	1.03[0.83,1.28]
Heinzl 1981	70/130	92/132		3.94%	0.77[0.64,0.94]
Hutton 1991	5/24	16/30		0.44%	0.39[0.17,0.91]
Hyman 1986	9/15	15/15		1.53%	0.61[0.4,0.93]
Jacobs 1971	9/15	12/39		0.76%	1.95[1.04,3.65]
Kerr 2003	28/33	32/36		4.13%	0.95[0.79,1.15]
Killen 1990	226/309	219/309		5.9%	1.03[0.94,1.14]
Klerman 1974	17/25	16/25		1.63%	1.06[0.71,1.58]
Malcolm 1980	40/63	44/58		3.25%	0.84[0.66,1.06]
McMillan 1994	14/26	24/46		1.34%	1.03[0.66,1.62]
Molsberger 2002	38/58	30/53		2.44%	1.16[0.86,1.56]
Najnigier 1997	21/30	24/30		2.5%	0.88[0.65,1.17]
Rabkin 1990	14/27	12/23		1.01%	0.99[0.58,1.7]
Roughan 1981	9/12	9/14		1.1%	1.17[0.7,1.94]
Schallreuter 2002	3/10	4/10		0.22%	0.75[0.22,2.52]
Scharf 2006	179/365	224/316		5.32%	0.69[0.61,0.78]
Scharff 2002	11/12	12/12		3.44%	0.92[0.74,1.15]
Stransky 1989	1/5	1/4		0.06%	0.8[0.07,9.18]
Tan 1986	8/10	8/9		1.71%	0.9[0.61,1.32]
Tarcin 2004	58/158	27/77		1.85%	1.05[0.73,1.51]
Tarrier 1998	22/26	25/28		3.71%	0.95[0.77,1.17]
Thomas 1987	47/100	50/100		2.6%	0.94[0.71,1.25]
Tyler 1946	89/260	106/303		3.38%	0.98[0.78,1.23]
Walton 1993	19/24	21/30		2.33%	1.13[0.83,1.54]
Watzl 1986	15/34	7/36		0.53%	2.27[1.06,4.88]
Whittaker 1963	3/13	7/13		0.26%	0.43[0.14,1.3]
Williams 1988	19/20	19/20		4.98%	1[0.87,1.15]
Wilson 1980	31/40	10/10		3.64%	0.8[0.65,0.99]
Total (95% CI)	**3000**	**3041**		**100%**	**0.93[0.88,0.99]**
Total events: 1607 (Placebo), 1802 (No-treatment)					
Heterogeneity: Tau^2=0.01; Chi^2=78.77, df=43(P=0); I^2=45.41%					
Test for overall effect: Z=2.28(P=0.02)					

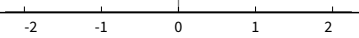


Favours placebo

Favours no-treatment

Analysis 1.2. Comparison 1 Main analysis: overall pooled analyses, Outcome 2 Continuous outcomes.

Study or subgroup	Placebo		No-treatment		Std. Mean Difference	Weight	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
Abikoff 2004	35	-91.4 (18.9)	34	-89.5 (22.8)		0.82%	-0.09[-0.56,0.38]
Alfano 2001	24	6.2 (2.8)	14	6.6 (2.7)		0.53%	-0.14[-0.8,0.52]
Allen 1998	11	-2.9 (7.9)	11	-6.1 (10.9)		0.37%	0.32[-0.52,1.17]
Allen 2006	45	12 (9.6)	44	19 (9.6)		0.91%	-0.72[-1.15,-0.29]
Andersen 1990	18	35 (27.2)	16	25 (23.6)		0.51%	0.38[-0.3,1.06]
Anderson 1999	30	-2.7 (0.8)	27	-2.7 (0.8)		0.73%	0.08[-0.44,0.6]
Antivalle 1990	11	-1.6 (5.6)	10	-3.9 (7.3)		0.35%	0.34[-0.52,1.21]
Antonio 1999	6	79.7 (12.2)	6	72.6 (11.2)		0.21%	0.56[-0.6,1.72]
Ascher 1979	8	50.6 (44.1)	9	62.4 (25.3)		0.3%	-0.32[-1.28,0.64]
Asmar 1996	34	-0.2 (7.7)	34	0.7 (6.5)		0.81%	-0.12[-0.6,0.35]
Benedetti 1995	13	-2 (1.2)	11	-0.8 (1)		0.35%	-1.07[-1.94,-0.2]
Benedetti 1997	106	0.3 (0.1)	115	0.3 (0.1)		1.33%	-0.17[-0.43,0.1]
Biro 1997	29	3.6 (2.5)	29	3.3 (2.1)		0.74%	0.13[-0.39,0.64]
Blades 2001	40	-16 (6)	40	-16 (6)		0.89%	0[-0.44,0.44]
Blanchard 1990a	13	8.3 (13.6)	11	22.5 (25.1)		0.37%	-0.7[-1.53,0.13]
Blanchard 1990b	18	11.9 (23.9)	24	20.7 (34.8)		0.59%	-0.28[-0.9,0.33]
Block 1980	16	22.4 (6.6)	8	24.7 (9.2)		0.36%	-0.3[-1.15,0.56]
Bosley 1989	13	86 (10)	14	89 (10)		0.43%	-0.29[-1.05,0.47]
Bova 1999	34	3.8 (2.2)	36	4.1 (2.3)		0.82%	-0.14[-0.61,0.33]
Bramston 1985	12	-78 (14.2)	12	-72 (13.8)		0.39%	-0.41[-1.22,0.4]
Brinkhaus 2006	70	-23.6 (31)	74	-6.9 (22)		1.14%	-0.62[-0.96,-0.29]
Cabrini 2006	16	61.7 (24)	16	66.6 (28)		0.49%	-0.18[-0.88,0.51]
Canino 1994	4	99 (2.7)	9	95.6 (7.6)		0.2%	0.48[-0.72,1.67]
Carbajal 1999	25	7.2 (2.8)	25	6.9 (2.6)		0.67%	0.1[-0.45,0.66]
Chenard 1991	12	29 (19)	16	30 (19)		0.44%	-0.05[-0.8,0.7]
Classen 1983	15	11.3 (8.3)	15	14.4 (6.1)		0.46%	-0.41[-1.14,0.31]
Colker 1999	7	82.7 (18)	4	77.7 (10.5)		0.19%	0.29[-0.95,1.53]
Conn 1986	13	28.2 (18.4)	14	44.4 (15.7)		0.4%	-0.92[-1.72,-0.12]
Costello 2006	48	33 (25)	42	31 (25)		0.94%	0.08[-0.33,0.49]
Coyne 1995	21	0.7 (0.7)	21	0.6 (0.7)		0.6%	0.13[-0.47,0.74]
Crosby 1994	26	13.6 (1.3)	33	13.5 (1.3)		0.74%	0.08[-0.44,0.59]
Cupal 2001	10	2.7 (1)	10	2.7 (1.3)		0.34%	0[-0.88,0.88]
Davidson 1980	10	1.8 (0.9)	10	2.9 (1.3)		0.31%	-0.94[-1.88,-0.01]
Defrin 2005	9	7.3 (0.8)	8	7.6 (0.7)		0.29%	-0.39[-1.35,0.58]
Dibble 2007	49	3.1 (2.9)	51	3.5 (3.1)		0.99%	-0.12[-0.51,0.27]
Ditto 2003	200	0.5 (0.4)	189	0.5 (0.4)		1.52%	-0.02[-0.22,0.17]
Ditto 2006	140	0.4 (0.4)	155	0.5 (0.4)		1.44%	-0.06[-0.28,0.17]
Erdogmus 2007	40	-27.4 (19.7)	40	-20.3 (19.7)		0.88%	-0.36[-0.8,0.08]
Espie 1989	14	63.5 (30.6)	13	96.5 (63.5)		0.42%	-0.65[-1.43,0.13]
Etringer 1982	13	-11.4 (4)	12	-10.1 (3.7)		0.41%	-0.33[-1.12,0.46]
Etter 2002	269	20.6 (10)	389	25.4 (12.6)		1.64%	-0.41[-0.57,-0.26]
Fisher 2006	12	3.8 (1.9)	15	4.1 (2.5)		0.43%	-0.13[-0.89,0.63]
Forster 1994	15	3.2 (2.8)	15	4.6 (2.2)		0.46%	-0.54[-1.27,0.19]
Foster 2004	6	-3.6 (0.6)	12	-2.6 (1.1)		0.26%	-0.98[-2.02,0.06]
Foster 2007	112	6.5 (4.8)	105	6.8 (4.5)		1.33%	-0.06[-0.33,0.21]
Frankel 1978	7	93 (5)	8	95 (3)		0.26%	-0.47[-1.5,0.57]
Frega 1994	21	20 (16)	21	23 (16)		0.6%	-0.18[-0.79,0.42]
Fuchs 1977	10	14.3 (7)	10	21.4 (7)		0.31%	-0.97[-1.91,-0.03]
Godfrey 1973	44	34.9 (16.7)	44	46.9 (16.2)		0.9%	-0.72[-1.15,-0.29]
Goodenough 1997	39	1.1 (1.6)	39	1.6 (1.9)		0.87%	-0.28[-0.73,0.16]



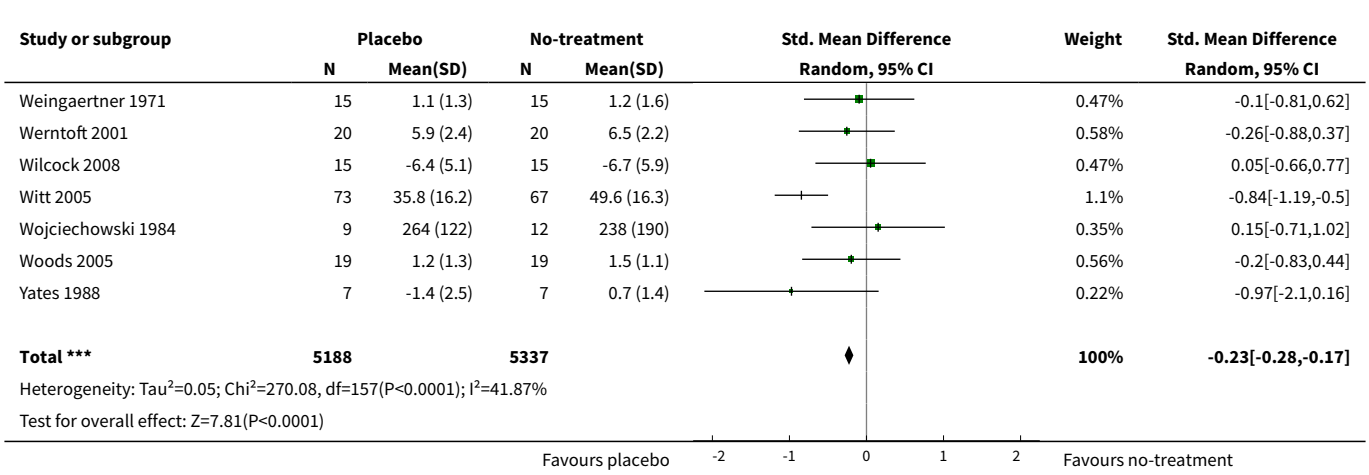
Favours placebo — Favours no-treatment

Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Gracely 1983	17	-2.9 (5.4)	12	0.2 (5.5)		0.44%	-0.54[-1.3,0.21]
GRECHO 1989	150	94.4 (40.7)	150	95.4 (33)		1.44%	-0.03[-0.25,0.2]
Hall 1974	23	-0.5 (7.8)	22	0.9 (7.8)		0.63%	-0.17[-0.76,0.41]
Hanson 1976	11	-0.9 (3.8)	10	-0.3 (2.2)		0.36%	-0.19[-1.05,0.67]
Hargreaves 1989	25	4.5 (2.5)	25	4.9 (2.4)		0.67%	-0.16[-0.72,0.39]
Hashish 1986	25	16 (11.7)	50	30 (18.9)		0.77%	-0.82[-1.32,-0.32]
Hashish 1988	25	42 (25)	25	60 (23)		0.64%	-0.74[-1.31,-0.16]
Hawkins 1995	10	37.4 (8.5)	10	52.1 (9.3)		0.26%	-1.58[-2.61,-0.55]
Helms 1987	11	103 (91)	11	79 (99)		0.37%	0.24[-0.6,1.08]
Hong 1993	16	-1.1 (0.2)	21	-1 (0.1)		0.53%	-0.53[-1.19,0.13]
Hossmann 1981	12	94.2 (4.8)	12	95.1 (4.8)		0.4%	-0.18[-0.98,0.62]
Hovell 2003	98	-155.4 (69.9)	96	-151 (73.8)		1.28%	-0.06[-0.34,0.22]
Hruby 2006	49	1.2 (2.1)	51	0.9 (1.5)		0.99%	0.21[-0.19,0.6]
Hyland 2006	10	6 (0.9)	10	6.2 (0.9)		0.34%	-0.21[-1.09,0.67]
Irvin 1996	11	3.3 (0.7)	11	3.7 (1.4)		0.37%	-0.35[-1.19,0.5]
Jacobson 1978	7	2.5 (0.9)	6	3.5 (0.5)		0.2%	-1.17[-2.39,0.04]
Kaptchuk 2008	88	-4.3 (1.4)	87	-3.8 (1)		1.23%	-0.41[-0.71,-0.11]
Karst 2007	19	45.2 (10.8)	10	56.5 (9.1)		0.38%	-1.07[-1.89,-0.25]
Karunakaran 1997	58	6.2 (1.2)	57	5.9 (0.6)		1.05%	0.31[-0.05,0.68]
Kendall 1979	11	7.5 (2.3)	11	8.2 (3)		0.37%	-0.23[-1.07,0.61]
Killeen 2004	24	1 (2.5)	35	1.9 (3.5)		0.73%	-0.28[-0.81,0.24]
Kilmann 1987	4	-33 (47)	4	-35 (47)		0.15%	0.04[-1.35,1.42]
Kober 2002	20	66.7 (10)	21	64.4 (13.3)		0.59%	0.19[-0.42,0.8]
Kokol 2005	16	9.5 (10.5)	10	7.3 (6.6)		0.4%	0.23[-0.56,1.02]
Kotani 2001	23	15 (4.5)	24	18 (6)		0.63%	-0.55[-1.14,0.03]
Lander 1993	172	28.5 (29.3)	168	32.3 (33.4)		1.48%	-0.12[-0.33,0.09]
Lee 2005	27	-21.4 (25.9)	27	-5.9 (9.2)		0.67%	-0.79[-1.34,-0.23]
Leibing 2002	40	3.2 (1.8)	39	4.3 (1.9)		0.86%	-0.59[-1.04,-0.14]
Levine 1984	12	-0.3 (0.7)	24	0.4 (2.5)		0.49%	-0.31[-1.01,0.38]
Licciardone 2003	19	2.5 (1.7)	15	3.5 (2.7)		0.5%	-0.49[-1.17,0.2]
Lick 1975	9	60.6 (32.7)	9	92.2 (22.1)		0.27%	-1.08[-2.09,-0.07]
Lick 1977	10	66 (25)	10	63 (32)		0.34%	0.1[-0.78,0.98]
Limoges 2004	30	2.3 (1)	30	2.2 (1)		0.75%	0.04[-0.47,0.55]
Lin 2002	25	30.2 (14.4)	25	38.1 (16)		0.66%	-0.51[-1.07,0.05]
Lincoln 2003	42	14.4 (10)	38	16.7 (10)		0.88%	-0.23[-0.67,0.21]
Linde 2005	76	-2.2 (2.7)	76	-0.8 (2.2)		1.16%	-0.57[-0.89,-0.24]
Lindholm 1996	227	6.8 (0.5)	226	6.8 (0.5)		1.56%	0.15[-0.04,0.33]
Liossi 2003	20	4.3 (0.6)	20	4.6 (0.6)		0.57%	-0.49[-1.12,0.14]
Longo 1988	10	3.6 (0.6)	9	3.6 (0.4)		0.33%	0[-0.9,0.9]
Lorr 1961	42	58.3 (9.9)	38	57.5 (9.9)		0.88%	0.08[-0.36,0.52]
Macaluso 1995	30	-3.3 (3.8)	30	-1.8 (3.3)		0.74%	-0.41[-0.93,0.1]
Markland 1993	7	37.3 (11.8)	7	36.9 (11.9)		0.25%	0.03[-1.01,1.08]
Matros 2006	23	76 (36.3)	21	72 (28.3)		0.62%	0.12[-0.47,0.71]
May 1988	24	-1.2 (0.5)	24	-1.2 (0.5)		0.66%	-0.02[-0.59,0.54]
McLachlan 1991	8	6.3 (12.3)	12	5.7 (17.4)		0.33%	0.04[-0.86,0.93]
Medici 2002	23	-0.2 (0.3)	18	-0.1 (0.3)		0.58%	-0.31[-0.93,0.32]
Melchart 2005	57	10.8 (8.3)	63	16.3 (7.4)		1.05%	-0.7[-1.07,-0.33]
Moffet 1996	22	24 (18.6)	27	34.6 (23.2)		0.65%	-0.49[-1.06,0.08]
Moreland 2006	50	-2 (1.3)	99	-2.1 (1.7)		1.12%	0.06[-0.28,0.4]
Morey 2006	38	-16.5 (9.3)	42	-14.7 (9.5)		0.88%	-0.19[-0.63,0.25]
Morton 1993	13	22.1 (16.4)	13	24.5 (16.4)		0.42%	-0.14[-0.91,0.63]

Favours placebo -2 -1 0 1 2 Favours no-treatment

Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Murphy 1982	6	-16.5 (9.3)	11	-0.8 (6.4)		0.19%	-1.99[-3.24,-0.74]
Nandi 1976	10	53.2 (11.2)	8	57.5 (13.8)		0.31%	-0.33[-1.27,0.61]
Nawrocki 1997	40	9.5 (6)	42	17 (4.8)		0.8%	-1.37[-1.85,-0.89]
Nicassio 1974	7	117.3 (133.7)	9	99.3 (35.3)		0.28%	0.19[-0.8,1.18]
Nocella 1982	10	0.8 (0.9)	10	0.8 (0.7)		0.34%	-0.02[-0.9,0.85]
O'Brien 1996	53	6.7 (5.6)	54	7.5 (5.1)		1.02%	-0.15[-0.53,0.23]
Parker 1995	49	4 (1.9)	45	3.8 (2.2)		0.96%	0.1[-0.31,0.5]
Parker 2003	13	16.2 (7.5)	14	14.2 (7.5)		0.43%	0.26[-0.5,1.02]
Pelham 1992	38	-8.7 (1.7)	38	-8.5 (1.6)		0.86%	-0.12[-0.57,0.33]
Quahagen 1995	28	-108.3 (14.8)	25	-104.8 (13.9)		0.69%	-0.24[-0.78,0.3]
Rawling 2001	89	5.3 (4.7)	96	5.6 (4.9)		1.26%	-0.06[-0.35,0.23]
Reading 1982	18	1.6 (1.3)	20	2.3 (2)		0.55%	-0.4[-1.05,0.24]
Ristikankare 1999	61	40.3 (21.5)	61	36 (21.5)		1.08%	0.2[-0.16,0.55]
Robinson 2001	13	3.9 (3.5)	10	4.3 (3.7)		0.38%	-0.11[-0.93,0.72]
Roongpisuthip 1999	18	-3.3 (4.2)	19	-2.9 (3.1)		0.55%	-0.11[-0.75,0.54]
Roscoe 2002	27	5.9 (5.2)	27	6.6 (3.6)		0.71%	-0.15[-0.69,0.38]
Roscoe 2005	31	2.4 (1.3)	33	2.8 (1.3)		0.78%	-0.3[-0.8,0.19]
Rosen 1976	9	6.9 (2)	5	8.3 (1.9)		0.22%	-0.67[-1.8,0.46]
Rossi 1982	6	107 (17)	6	108 (20)		0.22%	-0.05[-1.18,1.08]
Rowbotham 1996	35	-4.4 (8.7)	35	1.9 (8.7)		0.79%	-0.72[-1.2,-0.23]
Rybarczyk 1990	25	7.1 (2.2)	24	7.5 (2.8)		0.66%	-0.16[-0.73,0.4]
Röschke 2000	24	23 (16.2)	24	26 (16)		0.65%	-0.18[-0.75,0.38]
Rösler 2003	13	5.9 (3.4)	14	6 (3)		0.44%	-0.02[-0.78,0.73]
Sanders 1990	6	2 (0.4)	6	2.1 (0.3)		0.22%	-0.13[-1.26,1]
Seer 1980	14	92.5 (9.8)	13	104.5 (11)		0.38%	-1.12[-1.94,-0.3]
Senediak 1985	11	47.5 (8.4)	10	47.9 (7.5)		0.36%	-0.04[-0.9,0.81]
Shen 2000	33	40.7 (12.4)	34	43.7 (11.3)		0.8%	-0.25[-0.73,0.23]
Sinaiko 1991	60	66.5 (9.7)	27	64.1 (13.9)		0.85%	0.21[-0.24,0.67]
Sipich 1974	10	8 (14)	10	32.5 (14)		0.25%	-1.68[-2.73,-0.63]
Spanos 1995	13	21.4 (9.7)	12	19.1 (10.3)		0.41%	0.22[-0.56,1.01]
Sprott 1993	10	7.9 (3)	10	7.4 (3)		0.34%	0.16[-0.72,1.04]
Stabholz 1991	10	1.4 (0.5)	10	1.8 (0.6)		0.32%	-0.69[-1.6,0.22]
Steinsbekk 2004	102	44.5 (58.9)	74	53 (45.2)		1.23%	-0.16[-0.46,0.14]
Stewart 1991	25	-14.3 (5.5)	25	-12.8 (5.2)		0.67%	-0.28[-0.83,0.28]
Straub 2001	5	-5.8 (0.3)	5	-6 (0.7)		0.19%	0.27[-0.98,1.52]
Sumaya 2001	10	15.4 (2.7)	10	14.9 (1.8)		0.34%	0.21[-0.67,1.09]
Tan 1982	12	1.3 (0.6)	12	1.7 (0.8)		0.38%	-0.55[-1.36,0.27]
Tashjian 2006	19	3.4 (2.2)	24	3.3 (1.8)		0.6%	0.05[-0.55,0.65]
Theroux 1993	17	3.2 (0.7)	15	2.9 (0.6)		0.48%	0.48[-0.22,1.19]
Thomas 1999	14	13.4 (10.3)	26	16.5 (9.7)		0.54%	-0.31[-0.96,0.35]
Thomas 2002a	78	-0.9 (3)	78	-0.1 (2.9)		1.19%	-0.27[-0.59,0.04]
Thomas 2002b	114	-1.2 (3.5)	119	-1.6 (3.3)		1.35%	0.12[-0.14,0.37]
Tremeau 1992	39	-0.9 (1.3)	25	-1.1 (1.4)		0.76%	0.14[-0.36,0.65]
Tritrakarn 2000	41	49 (16)	41	61 (17)		0.87%	-0.72[-1.17,-0.27]
Tsay 2003	32	9.2 (4.4)	32	9.6 (4)		0.78%	-0.08[-0.57,0.41]
Tsay 2004	35	4.7 (1.5)	36	5.7 (1.8)		0.81%	-0.6[-1.07,-0.12]
Tuomilehto 1980	11	9 (1.4)	11	8.7 (1.6)		0.37%	0.24[-0.6,1.08]
Turner 1979	10	44.2 (41.3)	10	59.8 (22.9)		0.34%	-0.45[-1.34,0.44]
Vlaeyen 1996	39	0.4 (1.8)	40	0.4 (1.8)		0.88%	0[-0.44,0.44]
Wang 1997	25	10.7 (7.3)	26	13.4 (5.8)		0.67%	-0.4[-0.96,0.15]

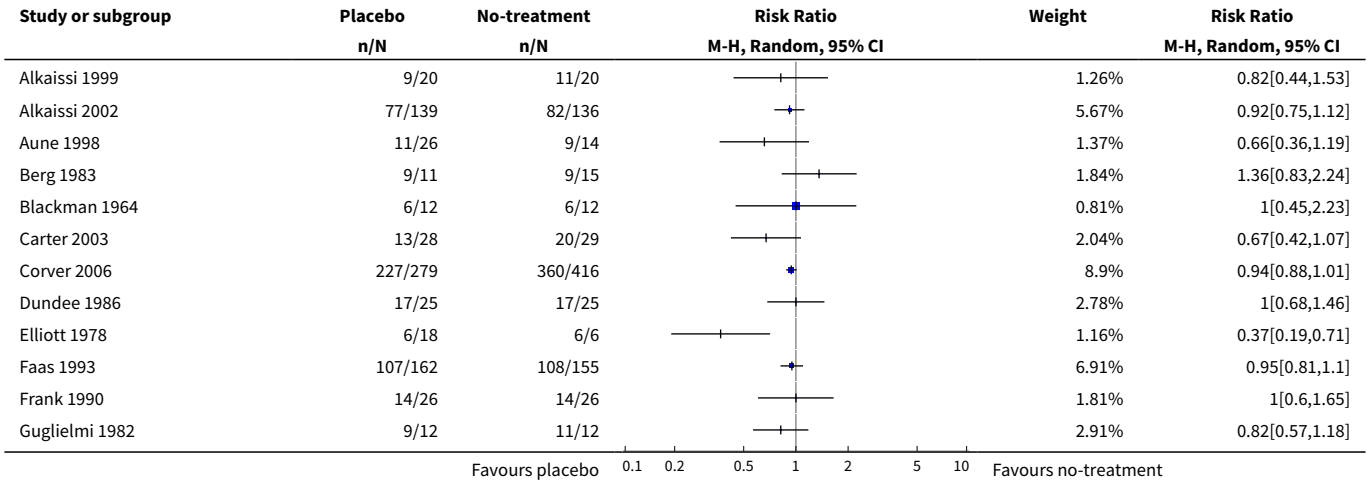
Favours placebo -2 -1 0 1 2 Favours no-treatment



Comparison 2. Main analysis: patient-reported or observer-reported outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Patient-reported binary outcomes	31	4046	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.86, 1.00]
2 Observer-reported binary outcomes	13	1995	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.85, 1.02]
3 Patient-reported continuous outcomes	109	8000	Std. Mean Difference (IV, Random, 95% CI)	-0.26 [-0.32, -0.19]
4 Observer-reported continuous outcomes	49	2513	Std. Mean Difference (IV, Random, 95% CI)	-0.13 [-0.24, -0.02]

Analysis 2.1. Comparison 2 Main analysis: patient-reported or observer-reported outcomes, Outcome 1 Patient-reported binary outcomes.



Study or subgroup	Placebo n/N	No-treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Hutton 1991	5/24	16/30		0.73%	0.39[0.17,0.91]
Jacobs 1971	9/15	12/39		1.25%	1.95[1.04,3.65]
Klerman 1974	17/25	16/25		2.6%	1.06[0.71,1.58]
McMillan 1994	14/26	24/46		2.16%	1.03[0.66,1.62]
Molsberger 2002	38/58	30/53		3.79%	1.16[0.86,1.56]
Najnigier 1997	21/30	24/30		3.88%	0.88[0.65,1.17]
Rabkin 1990	14/27	12/23		1.64%	0.99[0.58,1.7]
Roughan 1981	9/12	9/14		1.78%	1.17[0.7,1.94]
Scharf 2006	179/365	224/316		7.56%	0.69[0.61,0.78]
Scharff 2002	11/12	12/12		5.18%	0.92[0.74,1.15]
Stransky 1989	1/5	1/4		0.09%	0.8[0.07,9.18]
Tan 1986	8/10	8/9		2.72%	0.9[0.61,1.32]
Tarcin 2004	58/158	27/77		2.93%	1.05[0.73,1.51]
Thomas 1987	47/100	50/100		4.02%	0.94[0.71,1.25]
Tyler 1946	89/260	106/303		5.1%	0.98[0.78,1.23]
Walton 1993	19/24	21/30		3.63%	1.13[0.83,1.54]
Watzl 1986	15/34	7/36		0.88%	2.27[1.06,4.88]
Williams 1988	19/20	19/20		7.15%	1[0.87,1.15]
Wilson 1980	31/40	10/10		5.45%	0.8[0.65,0.99]
Total (95% CI)	**2003**	**2043**		**100%**	**0.93[0.86,1]**
Total events: 1109 (Placebo), 1281 (No-treatment)					
Heterogeneity: Tau²=0.02; Chi²=58.22, df=30(P=0); I²=48.47%					
Test for overall effect: Z=1.9(P=0.06)					

Favours placebo — Favours no-treatment

Analysis 2.2. Comparison 2 Main analysis: patient-reported or observer-reported outcomes, Outcome 2 Observer-reported binary outcomes.

Study or subgroup	Placebo n/N	No-treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Adriaanse 1995	50/328	38/326		4.51%	1.31[0.88,1.94]
De Sanctis 2001	9/10	8/9		6.61%	1.01[0.74,1.38]
Double 1993	3/22	3/22		0.37%	1[0.23,4.42]
Fanti 2003	8/10	9/10		4.93%	0.89[0.61,1.29]
Harrison 1975	24/28	25/30		10.64%	1.03[0.83,1.28]
Heinzl 1981	70/130	92/132		12.3%	0.77[0.64,0.94]
Hyman 1986	9/15	15/15		4.12%	0.61[0.4,0.93]
Kerr 2003	28/33	32/36		13.04%	0.95[0.79,1.15]
Killen 1990	226/309	219/309		21.18%	1.03[0.94,1.14]
Malcolm 1980	40/63	44/58		9.69%	0.84[0.66,1.06]
Schallreuter 2002	3/10	4/10		0.55%	0.75[0.22,2.52]
Tarrier 1998	22/26	25/28		11.39%	0.95[0.77,1.17]
Whittaker 1963	3/13	7/13		0.65%	0.43[0.14,1.3]
Total (95% CI)	**997**	**998**		**100%**	**0.93[0.85,1.02]**
Total events: 495 (Placebo), 521 (No-treatment)					
Heterogeneity: Tau²=0.01; Chi²=17.84, df=12(P=0.12); I²=32.74%					
Test for overall effect: Z=1.54(P=0.12)					

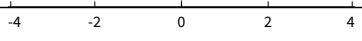
Favours placebo — Favours no-treatment

Analysis 2.3. Comparison 2 Main analysis: patient-reported or observer-reported outcomes, Outcome 3 Patient-reported continuous outcomes.

Study or subgroup	Placebo		No-treatment		Std. Mean Difference	Weight	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
Abikoff 2004	35	-91.4 (18.9)	34	-89.5 (22.8)		1.11%	-0.09[-0.56,0.38]
Alfano 2001	24	6.2 (2.8)	14	6.6 (2.7)		0.71%	-0.14[-0.8,0.52]
Andersen 1990	18	35 (27.2)	16	25 (23.6)		0.68%	0.38[-0.3,1.06]
Anderson 1999	30	-2.7 (0.8)	27	-2.7 (0.8)		0.99%	0.08[-0.44,0.6]
Ascher 1979	8	50.6 (44.1)	9	62.4 (25.3)		0.39%	-0.32[-1.28,0.64]
Benedetti 1995	13	-2 (1.2)	11	-0.8 (1)		0.46%	-1.07[-1.94,-0.2]
Benedetti 1997	106	0.3 (0.1)	115	0.3 (0.1)		1.85%	-0.17[-0.43,0.1]
Biro 1997	29	3.6 (2.5)	29	3.3 (2.1)		1%	0.13[-0.39,0.64]
Blanchard 1990a	13	8.3 (13.6)	11	22.5 (25.1)		0.5%	-0.7[-1.53,0.13]
Blanchard 1990b	18	11.9 (23.9)	24	20.7 (34.8)		0.79%	-0.28[-0.9,0.33]
Bova 1999	34	3.8 (2.2)	36	4.1 (2.3)		1.12%	-0.14[-0.61,0.33]
Brinkhaus 2006	70	-23.6 (31)	74	-6.9 (22)		1.56%	-0.62[-0.96,-0.29]
Cabrini 2006	16	61.7 (24)	16	66.6 (28)		0.66%	-0.18[-0.88,0.51]
Chenard 1991	12	29 (19)	16	30 (19)		0.59%	-0.05[-0.8,0.7]
Classen 1983	15	11.3 (8.3)	15	14.4 (6.1)		0.62%	-0.41[-1.14,0.31]
Conn 1986	13	28.2 (18.4)	14	44.4 (15.7)		0.53%	-0.92[-1.72,-0.12]
Costello 2006	48	33 (25)	42	31 (25)		1.28%	0.08[-0.33,0.49]
Coyne 1995	21	0.7 (0.7)	21	0.6 (0.7)		0.81%	0.13[-0.47,0.74]
Cupal 2001	10	2.7 (1)	10	2.7 (1.3)		0.46%	0[-0.88,0.88]
Davidson 1980	10	1.8 (0.9)	10	2.9 (1.3)		0.41%	-0.94[-1.88,-0.01]
Defrin 2005	9	7.3 (0.8)	8	7.6 (0.7)		0.39%	-0.39[-1.35,0.58]
Dibble 2007	49	3.1 (2.9)	51	3.5 (3.1)		1.35%	-0.12[-0.51,0.27]
Ditto 2003	200	0.5 (0.4)	189	0.5 (0.4)		2.13%	-0.02[-0.22,0.17]
Ditto 2006	140	0.4 (0.4)	155	0.5 (0.4)		2%	-0.06[-0.28,0.17]
Erdogmus 2007	40	-27.4 (19.7)	40	-20.3 (19.7)		1.2%	-0.36[-0.8,0.08]
Espie 1989	14	63.5 (30.6)	13	96.5 (63.5)		0.56%	-0.65[-1.43,0.13]
Etter 2002	269	20.6 (10)	389	25.4 (12.6)		2.3%	-0.41[-0.57,-0.26]
Fisher 2006	12	3.8 (1.9)	15	4.1 (2.5)		0.58%	-0.13[-0.89,0.63]
Forster 1994	15	3.2 (2.8)	15	4.6 (2.2)		0.61%	-0.54[-1.27,0.19]
Foster 2004	6	-3.6 (0.6)	12	-2.6 (1.1)		0.34%	-0.98[-2.02,0.06]
Foster 2007	112	6.5 (4.8)	105	6.8 (4.5)		1.84%	-0.06[-0.33,0.21]
Frega 1994	21	20 (16)	21	23 (16)		0.81%	-0.18[-0.79,0.42]
Fuchs 1977	10	14.3 (7)	10	21.4 (7)		0.41%	-0.97[-1.91,-0.03]
Goodenough 1997	39	1.1 (1.6)	39	1.6 (1.9)		1.18%	-0.28[-0.73,0.16]
Gracely 1983	17	-2.9 (5.4)	12	0.2 (5.5)		0.58%	-0.54[-1.3,0.21]
Hargreaves 1989	25	4.5 (2.5)	25	4.9 (2.4)		0.91%	-0.16[-0.72,0.39]
Hashish 1986	25	16 (11.7)	50	30 (18.9)		1.04%	-0.82[-1.32,-0.32]
Hashish 1988	25	42 (25)	25	60 (23)		0.87%	-0.74[-1.31,-0.16]
Hawkins 1995	10	37.4 (8.5)	10	52.1 (9.3)		0.35%	-1.58[-2.61,-0.55]
Helms 1987	11	103 (91)	11	79 (99)		0.49%	0.24[-0.6,1.08]
Hong 1993	16	-1.1 (0.2)	21	-1 (0.1)		0.71%	-0.53[-1.19,0.13]
Hovell 2003	98	-155.4 (69.9)	96	-151 (73.8)		1.78%	-0.06[-0.34,0.22]
Hruby 2006	49	1.2 (2.1)	51	0.9 (1.5)		1.35%	0.21[-0.19,0.6]
Hyland 2006	10	6 (0.9)	10	6.2 (0.9)		0.46%	-0.21[-1.09,0.67]
Irvin 1996	11	3.3 (0.7)	11	3.7 (1.4)		0.49%	-0.35[-1.19,0.5]
Jacobson 1978	7	2.5 (0.9)	6	3.5 (0.5)		0.26%	-1.17[-2.39,0.04]
Kaptchuk 2008	88	-4.3 (1.4)	87	-3.8 (1)		1.7%	-0.41[-0.71,-0.11]

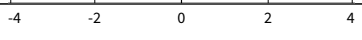
Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Karst 2007	19	45.2 (10.8)	10	56.5 (9.1)		0.51%	-1.07[-1.89,-0.25]
Kendall 1979	11	7.5 (2.3)	11	8.2 (3)		0.49%	-0.23[-1.07,0.61]
Killeen 2004	24	1 (2.5)	35	1.9 (3.5)		0.98%	-0.28[-0.81,0.24]
Kilmann 1987	4	-33 (47)	4	-35 (47)		0.2%	0.04[-1.35,1.42]
Kober 2002	20	66.7 (10)	21	64.4 (13.3)		0.79%	0.19[-0.42,0.8]
Kotani 2001	23	15 (4.5)	24	18 (6)		0.85%	-0.55[-1.14,0.03]
Lander 1993	172	28.5 (29.3)	168	32.3 (33.4)		2.07%	-0.12[-0.33,0.09]
Leibing 2002	40	3.2 (1.8)	39	4.3 (1.9)		1.17%	-0.59[-1.04,-0.14]
Levine 1984	12	-0.3 (0.7)	24	0.4 (2.5)		0.66%	-0.31[-1.01,0.38]
Licciardone 2003	19	2.5 (1.7)	15	3.5 (2.7)		0.67%	-0.49[-1.17,0.2]
Lick 1975	9	60.6 (32.7)	9	92.2 (22.1)		0.36%	-1.08[-2.09,-0.07]
Lick 1977	10	66 (25)	10	63 (32)		0.46%	0.1[-0.78,0.98]
Limoges 2004	30	2.3 (1)	30	2.2 (1)		1.02%	0.04[-0.47,0.55]
Lincoln 2003	42	14.4 (10)	38	16.7 (10)		1.2%	-0.23[-0.67,0.21]
Linde 2005	76	-2.2 (2.7)	64	-0.8 (2.2)		1.55%	-0.56[-0.9,-0.22]
Liossi 2003	20	4.3 (0.6)	20	4.6 (0.6)		0.76%	-0.49[-1.12,0.14]
Longo 1988	10	3.6 (0.6)	9	3.6 (0.4)		0.44%	0[-0.9,0.9]
Lorr 1961	42	58.3 (9.9)	38	57.5 (9.9)		1.2%	0.08[-0.36,0.52]
Macaluso 1995	30	-3.3 (3.8)	30	-1.8 (3.3)		1.01%	-0.41[-0.93,0.1]
Markland 1993	7	37.3 (11.8)	7	36.9 (11.9)		0.34%	0.03[-1.01,1.08]
Matros 2006	23	76 (36.3)	21	72 (28.3)		0.83%	0.12[-0.47,0.71]
Medici 2002	23	-0.2 (0.3)	18	-0.1 (0.3)		0.78%	-0.31[-0.93,0.32]
Melchart 2005	57	10.8 (8.3)	63	16.3 (7.4)		1.43%	-0.7[-1.07,-0.33]
Moffet 1996	22	24 (18.6)	27	34.6 (23.2)		0.87%	-0.49[-1.06,0.08]
Moreland 2006	50	-2 (1.3)	99	-2.1 (1.7)		1.54%	0.06[-0.28,0.4]
Morey 2006	38	-16.5 (9.3)	42	-14.7 (9.5)		1.2%	-0.19[-0.63,0.25]
Nawrocki 1997	40	9.5 (6)	42	17 (4.8)		1.08%	-1.37[-1.85,-0.89]
Nicassio 1974	7	117.3 (133.7)	9	99.3 (35.3)		0.37%	0.19[-0.8,1.18]
O'Brien 1996	53	6.7 (5.6)	54	7.5 (5.1)		1.4%	-0.15[-0.53,0.23]
Parker 1995	49	4 (1.9)	45	3.8 (2.2)		1.31%	0.1[-0.31,0.5]
Parker 2003	13	16.2 (7.5)	14	14.2 (7.5)		0.58%	0.26[-0.5,1.02]
Pelham 1992	38	-8.7 (1.7)	38	-8.5 (1.6)		1.17%	-0.12[-0.57,0.33]
Rawling 2001	89	5.3 (4.7)	96	5.6 (4.9)		1.75%	-0.06[-0.35,0.23]
Reading 1982	18	1.6 (1.3)	20	2.3 (2)		0.74%	-0.4[-1.05,0.24]
Ristikankare 1999	61	40.3 (21.5)	61	36 (21.5)		1.48%	0.2[-0.16,0.55]
Roscoe 2002	27	5.9 (5.2)	27	6.6 (3.6)		0.95%	-0.15[-0.69,0.38]
Roscoe 2005	31	2.4 (1.3)	33	2.8 (1.3)		1.05%	-0.3[-0.8,0.19]
Rosen 1976	9	6.9 (2)	5	8.3 (1.9)		0.29%	-0.67[-1.8,0.46]
Rowbotham 1996	35	-4.4 (8.7)	35	1.9 (8.7)		1.08%	-0.72[-1.2,-0.23]
Rybarczyk 1990	25	7.1 (2.2)	24	7.5 (2.8)		0.89%	-0.16[-0.73,0.4]
Röschke 2000	24	23 (16.2)	24	26 (16)		0.88%	-0.18[-0.75,0.38]
Rösler 2003	13	5.9 (3.4)	14	6 (3)		0.58%	-0.02[-0.78,0.73]
Sanders 1990	6	2 (0.4)	6	2.1 (0.3)		0.29%	-0.13[-1.26,1]
Sipich 1974	10	8 (14)	10	32.5 (14)		0.34%	-1.68[-2.73,-0.63]
Spanos 1995	13	21.4 (9.7)	12	19.1 (10.3)		0.54%	0.22[-0.56,1.01]
Sprott 1993	10	7.9 (3)	10	7.4 (3)		0.46%	0.16[-0.72,1.04]
Steinsbekk 2004	102	44.5 (58.9)	74	53 (45.2)		1.7%	-0.16[-0.46,0.14]
Stewart 1991	25	-14.3 (5.5)	25	-12.8 (5.2)		0.9%	-0.28[-0.83,0.28]
Straub 2001	5	-5.8 (0.3)	5	-6 (0.7)		0.25%	0.27[-0.98,1.52]
Tan 1982	12	1.3 (0.6)	12	1.7 (0.8)		0.51%	-0.55[-1.36,0.27]
Tashjian 2006	19	3.4 (2.2)	24	3.3 (1.8)		0.81%	0.05[-0.55,0.65]

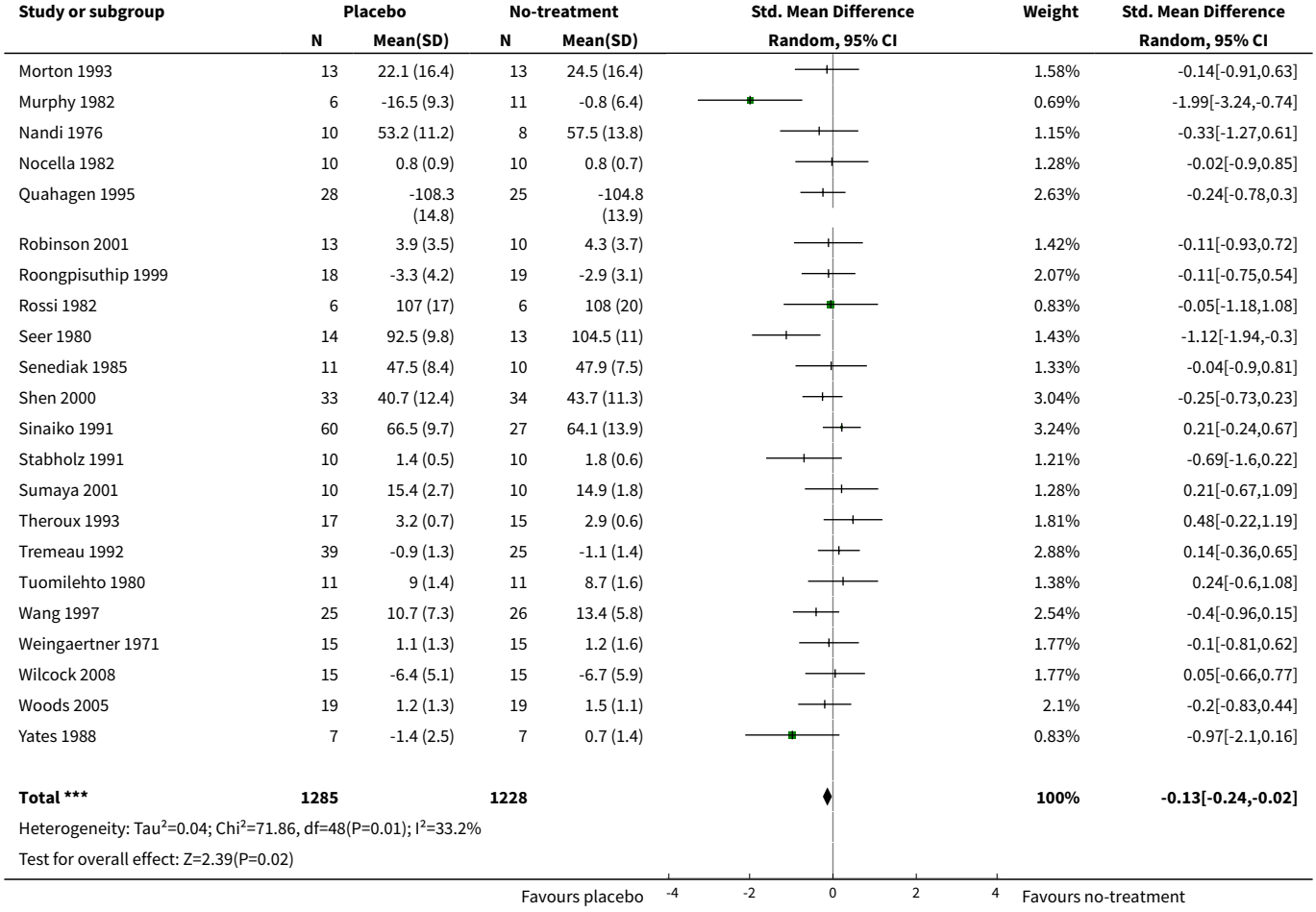
Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Thomas 1999	14	13.4 (10.3)	26	16.5 (9.7)		0.72%	-0.31[-0.96,0.35]
Thomas 2002a	78	-0.9 (3)	78	-0.1 (2.9)		1.64%	-0.27[-0.59,0.04]
Thomas 2002b	114	-1.2 (3.5)	119	-1.6 (3.3)		1.88%	0.12[-0.14,0.37]
Tritrakarn 2000	41	49 (16)	41	61 (17)		1.18%	-0.72[-1.17,-0.27]
Tsay 2003	32	9.2 (4.4)	32	9.6 (4)		1.06%	-0.08[-0.57,0.41]
Tsay 2004	35	4.7 (1.5)	36	5.7 (1.8)		1.1%	-0.6[-1.07,-0.12]
Turner 1979	10	44.2 (41.3)	10	59.8 (22.9)		0.45%	-0.45[-1.34,0.44]
Vlaeyen 1996	39	0.4 (1.8)	40	0.4 (1.8)		1.2%	0[-0.44,0.44]
Werntoft 2001	20	5.9 (2.4)	20	6.5 (2.2)		0.78%	-0.26[-0.88,0.37]
Witt 2005	73	35.8 (16.2)	67	49.6 (16.3)		1.52%	-0.84[-1.19,-0.5]
Wojciechowski 1984	9	264 (122)	12	238 (190)		0.47%	0.15[-0.71,1.02]
Total * **	**3903**		**4097**			**100%**	**-0.26[-0.32,-0.19]**
Heterogeneity: Tau^2=0.04; Chi^2=186.96, df=108(P<0.0001); I^2=42.24%							
Test for overall effect: Z=7.78(P<0.0001)							



Analysis 2.4. Comparison 2 Main analysis: patient-reported or observer-reported outcomes, Outcome 4 Observer-reported continuous outcomes.

Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Allen 1998	11	-2.9 (7.9)	11	-6.1 (10.9)		1.37%	0.32[-0.52,1.17]
Allen 2006	45	12 (9.6)	44	19 (9.6)		3.46%	-0.72[-1.15,-0.29]
Antivalle 1990	11	-1.6 (5.6)	10	-3.9 (7.3)		1.31%	0.34[-0.52,1.21]
Antonio 1999	6	79.7 (12.2)	6	72.6 (11.2)		0.79%	0.56[-0.6,1.72]
Asmar 1996	34	-0.2 (7.7)	34	0.7 (6.5)		3.08%	-0.12[-0.6,0.35]
Blades 2001	40	-16 (6)	40	-16 (6)		3.38%	0[-0.44,0.44]
Block 1980	16	22.4 (6.6)	8	24.7 (9.2)		1.34%	-0.3[-1.15,0.56]
Bosley 1989	13	86 (10)	14	89 (10)		1.62%	-0.29[-1.05,0.47]
Bramston 1985	12	-78 (14.2)	12	-72 (13.8)		1.46%	-0.41[-1.22,0.4]
Canino 1994	4	99 (2.7)	9	95.6 (7.6)		0.75%	0.48[-0.72,1.67]
Carbajal 1999	25	7.2 (2.8)	25	6.9 (2.6)		2.55%	0.1[-0.45,0.66]
Colker 1999	7	82.7 (18)	4	77.7 (10.5)		0.7%	0.29[-0.95,1.53]
Crosby 1994	26	13.6 (1.3)	33	13.5 (1.3)		2.81%	0.08[-0.44,0.59]
Etringer 1982	13	-11.4 (4)	12	-10.1 (3.7)		1.52%	-0.33[-1.12,0.46]
Frankel 1978	7	93 (5)	8	95 (3)		0.97%	-0.47[-1.5,0.57]
Godfrey 1973	44	34.9 (16.7)	44	46.9 (16.2)		3.44%	-0.72[-1.15,-0.29]
GRECHO 1989	150	94.4 (40.7)	150	95.4 (33)		5.63%	-0.03[-0.25,0.2]
Hall 1974	23	-0.5 (7.8)	22	0.9 (7.8)		2.37%	-0.17[-0.76,0.41]
Hanson 1976	11	-0.9 (3.8)	10	-0.3 (2.2)		1.33%	-0.19[-1.05,0.67]
Hossmann 1981	12	94.2 (4.8)	12	95.1 (4.8)		1.48%	-0.18[-0.98,0.62]
Karunakaran 1997	58	6.2 (1.2)	57	5.9 (0.6)		4.03%	0.31[-0.05,0.68]
Kokol 2005	16	9.5 (10.5)	10	7.3 (6.6)		1.51%	0.23[-0.56,1.02]
Lee 2005	27	-21.4 (25.9)	27	-5.9 (9.2)		2.54%	-0.79[-1.34,-0.23]
Lin 2002	25	30.2 (14.4)	25	38.1 (16)		2.49%	-0.51[-1.07,0.05]
Lindholm 1996	227	6.8 (0.5)	226	6.8 (0.5)		6.13%	0.15[-0.04,0.33]
May 1988	24	-1.2 (0.5)	24	-1.2 (0.5)		2.48%	-0.02[-0.59,0.54]
McLachlan 1991	8	6.3 (12.3)	12	5.7 (17.4)		1.24%	0.04[-0.86,0.93]





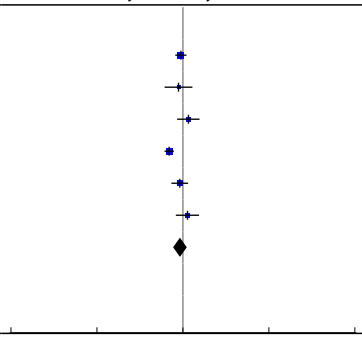
Comparison 3. Main analysis: clinical conditions investigated in three trials or more

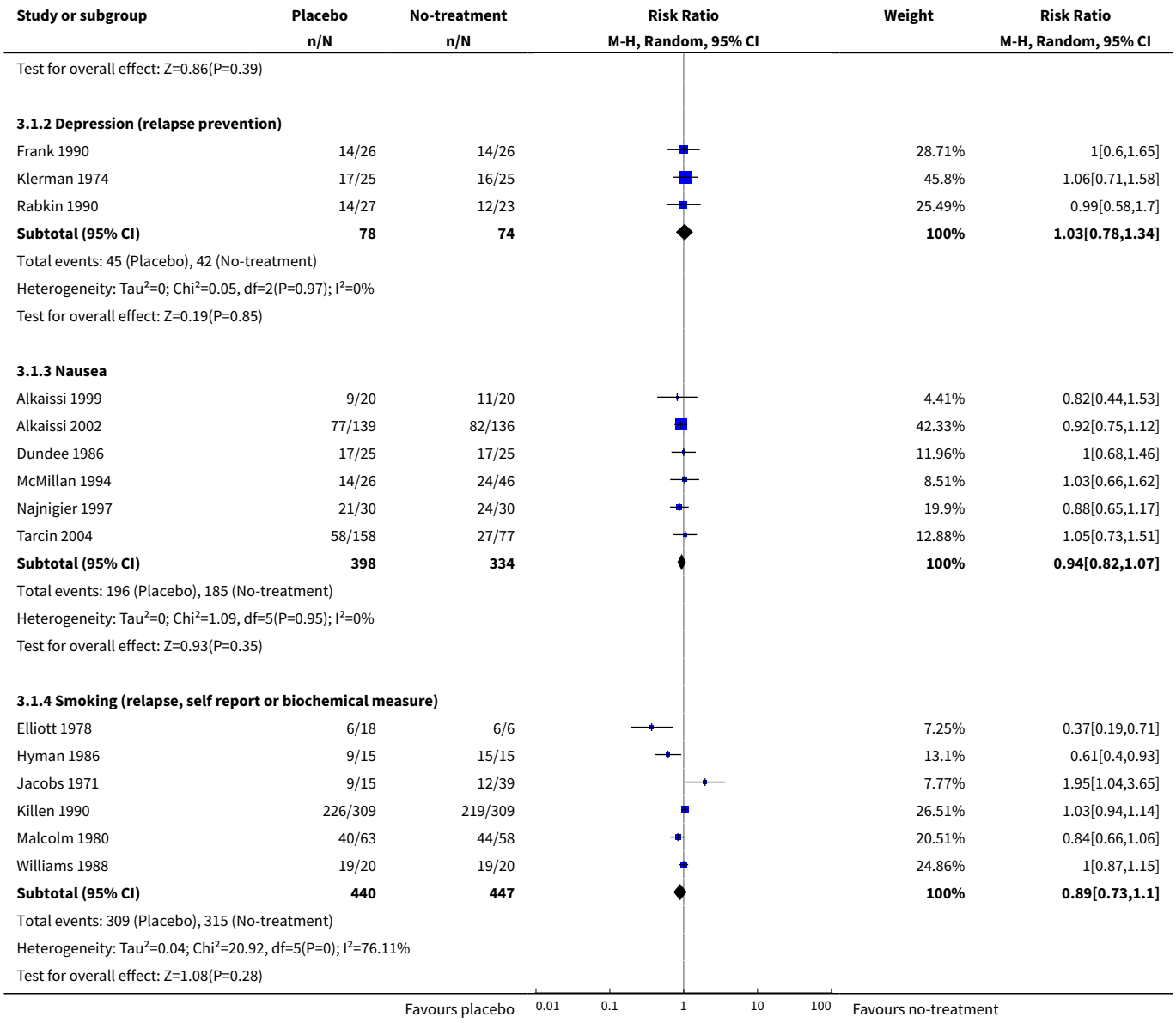
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Binary outcomes	21		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Pain (incidence)	6	1207	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.77, 1.11]
1.2 Depression (relapse prevention)	3	152	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.78, 1.34]
1.3 Nausea	6	732	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.82, 1.07]
1.4 Smoking (relapse, self report or biochemical measure)	6	887	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.73, 1.10]
2 Continuous outcomes	119		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Pain (VAS, ordinal scales, McGill score, escape medication, WOMAC index; absolute or improvement)	60	4154	Std. Mean Difference (IV, Random, 95% CI)	-0.28 [-0.36, -0.19]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.2 Insomnia (sleep onset latency in min, Pittsburgh sleep quality index change)	6	164	Std. Mean Difference (IV, Random, 95% CI)	-0.19 [-0.50, 0.12]
2.3 Hypertension (diastolic, mm Hg; absolute or improvement)	10	308	Std. Mean Difference (IV, Random, 95% CI)	-0.17 [-0.46, 0.12]
2.4 Nausea (VAS, Rhodes Inventory of Nausea and Vomiting, escape medication)	7	452	Std. Mean Difference (IV, Random, 95% CI)	-0.25 [-0.46, -0.04]
2.5 Smoking (cigarettes per day, self report)	3	703	Std. Mean Difference (IV, Random, 95% CI)	-0.53 [-1.29, 0.23]
2.6 Phobia (fear of snakes and spiders: snake slides test, behavioral avoidance test; absolute or improvement)	3	57	Std. Mean Difference (IV, Random, 95% CI)	-0.63 [-1.17, -0.08]
2.7 Asthma (bronchoconstriction: FEV1 or PEF; absolute or improvement)	4	203	Std. Mean Difference (IV, Random, 95% CI)	-0.35 [-0.70, -0.01]
2.8 Obesity (kg, pounds,%; absolute or improvement)	8	188	Std. Mean Difference (IV, Random, 95% CI)	-0.20 [-0.57, 0.17]
2.9 Depression (Hamilton's score, Beck Depression Inventory, Geriatric Depression Scale, Bf-S scale)	8	324	Std. Mean Difference (IV, Random, 95% CI)	-0.25 [-0.55, 0.05]
2.10 Anxiety (modified versions of Spielberger's anxiety inventory, situational anxiety scale, cry score)	7	286	Std. Mean Difference (IV, Random, 95% CI)	-0.16 [-0.48, 0.16]
2.11 Dementia (various scales)	3	111	Std. Mean Difference (IV, Random, 95% CI)	-0.18 [-0.55, 0.20]

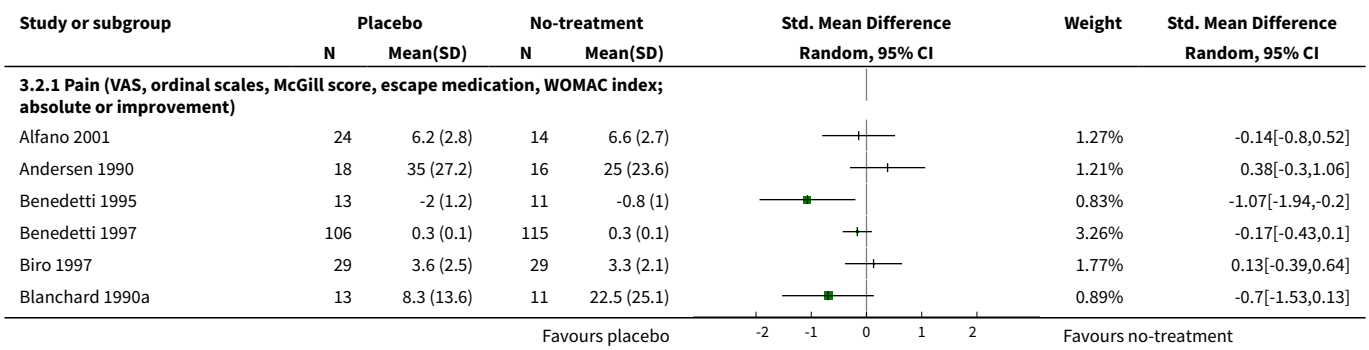
Analysis 3.1. Comparison 3 Main analysis: clinical conditions investigated in three trials or more, Outcome 1 Binary outcomes.

Study or subgroup	Placebo n/N	No-treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 Pain (incidence)					
Faas 1993	107/162	108/155		20.51%	0.95[0.81,1.1]
Fanti 2003	8/10	9/10		11.95%	0.89[0.61,1.29]
Molsberger 2002	38/58	30/53		14.47%	1.16[0.86,1.56]
Scharf 2006	179/365	224/316		21.45%	0.69[0.61,0.78]
Scharff 2002	11/12	12/12		17.54%	0.92[0.74,1.15]
Walton 1993	19/24	21/30		14.07%	1.13[0.83,1.54]
Subtotal (95% CI)	**631**	**576**		**100%**	**0.92[0.77,1.11]**
Total events: 362 (Placebo), 404 (No-treatment)					
Heterogeneity: Tau^2=0.04; Chi^2=20.63, df=5(P=0); I^2=75.76%					

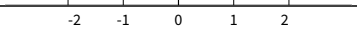




Analysis 3.2. Comparison 3 Main analysis: clinical conditions investigated in three trials or more, Outcome 2 Continuous outcomes.



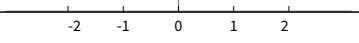
Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Blanchard 1990b	18	11.9 (23.9)	24	20.7 (34.8)		1.41%	-0.28[-0.9,0.33]
Bova 1999	34	3.8 (2.2)	36	4.1 (2.3)		1.98%	-0.14[-0.61,0.33]
Brinkhaus 2006	70	-23.6 (31)	74	-6.9 (22)		2.76%	-0.62[-0.96,-0.29]
Carbajal 1999	25	7.2 (2.8)	25	6.9 (2.6)		1.61%	0.1[-0.45,0.66]
Chenard 1991	12	29 (19)	16	30 (19)		1.05%	-0.05[-0.8,0.7]
Classen 1983	15	11.3 (8.3)	15	14.4 (6.1)		1.11%	-0.41[-1.14,0.31]
Conn 1986	13	28.2 (18.4)	14	44.4 (15.7)		0.95%	-0.92[-1.72,-0.12]
Costello 2006	48	33 (25)	42	31 (25)		2.27%	0.08[-0.33,0.49]
Coyne 1995	21	0.7 (0.7)	21	0.6 (0.7)		1.44%	0.13[-0.47,0.74]
Cupal 2001	10	2.7 (1)	10	2.7 (1.3)		0.82%	0[-0.88,0.88]
Defrin 2005	9	7.3 (0.8)	8	7.6 (0.7)		0.7%	-0.39[-1.35,0.58]
Erdogmus 2007	40	-27.4 (19.7)	40	-20.3 (19.7)		2.12%	-0.36[-0.8,0.08]
Forster 1994	15	3.2 (2.8)	15	4.6 (2.2)		1.09%	-0.54[-1.27,0.19]
Foster 2004	6	-3.6 (0.6)	12	-2.6 (1.1)		0.61%	-0.98[-2.02,0.06]
Foster 2007	112	6.5 (4.8)	105	6.8 (4.5)		3.25%	-0.06[-0.33,0.21]
Frega 1994	21	20 (16)	21	23 (16)		1.43%	-0.18[-0.79,0.42]
Goodenough 1997	39	1.1 (1.6)	39	1.6 (1.9)		2.1%	-0.28[-0.73,0.16]
Gracely 1983	17	-2.9 (5.4)	12	0.2 (5.5)		1.04%	-0.54[-1.3,0.21]
Hargreaves 1989	25	4.5 (2.5)	25	4.9 (2.4)		1.61%	-0.16[-0.72,0.39]
Hashish 1986	25	16 (11.7)	50	30 (18.9)		1.85%	-0.82[-1.32,-0.32]
Hashish 1988	25	42 (25)	25	60 (23)		1.54%	-0.74[-1.31,-0.16]
Helms 1987	11	103 (91)	11	79 (99)		0.88%	0.24[-0.6,1.08]
Hong 1993	16	-1.1 (0.2)	21	-1 (0.1)		1.26%	-0.53[-1.19,0.13]
Hruby 2006	49	1.2 (2.1)	51	0.9 (1.5)		2.39%	0.21[-0.19,0.6]
Hyland 2006	10	6 (0.9)	10	6.2 (0.9)		0.81%	-0.21[-1.09,0.67]
Kober 2002	20	66.7 (10)	21	64.4 (13.3)		1.41%	0.19[-0.42,0.8]
Kotani 2001	23	15 (4.5)	24	18 (6)		1.51%	-0.55[-1.14,0.03]
Lander 1993	172	28.5 (29.3)	168	32.3 (33.4)		3.65%	-0.12[-0.33,0.09]
Leibing 2002	40	3.2 (1.8)	39	4.3 (1.9)		2.07%	-0.59[-1.04,-0.14]
Levine 1984	12	-0.3 (0.7)	24	0.4 (2.5)		1.17%	-0.31[-1.01,0.38]
Licciardone 2003	19	2.5 (1.7)	15	3.5 (2.7)		1.19%	-0.49[-1.17,0.2]
Limoges 2004	30	2.3 (1)	30	2.2 (1)		1.81%	0.04[-0.47,0.55]
Lin 2002	25	30.2 (14.4)	25	38.1 (16)		1.58%	-0.51[-1.07,0.05]
Linde 2005	76	-2.2 (2.7)	64	-0.8 (2.2)		2.73%	-0.56[-0.9,-0.22]
Liossi 2003	20	4.3 (0.6)	20	4.6 (0.6)		1.36%	-0.49[-1.12,0.14]
Melchart 2005	57	10.8 (8.3)	63	16.3 (7.4)		2.54%	-0.7[-1.07,-0.33]
Moffet 1996	22	24 (18.6)	27	34.6 (23.2)		1.55%	-0.49[-1.06,0.08]
Parker 1995	49	4 (1.9)	45	3.8 (2.2)		2.33%	0.1[-0.31,0.5]
Rawling 2001	89	5.3 (4.7)	96	5.6 (4.9)		3.09%	-0.06[-0.35,0.23]
Reading 1982	18	1.6 (1.3)	20	2.3 (2)		1.32%	-0.4[-1.05,0.24]
Robinson 2001	13	3.9 (3.5)	10	4.3 (3.7)		0.9%	-0.11[-0.93,0.72]
Rowbotham 1996	35	-4.4 (8.7)	35	1.9 (8.7)		1.91%	-0.72[-1.2,-0.23]
Sanders 1990	6	2 (0.4)	6	2.1 (0.3)		0.53%	-0.13[-1.26,1]
Sprott 1993	10	7.9 (3)	10	7.4 (3)		0.81%	0.16[-0.72,1.04]
Tan 1982	12	1.3 (0.6)	12	1.7 (0.8)		0.91%	-0.55[-1.36,0.27]
Tashjian 2006	19	3.4 (2.2)	24	3.3 (1.8)		1.45%	0.05[-0.55,0.65]
Thomas 1999	14	13.4 (10.3)	26	16.5 (9.7)		1.29%	-0.31[-0.96,0.35]
Thomas 2002a	78	-0.9 (3)	78	-0.1 (2.9)		2.9%	-0.27[-0.59,0.04]
Thomas 2002b	114	-1.2 (3.5)	119	-1.6 (3.3)		3.32%	0.12[-0.14,0.37]
Tritrakarn 2000	41	49 (16)	41	61 (17)		2.09%	-0.72[-1.17,-0.27]
Vlaeyen 1996	39	0.4 (1.8)	40	0.4 (1.8)		2.13%	0[-0.44,0.44]
Wang 1997	25	10.7 (7.3)	26	13.4 (5.8)		1.61%	-0.4[-0.96,0.15]



Favours placebo

Favours no-treatment

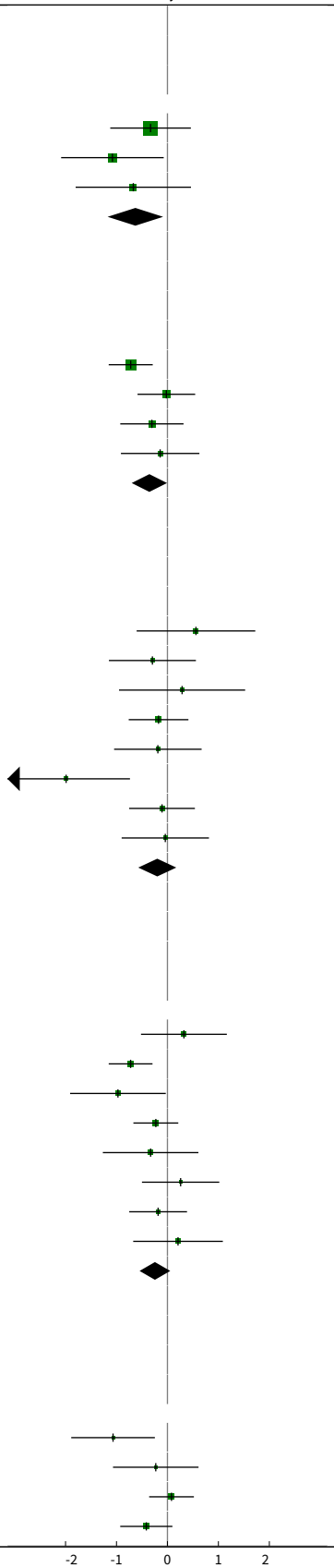
Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Witt 2005	73	35.8 (16.2)	67	49.6 (16.3)		2.69%	-0.84[-1.19,-0.5]
Wojciechowski 1984	9	264 (122)	12	238 (190)		0.83%	0.15[-0.71,1.02]
Subtotal ***	**2049**		**2105**			**100%**	**-0.28[-0.36,-0.19]**
Heterogeneity: Tau^2=0.04; Chi^2=100.47, df=59(P=0); I^2=41.28%							
Test for overall effect: Z=6.23(P<0.0001)							
3.2.2 Insomnia (sleep onset latency in min, Pittsburgh sleep quality index change)							
Ascher 1979	8	50.6 (44.1)	9	62.4 (25.3)		10.35%	-0.32[-1.28,0.64]
Espie 1989	14	63.5 (30.6)	13	96.5 (63.5)		15.77%	-0.65[-1.43,0.13]
Lick 1977	10	66 (25)	10	63 (32)		12.4%	0.1[-0.78,0.98]
Nicassio 1974	7	117.3 (133.7)	9	99.3 (35.3)		9.73%	0.19[-0.8,1.18]
Tsay 2003	32	9.2 (4.4)	32	9.6 (4)		39.71%	-0.08[-0.57,0.41]
Turner 1979	10	44.2 (41.3)	10	59.8 (22.9)		12.04%	-0.45[-1.34,0.44]
Subtotal ***	**81**		**83**			**100%**	**-0.19[-0.5,0.12]**
Heterogeneity: Tau^2=0; Chi^2=2.91, df=5(P=0.71); I^2=0%							
Test for overall effect: Z=1.2(P=0.23)							
3.2.3 Hypertension (diastolic, mm Hg; absolute or improvement)							
Antivalle 1990	11	-1.6 (5.6)	10	-3.9 (7.3)		8.77%	0.34[-0.52,1.21]
Asmar 1996	34	-0.2 (7.7)	34	0.7 (6.5)		18.7%	-0.12[-0.6,0.35]
Bosley 1989	13	86 (10)	14	89 (10)		10.61%	-0.29[-1.05,0.47]
Canino 1994	4	99 (2.7)	9	95.6 (7.6)		5.15%	0.48[-0.72,1.67]
Frankel 1978	7	93 (5)	8	95 (3)		6.61%	-0.47[-1.5,0.57]
Hossmann 1981	12	94.2 (4.8)	12	95.1 (4.8)		9.81%	-0.18[-0.98,0.62]
Rossi 1982	6	107 (17)	6	108 (20)		5.68%	-0.05[-1.18,1.08]
Seer 1980	14	92.5 (9.8)	13	104.5 (11)		9.47%	-1.12[-1.94,-0.3]
Sinaiko 1991	60	66.5 (9.7)	27	64.1 (13.9)		19.51%	0.21[-0.24,0.67]
Yates 1988	7	-1.4 (2.5)	7	0.7 (1.4)		5.69%	-0.97[-2.1,0.16]
Subtotal ***	**168**		**140**			**100%**	**-0.17[-0.46,0.12]**
Heterogeneity: Tau^2=0.06; Chi^2=12.64, df=9(P=0.18); I^2=28.8%							
Test for overall effect: Z=1.14(P=0.25)							
3.2.4 Nausea (VAS, Rhodes Inventory of Nausea and Vomiting, escape medication)							
Dibble 2007	49	3.1 (2.9)	51	3.5 (3.1)		21.13%	-0.12[-0.51,0.27]
Hawkins 1995	10	37.4 (8.5)	10	52.1 (9.3)		3.87%	-1.58[-2.61,-0.55]
O'Brien 1996	53	6.7 (5.6)	54	7.5 (5.1)		22.22%	-0.15[-0.53,0.23]
Roscoe 2002	27	5.9 (5.2)	27	6.6 (3.6)		12.87%	-0.15[-0.69,0.38]
Roscoe 2005	31	2.4 (1.3)	33	2.8 (1.3)		14.71%	-0.3[-0.8,0.19]
Shen 2000	33	40.7 (12.4)	34	43.7 (11.3)		15.34%	-0.25[-0.73,0.23]
Werntoft 2001	20	5.9 (2.4)	20	6.5 (2.2)		9.87%	-0.26[-0.88,0.37]
Subtotal ***	**223**		**229**			**100%**	**-0.25[-0.46,-0.04]**
Heterogeneity: Tau^2=0.01; Chi^2=7.21, df=6(P=0.3); I^2=16.75%							
Test for overall effect: Z=2.34(P=0.02)							
3.2.5 Smoking (cigarettes per day, self report)							
Etter 2002	269	20.6 (10)	389	25.4 (12.6)		44.92%	-0.41[-0.57,-0.26]
Sipich 1974	10	8 (14)	10	32.5 (14)		24.4%	-1.68[-2.73,-0.63]
Spanos 1995	13	21.4 (9.7)	12	19.1 (10.3)		30.68%	0.22[-0.56,1.01]
Subtotal ***	**292**		**411**			**100%**	**-0.53[-1.29,0.23]**
Heterogeneity: Tau^2=0.33; Chi^2=8.06, df=2(P=0.02); I^2=75.17%							

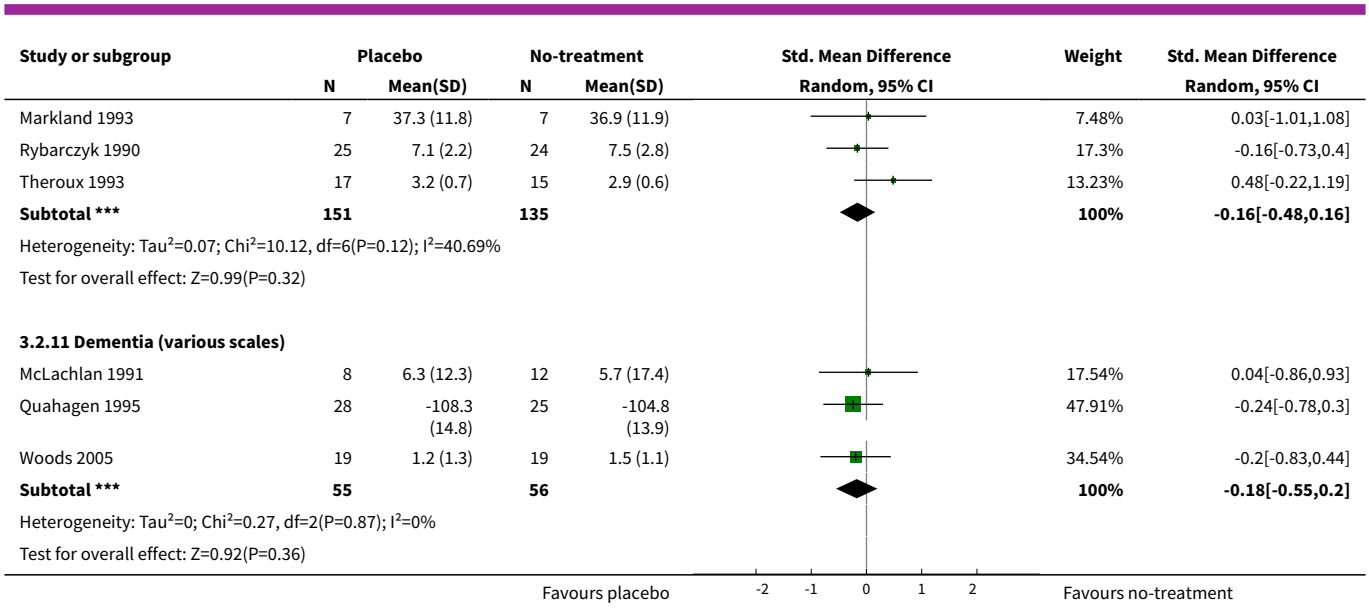


Favours placebo

Favours no-treatment

Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Test for overall effect: Z=1.36(P=0.17)							
3.2.6 Phobia (fear of snakes and spiders: snake slides test, behavioral avoidance test; absolute or improvement)							
Etringer 1982	13	-11.4 (4)	12	-10.1 (3.7)		47.48%	-0.33[-1.12,0.46]
Lick 1975	9	60.6 (32.7)	9	92.2 (22.1)		29.33%	-1.08[-2.09,-0.07]
Rosen 1976	9	6.9 (2)	5	8.3 (1.9)		23.19%	-0.67[-1.8,0.46]
Subtotal ***	**31**		**26**			**100%**	**-0.63[-1.17,-0.08]**
Heterogeneity: Tau^2=0; Chi^2=1.32, df=2(P=0.52); I^2=0%							
Test for overall effect: Z=2.26(P=0.02)							
3.2.7 Asthma (bronchoconstriction: FEV1 or PEF; absolute or improvement)							
Godfrey 1973	44	34.9 (16.7)	44	46.9 (16.2)		35.74%	-0.72[-1.15,-0.29]
May 1988	24	-1.2 (0.5)	24	-1.2 (0.5)		25.59%	-0.02[-0.59,0.54]
Medici 2002	23	-0.2 (0.3)	18	-0.1 (0.3)		22.47%	-0.31[-0.93,0.32]
Morton 1993	13	22.1 (16.4)	13	24.5 (16.4)		16.2%	-0.14[-0.91,0.63]
Subtotal ***	**104**		**99**			**100%**	**-0.35[-0.7,-0.01]**
Heterogeneity: Tau^2=0.04; Chi^2=4.35, df=3(P=0.23); I^2=31.07%							
Test for overall effect: Z=2(P=0.04)							
3.2.8 Obesity (kg, pounds,%; absolute or improvement)							
Antonio 1999	6	79.7 (12.2)	6	72.6 (11.2)		8.18%	0.56[-0.6,1.72]
Block 1980	16	22.4 (6.6)	8	24.7 (9.2)		12.95%	-0.3[-1.15,0.56]
Colker 1999	7	82.7 (18)	4	77.7 (10.5)		7.41%	0.29[-0.95,1.53]
Hall 1974	23	-0.5 (7.8)	22	0.9 (7.8)		20.2%	-0.17[-0.76,0.41]
Hanson 1976	11	-0.9 (3.8)	10	-0.3 (2.2)		12.85%	-0.19[-1.05,0.67]
Murphy 1982	6	-16.5 (9.3)	11	-0.8 (6.4)		7.26%	-1.99[-3.24,-0.74]
Roongpisuthip 1999	18	-3.3 (4.2)	19	-2.9 (3.1)		18.26%	-0.11[-0.75,0.54]
Senediak 1985	11	47.5 (8.4)	10	47.9 (7.5)		12.89%	-0.04[-0.9,0.81]
Subtotal ***	**98**		**90**			**100%**	**-0.2[-0.57,0.17]**
Heterogeneity: Tau^2=0.09; Chi^2=10.32, df=7(P=0.17); I^2=32.15%							
Test for overall effect: Z=1.05(P=0.29)							
3.2.9 Depression (Hamilton's score, Beck Depression Inventory, Geriatric Depression Scale, Bf-S scale)							
Allen 1998	11	-2.9 (7.9)	11	-6.1 (10.9)		9.3%	0.32[-0.52,1.17]
Allen 2006	45	12 (9.6)	44	19 (9.6)		20.17%	-0.72[-1.15,-0.29]
Fuchs 1977	10	14.3 (7)	10	21.4 (7)		7.9%	-0.97[-1.91,-0.03]
Lincoln 2003	42	14.4 (10)	38	16.7 (10)		19.76%	-0.23[-0.67,0.21]
Nandi 1976	10	53.2 (11.2)	8	57.5 (13.8)		7.92%	-0.33[-1.27,0.61]
Parker 2003	13	16.2 (7.5)	14	14.2 (7.5)		10.78%	0.26[-0.5,1.02]
Röschke 2000	24	23 (16.2)	24	26 (16)		15.45%	-0.18[-0.75,0.38]
Sumaya 2001	10	15.4 (2.7)	10	14.9 (1.8)		8.72%	0.21[-0.67,1.09]
Subtotal ***	**165**		**159**			**100%**	**-0.25[-0.55,0.05]**
Heterogeneity: Tau^2=0.07; Chi^2=11.42, df=7(P=0.12); I^2=38.71%							
Test for overall effect: Z=1.6(P=0.11)							
3.2.10 Anxiety (modified versions of Spielberger's anxiety inventory, situational anxiety scale, cry score)							
Karst 2007	19	45.2 (10.8)	10	56.5 (9.1)		10.8%	-1.07[-1.89,-0.25]
Kendall 1979	11	7.5 (2.3)	11	8.2 (3)		10.46%	-0.23[-1.07,0.61]
Lorr 1961	42	58.3 (9.9)	38	57.5 (9.9)		21.75%	0.08[-0.36,0.52]
Macaluso 1995	30	-3.3 (3.8)	30	-1.8 (3.3)		18.98%	-0.41[-0.93,0.1]



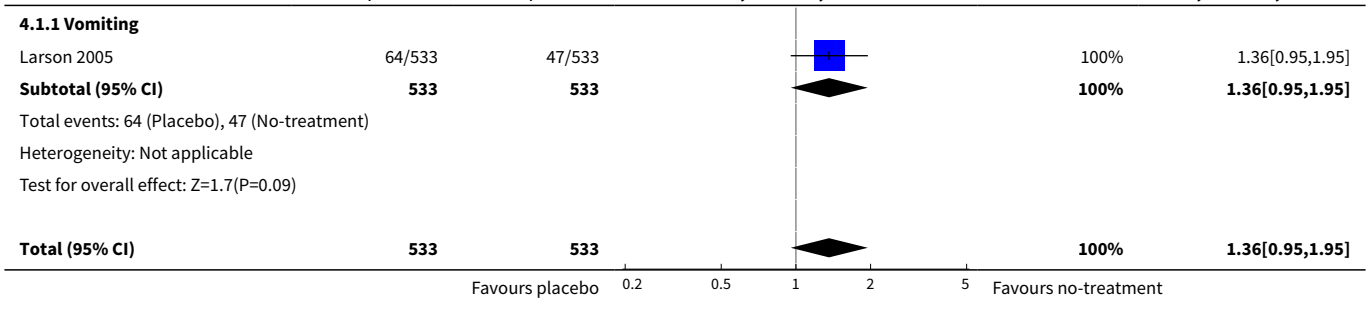


Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Markland 1993	7	37.3 (11.8)	7	36.9 (11.9)		7.48%	0.03[-1.01,1.08]
Rybarczyk 1990	25	7.1 (2.2)	24	7.5 (2.8)		17.3%	-0.16[-0.73,0.4]
Theroux 1993	17	3.2 (0.7)	15	2.9 (0.6)		13.23%	0.48[-0.22,1.19]
Subtotal ***	**151**		**135**			**100%**	**-0.16[-0.48,0.16]**
Heterogeneity: Tau²=0.07; Chi²=10.12, df=6(P=0.12); I²=40.69%							
Test for overall effect: Z=0.99(P=0.32)							
3.2.11 Dementia (various scales)							
McLachlan 1991	8	6.3 (12.3)	12	5.7 (17.4)		17.54%	0.04[-0.86,0.93]
Quahagen 1995	28	-108.3 (14.8)	25	-104.8 (13.9)		47.91%	-0.24[-0.78,0.3]
Woods 2005	19	1.2 (1.3)	19	1.5 (1.1)		34.54%	-0.2[-0.83,0.44]
Subtotal ***	**55**		**56**			**100%**	**-0.18[-0.55,0.2]**
Heterogeneity: Tau²=0; Chi²=0.27, df=2(P=0.87); I²=0%							
Test for overall effect: Z=0.92(P=0.36)							

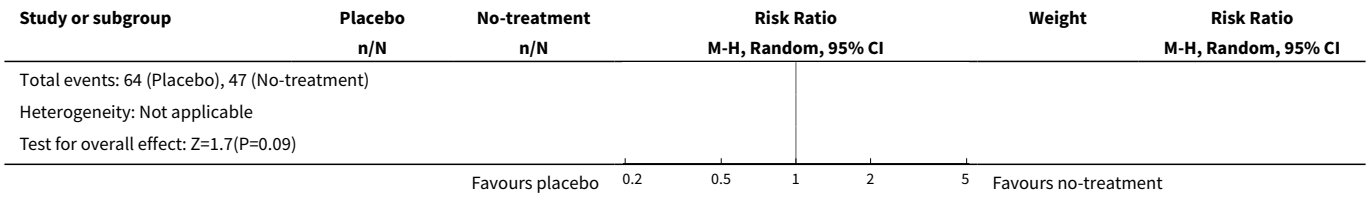
Comparison 4. Supplementary analysis: adverse effects

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Binary outcomes	1	1066	Risk Ratio (M-H, Random, 95% CI)	1.36 [0.95, 1.95]
1.1 Vomiting	1	1066	Risk Ratio (M-H, Random, 95% CI)	1.36 [0.95, 1.95]
2 Continuous outcomes	2	152	Std. Mean Difference (IV, Random, 95% CI)	0.25 [-0.74, 1.23]
2.1 Cardiorespiratory safety during gastroscopy (heart rate per min)	1	128	Std. Mean Difference (IV, Random, 95% CI)	-0.19 [-0.53, 0.16]
2.2 Respiratory depressant response (liter per min)	1	24	Std. Mean Difference (IV, Random, 95% CI)	0.83 [-0.01, 1.67]

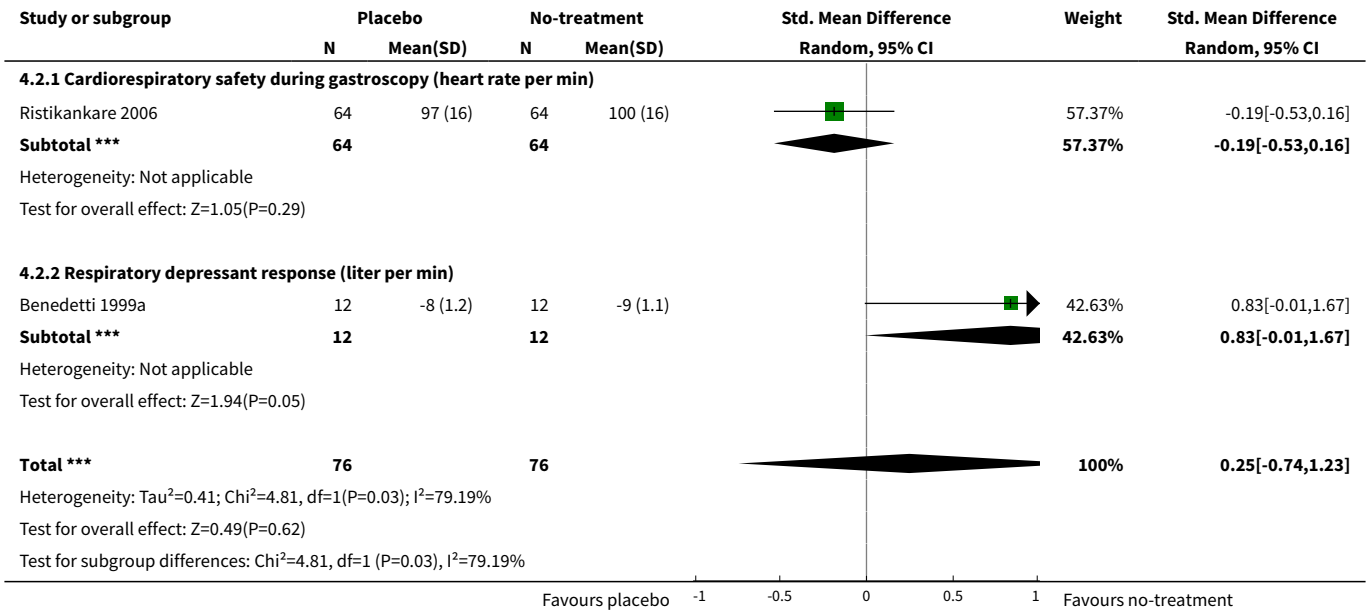
Analysis 4.1. Comparison 4 Supplementary analysis: adverse effects, Outcome 1 Binary outcomes.



Study or subgroup	Placebo n/N	No-treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.1.1 Vomiting					
Larson 2005	64/533	47/533		100%	1.36[0.95,1.95]
Subtotal (95% CI)	**533**	**533**		**100%**	**1.36[0.95,1.95]**
Total events: 64 (Placebo), 47 (No-treatment)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.7(P=0.09)					
Total (95% CI)	**533**	**533**		**100%**	**1.36[0.95,1.95]**



Analysis 4.2. Comparison 4 Supplementary analysis: adverse effects, Outcome 2 Continuous outcomes.



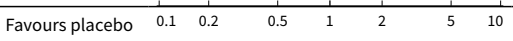
Comparison 5. Effect modification subgroup analysis: type of outcomes

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Patient-reported outcomes that are non-observable	12	2393	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.84, 1.06]
2 Patient-reported outcomes that are observable	19	1653	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.82, 1.02]
3 Observer-reported outcomes involving patient's cooperation	4	144	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.77, 1.09]
4 Observer-reported outcomes not involving patient's cooperation	5	428	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.80, 1.06]
5 Laboratory outcomes	4	1423	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.74, 1.17]
6 Patient-reported outcomes that are non-observable	83	6004	Std. Mean Difference (IV, Random, 95% CI)	-0.28 [-0.36, -0.20]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7 Patient-reported outcomes that are observable	26	1996	Std. Mean Difference (IV, Random, 95% CI)	-0.21 [-0.31, -0.11]
8 Observer-reported outcomes involving patient's cooperation	22	878	Std. Mean Difference (IV, Random, 95% CI)	-0.26 [-0.41, -0.12]
9 Observer-reported outcomes not involving patient's cooperation	22	906	Std. Mean Difference (IV, Random, 95% CI)	-0.12 [-0.29, 0.05]
10 Laboratory outcomes	5	729	Std. Mean Difference (IV, Random, 95% CI)	0.16 [0.01, 0.30]

Analysis 5.1. Comparison 5 Effect modification subgroup analysis: type of outcomes, Outcome 1 Patient-reported outcomes that are non-observable.

Study or subgroup	Placebo n/N	No-treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Dundee 1986	17/25	17/25		5.9%	1[0.68,1.46]
Faas 1993	107/162	108/155		13.14%	0.95[0.81,1.1]
McMillan 1994	14/26	24/46		4.66%	1.03[0.66,1.62]
Molsberger 2002	38/58	30/53		7.82%	1.16[0.86,1.56]
Najnigier 1997	21/30	24/30		7.99%	0.88[0.65,1.17]
Roughan 1981	9/12	9/14		3.89%	1.17[0.7,1.94]
Scharf 2006	179/365	224/316		14.15%	0.69[0.61,0.78]
Scharff 2002	11/12	12/12		10.3%	0.92[0.74,1.15]
Tarcin 2004	58/158	27/77		6.19%	1.05[0.73,1.51]
Thomas 1987	47/100	50/100		8.25%	0.94[0.71,1.25]
Tyler 1946	89/260	106/303		10.17%	0.98[0.78,1.23]
Walton 1993	19/24	21/30		7.52%	1.13[0.83,1.54]
Total (95% CI)	**1232**	**1161**		**100%**	**0.95[0.84,1.06]**
Total events: 609 (Placebo), 652 (No-treatment)					
Heterogeneity: Tau^2=0.02; Chi^2=24.68, df=11(P=0.01); I^2=55.44%					
Test for overall effect: Z=0.94(P=0.35)					



Analysis 5.2. Comparison 5 Effect modification subgroup analysis: type of outcomes, Outcome 2 Patient-reported outcomes that are observable.

Study or subgroup	Placebo n/N	No-treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Alkaissi 1999	9/20	11/20		2.53%	0.82[0.44,1.53]
Alkaissi 2002	77/139	82/136		11.23%	0.92[0.75,1.12]
Aune 1998	11/26	9/14		2.76%	0.66[0.36,1.19]
Berg 1983	9/11	9/15		3.7%	1.36[0.83,2.24]
Blackman 1964	6/12	6/12		1.63%	1[0.45,2.23]

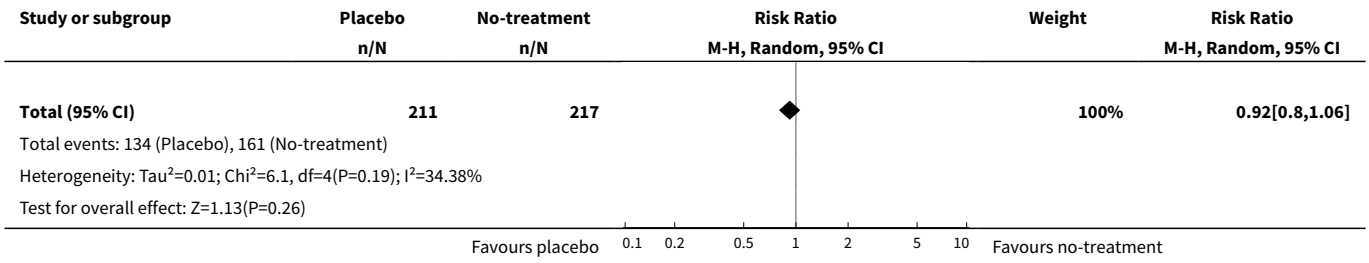
Study or subgroup	Placebo n/N	No-treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Carter 2003	13/28	20/29		4.11%	0.67[0.42,1.07]
Corver 2006	227/279	360/416		17.42%	0.94[0.88,1.01]
Elliott 1978	6/18	6/6		2.33%	0.37[0.19,0.71]
Frank 1990	14/26	14/26		3.65%	1[0.6,1.65]
Guglielmi 1982	9/12	11/12		5.82%	0.82[0.57,1.18]
Hutton 1991	5/24	16/30		1.47%	0.39[0.17,0.91]
Jacobs 1971	9/15	12/39		2.53%	1.95[1.04,3.65]
Klerman 1974	17/25	16/25		5.21%	1.06[0.71,1.58]
Rabkin 1990	14/27	12/23		3.31%	0.99[0.58,1.7]
Stransky 1989	1/5	1/4		0.19%	0.8[0.07,9.18]
Tan 1986	8/10	8/9		5.44%	0.9[0.61,1.32]
Watzl 1986	15/34	7/36		1.77%	2.27[1.06,4.88]
Williams 1988	19/20	19/20		14.08%	1[0.87,1.15]
Wilson 1980	31/40	10/10		10.81%	0.8[0.65,0.99]
Total (95% CI)	**771**	**882**		**100%**	**0.92[0.82,1.02]**
Total events: 500 (Placebo), 629 (No-treatment)					
Heterogeneity: Tau^2=0.02; Chi^2=31.8, df=18(P=0.02); I^2=43.4%					
Test for overall effect: Z=1.57(P=0.12)					

Analysis 5.3. Comparison 5 Effect modification subgroup analysis: type of outcomes, Outcome 3 Observer-reported outcomes involving patient's cooperation.

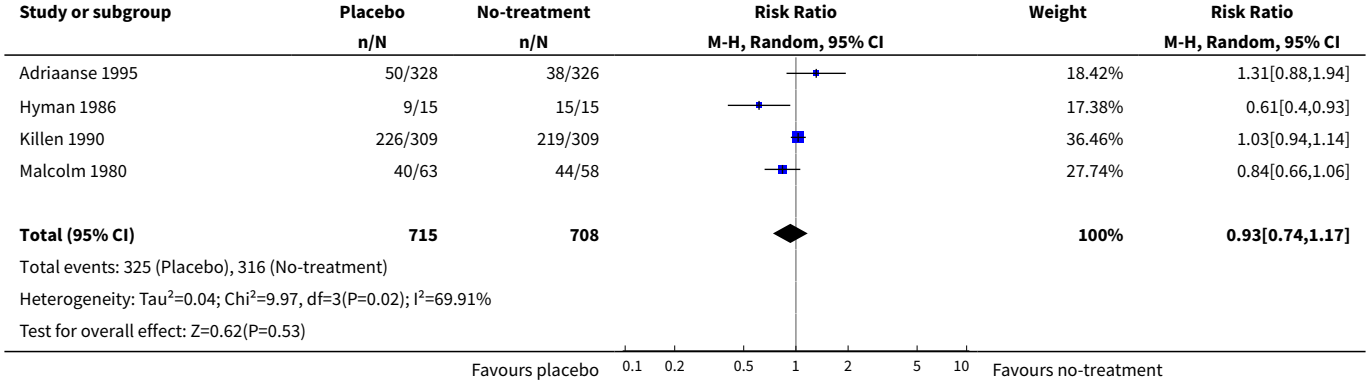
Study or subgroup	Placebo n/N	No-treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Double 1993	3/22	3/22		1.43%	1[0.23,4.42]
Fanti 2003	8/10	9/10		22.85%	0.89[0.61,1.29]
Tarrier 1998	22/26	25/28		73.16%	0.95[0.77,1.17]
Whittaker 1963	3/13	7/13		2.56%	0.43[0.14,1.3]
Total (95% CI)	**71**	**73**		**100%**	**0.92[0.77,1.09]**
Total events: 36 (Placebo), 44 (No-treatment)					
Heterogeneity: Tau^2=0; Chi^2=2.51, df=3(P=0.47); I^2=0%					
Test for overall effect: Z=0.97(P=0.33)					

Analysis 5.4. Comparison 5 Effect modification subgroup analysis: type of outcomes, Outcome 4 Observer-reported outcomes not involving patient's cooperation.

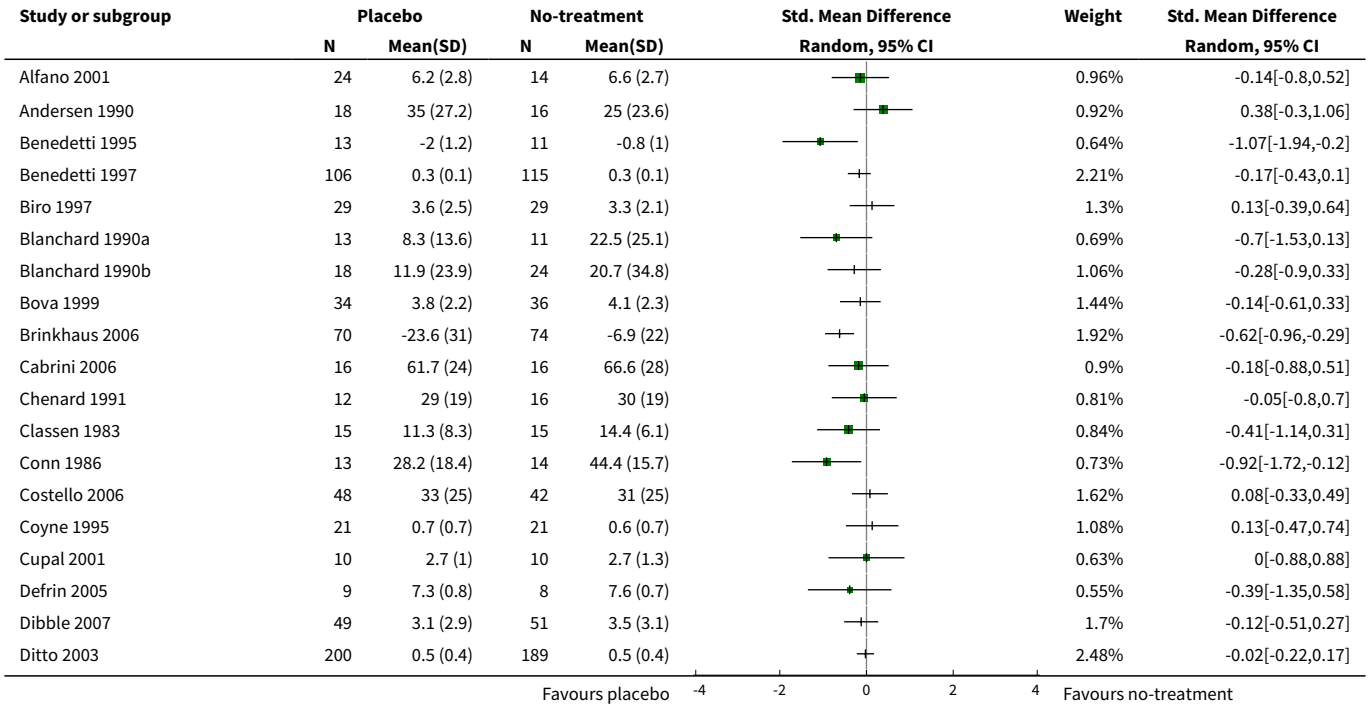
Study or subgroup	Placebo n/N	No-treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
De Sanctis 2001	9/10	8/9		15.6%	1.01[0.74,1.38]
Harrison 1975	24/28	25/30		24.71%	1.03[0.83,1.28]
Heinzl 1981	70/130	92/132		28.36%	0.77[0.64,0.94]
Kerr 2003	28/33	32/36		29.99%	0.95[0.79,1.15]
Schallreuter 2002	3/10	4/10		1.34%	0.75[0.22,2.52]



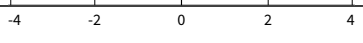
Analysis 5.5. Comparison 5 Effect modification subgroup analysis: type of outcomes, Outcome 5 Laboratory outcomes.



Analysis 5.6. Comparison 5 Effect modification subgroup analysis: type of outcomes, Outcome 6 Patient-reported outcomes that are non-observable.

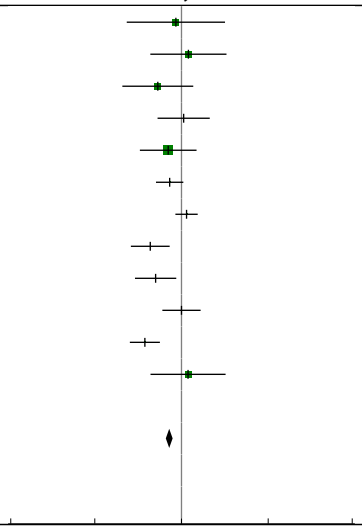


Study or subgroup	Placebo		No-treatment		Std. Mean Difference	Weight	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
Ditto 2006	140	0.4 (0.4)	155	0.5 (0.4)		2.36%	-0.06[-0.28,0.17]
Erdogmus 2007	40	-27.4 (19.7)	40	-20.3 (19.7)		1.53%	-0.36[-0.8,0.08]
Forster 1994	15	3.2 (2.8)	15	4.6 (2.2)		0.83%	-0.54[-1.27,0.19]
Foster 2004	6	-3.6 (0.6)	12	-2.6 (1.1)		0.48%	-0.98[-2.02,0.06]
Foster 2007	112	6.5 (4.8)	105	6.8 (4.5)		2.2%	-0.06[-0.33,0.21]
Frega 1994	21	20 (16)	21	23 (16)		1.07%	-0.18[-0.79,0.42]
Fuchs 1977	10	14.3 (7)	10	21.4 (7)		0.57%	-0.97[-1.91,-0.03]
Goodenough 1997	39	1.1 (1.6)	39	1.6 (1.9)		1.52%	-0.28[-0.73,0.16]
Gracely 1983	17	-2.9 (5.4)	12	0.2 (5.5)		0.8%	-0.54[-1.3,0.21]
Hargreaves 1989	25	4.5 (2.5)	25	4.9 (2.4)		1.2%	-0.16[-0.72,0.39]
Hashish 1986	25	16 (11.7)	50	30 (18.9)		1.35%	-0.82[-1.32,-0.32]
Hashish 1988	25	42 (25)	25	60 (23)		1.15%	-0.74[-1.31,-0.16]
Hawkins 1995	10	37.4 (8.5)	10	52.1 (9.3)		0.49%	-1.58[-2.61,-0.55]
Helms 1987	11	103 (91)	11	79 (99)		0.68%	0.24[-0.6,1.08]
Hong 1993	16	-1.1 (0.2)	21	-1 (0.1)		0.96%	-0.53[-1.19,0.13]
Hruby 2006	49	1.2 (2.1)	51	0.9 (1.5)		1.7%	0.21[-0.19,0.6]
Hyland 2006	10	6 (0.9)	10	6.2 (0.9)		0.63%	-0.21[-1.09,0.67]
Irvin 1996	11	3.3 (0.7)	11	3.7 (1.4)		0.67%	-0.35[-1.19,0.5]
Jacobson 1978	7	2.5 (0.9)	6	3.5 (0.5)		0.37%	-1.17[-2.39,0.04]
Kaptchuk 2008	88	-4.3 (1.4)	87	-3.8 (1)		2.07%	-0.41[-0.71,-0.11]
Karst 2007	19	45.2 (10.8)	10	56.5 (9.1)		0.7%	-1.07[-1.89,-0.25]
Kendall 1979	11	7.5 (2.3)	11	8.2 (3)		0.68%	-0.23[-1.07,0.61]
Kober 2002	20	66.7 (10)	21	64.4 (13.3)		1.06%	0.19[-0.42,0.8]
Kotani 2001	23	15 (4.5)	24	18 (6)		1.13%	-0.55[-1.14,0.03]
Lander 1993	172	28.5 (29.3)	168	32.3 (33.4)		2.42%	-0.12[-0.33,0.09]
Leibing 2002	40	3.2 (1.8)	39	4.3 (1.9)		1.5%	-0.59[-1.04,-0.14]
Levine 1984	12	-0.3 (0.7)	24	0.4 (2.5)		0.89%	-0.31[-1.01,0.38]
Licciardone 2003	19	2.5 (1.7)	15	3.5 (2.7)		0.91%	-0.49[-1.17,0.2]
Lick 1975	9	60.6 (32.7)	9	92.2 (22.1)		0.51%	-1.08[-2.09,-0.07]
Limoges 2004	30	2.3 (1)	30	2.2 (1)		1.33%	0.04[-0.47,0.55]
Lincoln 2003	42	14.4 (10)	38	16.7 (10)		1.54%	-0.23[-0.67,0.21]
Linde 2005	76	-2.2 (2.7)	64	-0.8 (2.2)		1.91%	-0.56[-0.9,-0.22]
Liossi 2003	20	4.3 (0.6)	20	4.6 (0.6)		1.02%	-0.49[-1.12,0.14]
Lorr 1961	42	58.3 (9.9)	38	57.5 (9.9)		1.54%	0.08[-0.36,0.52]
Macaluso 1995	30	-3.3 (3.8)	30	-1.8 (3.3)		1.31%	-0.41[-0.93,0.1]
Markland 1993	7	37.3 (11.8)	7	36.9 (11.9)		0.48%	0.03[-1.01,1.08]
Matros 2006	23	76 (36.3)	21	72 (28.3)		1.11%	0.12[-0.47,0.71]
Melchart 2005	57	10.8 (8.3)	63	16.3 (7.4)		1.79%	-0.7[-1.07,-0.33]
Moffet 1996	22	24 (18.6)	27	34.6 (23.2)		1.16%	-0.49[-1.06,0.08]
Nawrocki 1997	40	9.5 (6)	42	17 (4.8)		1.4%	-1.37[-1.85,-0.89]
O'Brien 1996	53	6.7 (5.6)	54	7.5 (5.1)		1.75%	-0.15[-0.53,0.23]
Parker 1995	49	4 (1.9)	45	3.8 (2.2)		1.66%	0.1[-0.31,0.5]
Parker 2003	13	16.2 (7.5)	14	14.2 (7.5)		0.79%	0.26[-0.5,1.02]
Rawling 2001	89	5.3 (4.7)	96	5.6 (4.9)		2.11%	-0.06[-0.35,0.23]
Reading 1982	18	1.6 (1.3)	20	2.3 (2)		0.99%	-0.4[-1.05,0.24]
Ristikankare 1999	61	40.3 (21.5)	61	36 (21.5)		1.84%	0.2[-0.16,0.55]
Roscoe 2005	31	2.4 (1.3)	33	2.8 (1.3)		1.37%	-0.3[-0.8,0.19]
Rosen 1976	9	6.9 (2)	5	8.3 (1.9)		0.42%	-0.67[-1.8,0.46]
Rowbotham 1996	35	-4.4 (8.7)	35	1.9 (8.7)		1.4%	-0.72[-1.2,-0.23]
Rybarczyk 1990	25	7.1 (2.2)	24	7.5 (2.8)		1.18%	-0.16[-0.73,0.4]
Röschke 2000	24	23 (16.2)	24	26 (16)		1.17%	-0.18[-0.75,0.38]
Rösler 2003	13	5.9 (3.4)	14	6 (3)		0.8%	-0.02[-0.78,0.73]



Favours placebo Favours no-treatment

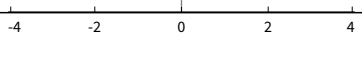
Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Sanders 1990	6	2 (0.4)	6	2.1 (0.3)		0.42%	-0.13[-1.26,1]
Sprott 1993	10	7.9 (3)	10	7.4 (3)		0.63%	0.16[-0.72,1.04]
Tan 1982	12	1.3 (0.6)	12	1.7 (0.8)		0.71%	-0.55[-1.36,0.27]
Tashjian 2006	19	3.4 (2.2)	24	3.3 (1.8)		1.08%	0.05[-0.55,0.65]
Thomas 1999	14	13.4 (10.3)	26	16.5 (9.7)		0.97%	-0.31[-0.96,0.35]
Thomas 2002a	78	-0.9 (3)	78	-0.1 (2.9)		2%	-0.27[-0.59,0.04]
Thomas 2002b	114	-1.2 (3.5)	119	-1.6 (3.3)		2.24%	0.12[-0.14,0.37]
Tritrakarn 2000	41	49 (16)	41	61 (17)		1.51%	-0.72[-1.17,-0.27]
Tsay 2004	35	4.7 (1.5)	36	5.7 (1.8)		1.42%	-0.6[-1.07,-0.12]
Vlaeyen 1996	39	0.4 (1.8)	40	0.4 (1.8)		1.53%	0[-0.44,0.44]
Witt 2005	73	35.8 (16.2)	67	49.6 (16.3)		1.88%	-0.84[-1.19,-0.5]
Wojciechowski 1984	9	264 (122)	12	238 (190)		0.65%	0.15[-0.71,1.02]
Total ***	**2979**		**3025**			**100%**	**-0.28[-0.36,-0.2]**
Heterogeneity: Tau^2=0.05; Chi^2=160.25, df=82(P<0.0001); I^2=48.83%							
Test for overall effect: Z=7.03(P<0.0001)							



Favours placebo — Favours no-treatment

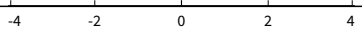
Analysis 5.7. Comparison 5 Effect modification subgroup analysis: type of outcomes, Outcome 7 Patient-reported outcomes that are observable.

Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Abikoff 2004	35	-91.4 (18.9)	34	-89.5 (22.8)		4.11%	-0.09[-0.56,0.38]
Anderson 1999	30	-2.7 (0.8)	27	-2.7 (0.8)		3.42%	0.08[-0.44,0.6]
Ascher 1979	8	50.6 (44.1)	9	62.4 (25.3)		1.05%	-0.32[-1.28,0.64]
Davidson 1980	10	1.8 (0.9)	10	2.9 (1.3)		1.1%	-0.94[-1.88,-0.01]
Espie 1989	14	63.5 (30.6)	13	96.5 (63.5)		1.58%	-0.65[-1.43,0.13]
Etter 2002	269	20.6 (10)	389	25.4 (12.6)		24.31%	-0.41[-0.57,-0.26]
Fisher 2006	12	3.8 (1.9)	15	4.1 (2.5)		1.65%	-0.13[-0.89,0.63]
Hovell 2003	98	-155.4 (69.9)	96	-151 (73.8)		10.33%	-0.06[-0.34,0.22]
Killeen 2004	24	1 (2.5)	35	1.9 (3.5)		3.4%	-0.28[-0.81,0.24]
Kilmann 1987	4	-33 (47)	4	-35 (47)		0.51%	0.04[-1.35,1.42]
Lick 1977	10	66 (25)	10	63 (32)		1.25%	0.1[-0.78,0.98]
Longo 1988	10	3.6 (0.6)	9	3.6 (0.4)		1.19%	0[-0.9,0.9]
Medici 2002	23	-0.2 (0.3)	18	-0.1 (0.3)		2.44%	-0.31[-0.93,0.32]
Moreland 2006	50	-2 (1.3)	99	-2.1 (1.7)		7.46%	0.06[-0.28,0.4]
Morey 2006	38	-16.5 (9.3)	42	-14.7 (9.5)		4.69%	-0.19[-0.63,0.25]
Nicassio 1974	7	117.3 (133.7)	9	99.3 (35.3)		0.98%	0.19[-0.8,1.18]
Pelham 1992	38	-8.7 (1.7)	38	-8.5 (1.6)		4.49%	-0.12[-0.57,0.33]
Roscoe 2002	27	5.9 (5.2)	27	6.6 (3.6)		3.25%	-0.15[-0.69,0.38]
Sipich 1974	10	8 (14)	10	32.5 (14)		0.87%	-1.68[-2.73,-0.63]
Spanos 1995	13	21.4 (9.7)	12	19.1 (10.3)		1.54%	0.22[-0.56,1.01]
Steinsbekk 2004	102	44.5 (58.9)	74	53 (45.2)		9.29%	-0.16[-0.46,0.14]
Stewart 1991	25	-14.3 (5.5)	25	-12.8 (5.2)		3%	-0.28[-0.83,0.28]
Straub 2001	5	-5.8 (0.3)	5	-6 (0.7)		0.62%	0.27[-0.98,1.52]
Tsay 2003	32	9.2 (4.4)	32	9.6 (4)		3.83%	-0.08[-0.57,0.41]
Turner 1979	10	44.2 (41.3)	10	59.8 (22.9)		1.21%	-0.45[-1.34,0.44]



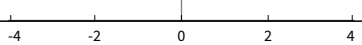
Favours placebo — Favours no-treatment

Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Werntoft 2001	20	5.9 (2.4)	20	6.5 (2.2)		2.43%	-0.26[-0.88,0.37]
Total ***	**924**		**1072**			**100%**	**-0.21[-0.31,-0.11]**
Heterogeneity: Tau²=0; Chi²=26.68, df=25(P=0.37); I²=6.31%							
Test for overall effect: Z=4.15(P<0.0001)							



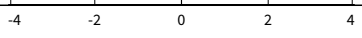
Analysis 5.8. Comparison 5 Effect modification subgroup analysis: type of outcomes, Outcome 8 Observer-reported outcomes involving patient's cooperation.

Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Allen 1998	11	-2.9 (7.9)	11	-6.1 (10.9)		2.81%	0.32[-0.52,1.17]
Allen 2006	45	12 (9.6)	44	19 (9.6)		8.55%	-0.72[-1.15,-0.29]
Bramston 1985	12	-78 (14.2)	12	-72 (13.8)		3.01%	-0.41[-1.22,0.4]
Carbajal 1999	25	7.2 (2.8)	25	6.9 (2.6)		5.78%	0.1[-0.45,0.66]
Etringer 1982	13	-11.4 (4)	12	-10.1 (3.7)		3.15%	-0.33[-1.12,0.46]
Godfrey 1973	44	34.9 (16.7)	44	46.9 (16.2)		8.49%	-0.72[-1.15,-0.29]
Lee 2005	27	-21.4 (25.9)	27	-5.9 (9.2)		5.77%	-0.79[-1.34,-0.23]
Lin 2002	25	30.2 (14.4)	25	38.1 (16)		5.62%	-0.51[-1.07,0.05]
May 1988	24	-1.2 (0.5)	24	-1.2 (0.5)		5.6%	-0.02[-0.59,0.54]
McLachlan 1991	8	6.3 (12.3)	12	5.7 (17.4)		2.52%	0.04[-0.86,0.93]
Morton 1993	13	22.1 (16.4)	13	24.5 (16.4)		3.3%	-0.14[-0.91,0.63]
Nandi 1976	10	53.2 (11.2)	8	57.5 (13.8)		2.31%	-0.33[-1.27,0.61]
Nocella 1982	10	0.8 (0.9)	10	0.8 (0.7)		2.61%	-0.02[-0.9,0.85]
Quahagen 1995	28	-108.3 (14.8)	25	-104.8 (13.9)		6.01%	-0.24[-0.78,0.3]
Robinson 2001	13	3.9 (3.5)	10	4.3 (3.7)		2.92%	-0.11[-0.93,0.72]
Shen 2000	33	40.7 (12.4)	34	43.7 (11.3)		7.23%	-0.25[-0.73,0.23]
Sumaya 2001	10	15.4 (2.7)	10	14.9 (1.8)		2.6%	0.21[-0.67,1.09]
Theroux 1993	17	3.2 (0.7)	15	2.9 (0.6)		3.85%	0.48[-0.22,1.19]
Wang 1997	25	10.7 (7.3)	26	13.4 (5.8)		5.77%	-0.4[-0.96,0.15]
Weingaertner 1971	15	1.1 (1.3)	15	1.2 (1.6)		3.75%	-0.1[-0.81,0.62]
Wilcock 2008	15	-6.4 (5.1)	15	-6.7 (5.9)		3.76%	0.05[-0.66,0.77]
Woods 2005	19	1.2 (1.3)	19	1.5 (1.1)		4.59%	-0.2[-0.83,0.44]
Total ***	**442**		**436**			**100%**	**-0.26[-0.41,-0.12]**
Heterogeneity: Tau²=0.02; Chi²=24.79, df=21(P=0.26); I²=15.29%							
Test for overall effect: Z=3.49(P=0)							



Analysis 5.9. Comparison 5 Effect modification subgroup analysis: type of outcomes, Outcome 9 Observer-reported outcomes not involving patient's cooperation.

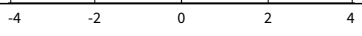
Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Antivalle 1990	11	-1.6 (5.6)	10	-3.9 (7.3)		3.38%	0.34[-0.52,1.21]



Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Antonio 1999	6	79.7 (12.2)	6	72.6 (11.2)		1.99%	0.56[-0.6,1.72]
Asmar 1996	34	-0.2 (7.7)	34	0.7 (6.5)		8.39%	-0.12[-0.6,0.35]
Block 1980	16	22.4 (6.6)	8	24.7 (9.2)		3.45%	-0.3[-1.15,0.56]
Bosley 1989	13	86 (10)	14	89 (10)		4.2%	-0.29[-1.05,0.47]
Canino 1994	4	99 (2.7)	9	95.6 (7.6)		1.89%	0.48[-0.72,1.67]
Colker 1999	7	82.7 (18)	4	77.7 (10.5)		1.78%	0.29[-0.95,1.53]
Frankel 1978	7	93 (5)	8	95 (3)		2.47%	-0.47[-1.5,0.57]
GRECHO 1989	150	94.4 (40.7)	150	95.4 (33)		16.77%	-0.03[-0.25,0.2]
Hall 1974	23	-0.5 (7.8)	22	0.9 (7.8)		6.3%	-0.17[-0.76,0.41]
Hanson 1976	11	-0.9 (3.8)	10	-0.3 (2.2)		3.41%	-0.19[-1.05,0.67]
Hossmann 1981	12	94.2 (4.8)	12	95.1 (4.8)		3.83%	-0.18[-0.98,0.62]
Kokol 2005	16	9.5 (10.5)	10	7.3 (6.6)		3.91%	0.23[-0.56,1.02]
Murphy 1982	6	-16.5 (9.3)	11	-0.8 (6.4)		1.74%	-1.99[-3.24,-0.74]
Roongpisuthip 1999	18	-3.3 (4.2)	19	-2.9 (3.1)		5.44%	-0.11[-0.75,0.54]
Rossi 1982	6	107 (17)	6	108 (20)		2.09%	-0.05[-1.18,1.08]
Seer 1980	14	92.5 (9.8)	13	104.5 (11)		3.68%	-1.12[-1.94,-0.3]
Senediak 1985	11	47.5 (8.4)	10	47.9 (7.5)		3.43%	-0.04[-0.9,0.81]
Sinaiko 1991	60	66.5 (9.7)	27	64.1 (13.9)		8.87%	0.21[-0.24,0.67]
Stabholz 1991	10	1.4 (0.5)	10	1.8 (0.6)		3.1%	-0.69[-1.6,0.22]
Tremeau 1992	39	-0.9 (1.3)	25	-1.1 (1.4)		7.8%	0.14[-0.36,0.65]
Yates 1988	7	-1.4 (2.5)	7	0.7 (1.4)		2.1%	-0.97[-2.1,0.16]
Total ***	**481**		**425**			**100%**	**-0.12[-0.29,0.05]**

Heterogeneity: Tau^2=0.03; Chi^2=26.94, df=21(P=0.17); I^2=22.04%

Test for overall effect: Z=1.41(P=0.16)

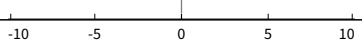


Analysis 5.10. Comparison 5 Effect modification subgroup analysis: type of outcomes, Outcome 10 Laboratory outcomes.

Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Blades 2001	40	-16 (6)	40	-16 (6)		11.03%	0[-0.44,0.44]
Crosby 1994	26	13.6 (1.3)	33	13.5 (1.3)		8.01%	0.08[-0.44,0.59]
Karunakaran 1997	58	6.2 (1.2)	57	5.9 (0.6)		15.66%	0.31[-0.05,0.68]
Lindholm 1996	227	6.8 (0.5)	226	6.8 (0.5)		62.29%	0.15[-0.04,0.33]
Tuomilehto 1980	11	9 (1.4)	11	8.7 (1.6)		3.01%	0.24[-0.6,1.08]
Total ***	**362**		**367**			**100%**	**0.16[0.01,0.3]**

Heterogeneity: Tau^2=0; Chi^2=1.32, df=4(P=0.86); I^2=0%

Test for overall effect: Z=2.1(P=0.04)

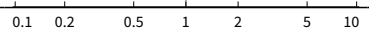


Comparison 6. Effect modification subgroup analysis: the purpose of the trials

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 To study the effect of placebo was an explicit trial purpose	11	1163	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.78, 1.04]
2 To study the effect of placebo was not an explicit trial purpose	33	4878	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.88, 1.01]
3 To study the effect of placebo was an explicit trial purpose	28	2027	Std. Mean Difference (IV, Random, 95% CI)	-0.34 [-0.46, -0.22]
4 To study the effect of placebo was not an explicit trial purpose	130	8486	Std. Mean Difference (IV, Random, 95% CI)	-0.20 [-0.26, -0.14]

Analysis 6.1. Comparison 6 Effect modification subgroup analysis: the purpose of the trials, Outcome 1 To study the effect of placebo was an explicit trial purpose.

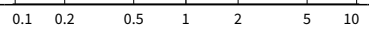
Study or subgroup	Placebo n/N	No-treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Frank 1990	14/26	14/26		6.33%	1[0.6,1.65]
Hutton 1991	5/24	16/30		2.62%	0.39[0.17,0.91]
Hyman 1986	9/15	15/15		8.42%	0.61[0.4,0.93]
Klerman 1974	17/25	16/25		8.89%	1.06[0.71,1.58]
Rabkin 1990	14/27	12/23		5.77%	0.99[0.58,1.7]
Schallreuter 2002	3/10	4/10		1.34%	0.75[0.22,2.52]
Scharff 2002	11/12	12/12		16.56%	0.92[0.74,1.15]
Thomas 1987	47/100	50/100		13.25%	0.94[0.71,1.25]
Tyler 1946	89/260	106/303		16.35%	0.98[0.78,1.23]
Watzl 1986	15/34	7/36		3.15%	2.27[1.06,4.88]
Wilson 1980	31/40	10/10		17.31%	0.8[0.65,0.99]
Total (95% CI)	**573**	**590**		**100%**	**0.9[0.78,1.04]**
Total events: 255 (Placebo), 262 (No-treatment)					
Heterogeneity: Tau^2=0.02; Chi^2=16.13, df=10(P=0.1); I^2=38%					
Test for overall effect: Z=1.38(P=0.17)					



Favours placebo — Favours no-treatment

Analysis 6.2. Comparison 6 Effect modification subgroup analysis: the purpose of the trials, Outcome 2 To study the effect of placebo was not an explicit trial purpose.

Study or subgroup	Placebo n/N	No-treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Adriaanse 1995	50/328	38/326		2.08%	1.31[0.88,1.94]
Alkaissi 1999	9/20	11/20		0.96%	0.82[0.44,1.53]
Alkaissi 2002	77/139	82/136		4.73%	0.92[0.75,1.12]
Aune 1998	11/26	9/14		1.05%	0.66[0.36,1.19]



Favours placebo — Favours no-treatment

Study or subgroup	Placebo n/N	No-treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Berg 1983	9/11	9/15		1.42%	1.36[0.83,2.24]
Blackman 1964	6/12	6/12		0.61%	1[0.45,2.23]
Carter 2003	13/28	20/29		1.59%	0.67[0.42,1.07]
Corver 2006	227/279	360/416		7.97%	0.94[0.88,1.01]
De Sanctis 2001	9/10	8/9		2.92%	1.01[0.74,1.38]
Double 1993	3/22	3/22		0.19%	1[0.23,4.42]
Dundee 1986	17/25	17/25		2.19%	1[0.68,1.46]
Elliott 1978	6/18	6/6		0.88%	0.37[0.19,0.71]
Faas 1993	107/162	108/155		5.92%	0.95[0.81,1.1]
Fanti 2003	8/10	9/10		2.26%	0.89[0.61,1.29]
Guglielmi 1982	12/12	11/12		4.28%	1.09[0.87,1.36]
Harrison 1975	24/28	25/30		4.36%	1.03[0.83,1.28]
Heinzl 1981	70/130	92/132		4.89%	0.77[0.64,0.94]
Jacobs 1971	9/15	12/39		0.96%	1.95[1.04,3.65]
Kerr 2003	28/33	32/36		5.12%	0.95[0.79,1.15]
Killen 1990	226/309	219/309		7.28%	1.03[0.94,1.14]
Malcolm 1980	40/63	44/58		4.04%	0.84[0.66,1.06]
McMillan 1994	14/26	24/46		1.68%	1.03[0.66,1.62]
Molsberger 2002	38/58	30/53		3.04%	1.16[0.86,1.56]
Najnigier 1997	21/30	24/30		3.12%	0.88[0.65,1.17]
Roughan 1981	9/12	9/14		1.37%	1.17[0.7,1.94]
Scharf 2006	179/365	224/316		6.57%	0.69[0.61,0.78]
Stransky 1989	1/5	1/4		0.07%	0.8[0.07,9.18]
Tan 1986	8/10	8/9		2.14%	0.9[0.61,1.32]
Tarcin 2004	58/158	27/77		2.31%	1.05[0.73,1.51]
Tarrier 1998	22/26	25/28		4.61%	0.95[0.77,1.17]
Walton 1993	19/24	21/30		2.91%	1.13[0.83,1.54]
Whittaker 1963	3/13	7/13		0.33%	0.43[0.14,1.3]
Williams 1988	19/20	19/20		6.16%	1[0.87,1.15]
Total (95% CI)	**2427**	**2451**		**100%**	**0.94[0.88,1.01]**
Total events: 1352 (Placebo), 1540 (No-treatment)					
Heterogeneity: Tau^2=0.01; Chi^2=63.53, df=32(P=0); I^2=49.63%					
Test for overall effect: Z=1.77(P=0.08)					

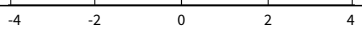
Analysis 6.3. Comparison 6 Effect modification subgroup analysis: the purpose of the trials, Outcome 3 To study the effect of placebo was an explicit trial purpose.

Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Antivalle 1990	11	-1.6 (5.6)	10	-3.9 (7.3)		1.76%	0.34[-0.52,1.21]
Asmar 1996	34	-0.2 (7.7)	34	0.7 (6.5)		4.6%	-0.12[-0.6,0.35]
Benedetti 1995	13	-2 (1.2)	11	-0.8 (1)		1.75%	-1.07[-1.94,-0.2]
Chenard 1991	12	29 (19)	16	30 (19)		2.26%	-0.05[-0.8,0.7]
Cupal 2001	10	2.7 (1)	10	2.7 (1.3)		1.72%	0[-0.88,0.88]
Etter 2002	269	20.6 (10)	389	25.4 (12.6)		12.25%	-0.41[-0.57,-0.26]
Fisher 2006	12	3.8 (1.9)	15	4.1 (2.5)		2.21%	-0.13[-0.89,0.63]
Godfrey 1973	44	34.9 (16.7)	44	46.9 (16.2)		5.25%	-0.72[-1.15,-0.29]

Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Goodenough 1997	39	1.1 (1.6)	39	1.6 (1.9)		5.03%	-0.28[-0.73,0.16]
Gracely 1983	17	-2.9 (5.4)	12	0.2 (5.5)		2.24%	-0.54[-1.3,0.21]
Hashish 1986	25	16 (11.7)	50	30 (18.9)		4.31%	-0.82[-1.32,-0.32]
Hashish 1988	25	42 (25)	25	60 (23)		3.49%	-0.74[-1.31,-0.16]
Hawkins 1995	10	37.4 (8.5)	10	52.1 (9.3)		1.28%	-1.58[-2.61,-0.55]
Hossmann 1981	12	94.2 (4.8)	12	95.1 (4.8)		2.01%	-0.18[-0.98,0.62]
Kaptchuk 2008	88	-4.3 (1.4)	87	-3.8 (1)		7.98%	-0.41[-0.71,-0.11]
Kokol 2005	16	9.5 (10.5)	10	7.3 (6.6)		2.05%	0.23[-0.56,1.02]
Lee 2005	27	-21.4 (25.9)	27	-5.9 (9.2)		3.67%	-0.79[-1.34,-0.23]
Levine 1984	12	-0.3 (0.7)	24	0.4 (2.5)		2.55%	-0.31[-1.01,0.38]
Lick 1975	9	60.6 (32.7)	9	92.2 (22.1)		1.34%	-1.08[-2.09,-0.07]
Lick 1977	10	66 (25)	10	63 (32)		1.72%	0.1[-0.78,0.98]
May 1988	24	-1.2 (0.5)	24	-1.2 (0.5)		3.57%	-0.02[-0.59,0.54]
Medici 2002	23	-0.2 (0.3)	18	-0.1 (0.3)		3.09%	-0.31[-0.93,0.32]
Pelham 1992	38	-8.7 (1.7)	38	-8.5 (1.6)		4.97%	-0.12[-0.57,0.33]
Rawling 2001	89	5.3 (4.7)	96	5.6 (4.9)		8.27%	-0.06[-0.35,0.23]
Reading 1982	18	1.6 (1.3)	20	2.3 (2)		2.91%	-0.4[-1.05,0.24]
Thomas 1999	14	13.4 (10.3)	26	16.5 (9.7)		2.84%	-0.31[-0.96,0.35]
Weingaertner 1971	15	1.1 (1.3)	15	1.2 (1.6)		2.44%	-0.1[-0.81,0.62]
Wilcock 2008	15	-6.4 (5.1)	15	-6.7 (5.9)		2.44%	0.05[-0.66,0.77]
Total * **	**931**		**1096**			**100%**	**-0.34[-0.46,-0.22]**

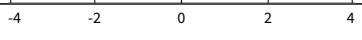
Heterogeneity: Tau^2=0.03; Chi^2=37.56, df=27(P=0.09); I^2=28.11%

Test for overall effect: Z=5.51(P<0.0001)

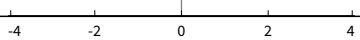


Analysis 6.4. Comparison 6 Effect modification subgroup analysis: the purpose of the trials, Outcome 4 To study the effect of placebo was not an explicit trial purpose.

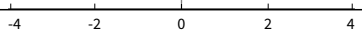
Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Abikoff 2004	35	-91.4 (18.9)	34	-89.5 (22.8)		0.99%	-0.09[-0.56,0.38]
Alfano 2001	24	6.2 (2.8)	14	6.6 (2.7)		0.64%	-0.14[-0.8,0.52]
Allen 1998	11	-2.9 (7.9)	11	-6.1 (10.9)		0.44%	0.32[-0.52,1.17]
Allen 2006	45	12 (9.6)	44	19 (9.6)		1.1%	-0.72[-1.15,-0.29]
Andersen 1990	18	35 (27.2)	16	25 (23.6)		0.61%	0.38[-0.3,1.06]
Anderson 1999	30	-2.7 (0.8)	27	-2.7 (0.8)		0.88%	0.08[-0.44,0.6]
Antonio 1999	6	79.7 (12.2)	6	72.6 (11.2)		0.25%	0.56[-0.6,1.72]
Ascher 1979	8	50.6 (44.1)	9	62.4 (25.3)		0.36%	-0.32[-1.28,0.64]
Benedetti 1997	106	0.3 (0.1)	115	0.3 (0.1)		1.63%	-0.17[-0.43,0.1]
Biro 1997	29	3.6 (2.5)	29	3.3 (2.1)		0.89%	0.13[-0.39,0.64]
Blades 2001	40	-16 (6)	40	-16 (6)		1.08%	0[-0.44,0.44]
Blanchard 1990a	13	8.3 (13.6)	11	22.5 (25.1)		0.45%	-0.7[-1.53,0.13]
Blanchard 1990b	18	11.9 (23.9)	24	20.7 (34.8)		0.71%	-0.28[-0.9,0.33]
Block 1980	16	22.4 (6.6)	8	24.7 (9.2)		0.43%	-0.3[-1.15,0.56]
Bosley 1989	13	86 (10)	14	89 (10)		0.52%	-0.29[-1.05,0.47]
Bova 1999	34	3.8 (2.2)	36	4.1 (2.3)		1%	-0.14[-0.61,0.33]
Bramston 1985	12	-78 (14.2)	12	-72 (13.8)		0.47%	-0.41[-1.22,0.4]
Brinkhaus 2006	70	-23.6 (31)	74	-6.9 (22)		1.38%	-0.62[-0.96,-0.29]



Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Cabrini 2006	16	61.7 (24)	16	66.6 (28)		0.6%	-0.18[-0.88,0.51]
Canino 1994	4	99 (2.7)	9	95.6 (7.6)		0.24%	0.48[-0.72,1.67]
Carbajal 1999	25	7.2 (2.8)	25	6.9 (2.6)		0.81%	0.1[-0.45,0.66]
Classen 1983	15	11.3 (8.3)	15	14.4 (6.1)		0.56%	-0.41[-1.14,0.31]
Colker 1999	7	82.7 (18)	4	77.7 (10.5)		0.23%	0.29[-0.95,1.53]
Conn 1986	13	28.2 (18.4)	14	44.4 (15.7)		0.48%	-0.92[-1.72,-0.12]
Costello 2006	48	33 (25)	42	31 (25)		1.14%	0.08[-0.33,0.49]
Coyne 1995	21	0.7 (0.7)	21	0.6 (0.7)		0.72%	0.13[-0.47,0.74]
Crosby 1994	26	13.6 (1.3)	33	13.5 (1.3)		0.9%	0.08[-0.44,0.59]
Davidson 1980	10	1.8 (0.9)	10	2.9 (1.3)		0.37%	-0.94[-1.88,-0.01]
Defrin 2005	9	7.3 (0.8)	8	7.6 (0.7)		0.35%	-0.39[-1.35,0.58]
Dibble 2007	49	3.1 (2.9)	51	3.5 (3.1)		1.2%	-0.12[-0.51,0.27]
Ditto 2003	200	0.5 (0.4)	189	0.5 (0.4)		1.87%	-0.02[-0.22,0.17]
Ditto 2006	140	0.4 (0.4)	155	0.5 (0.4)		1.76%	-0.06[-0.28,0.17]
Erdogmus 2007	40	-27.4 (19.7)	40	-20.3 (19.7)		1.07%	-0.36[-0.8,0.08]
Espie 1989	14	63.5 (30.6)	13	96.5 (63.5)		0.5%	-0.65[-1.43,0.13]
Etringer 1982	13	-11.4 (4)	12	-10.1 (3.7)		0.49%	-0.33[-1.12,0.46]
Forster 1994	15	3.2 (2.8)	15	4.6 (2.2)		0.55%	-0.54[-1.27,0.19]
Foster 2004	6	-3.6 (0.6)	12	-2.6 (1.1)		0.31%	-0.98[-2.02,0.06]
Foster 2007	112	6.5 (4.8)	105	6.8 (4.5)		1.62%	-0.06[-0.33,0.21]
Frankel 1978	7	93 (5)	8	95 (3)		0.31%	-0.47[-1.5,0.57]
Frega 1994	21	20 (16)	21	23 (16)		0.72%	-0.18[-0.79,0.42]
Fuchs 1977	10	14.3 (7)	10	21.4 (7)		0.37%	-0.97[-1.91,-0.03]
GRECHO 1989	150	94.4 (40.7)	150	95.4 (33)		1.77%	-0.03[-0.25,0.2]
Hall 1974	23	-0.5 (7.8)	22	0.9 (7.8)		0.76%	-0.17[-0.76,0.41]
Hanson 1976	11	-0.9 (3.8)	10	-0.3 (2.2)		0.43%	-0.19[-1.05,0.67]
Hargreaves 1989	25	4.5 (2.5)	25	4.9 (2.4)		0.81%	-0.16[-0.72,0.39]
Helms 1987	11	103 (91)	11	79 (99)		0.44%	0.24[-0.6,1.08]
Hong 1993	16	-1.1 (0.2)	21	-1 (0.1)		0.64%	-0.53[-1.19,0.13]
Hovell 2003	98	-155.4 (69.9)	96	-151 (73.8)		1.57%	-0.06[-0.34,0.22]
Hruby 2006	49	1.2 (2.1)	51	0.9 (1.5)		1.2%	0.21[-0.19,0.6]
Hyland 2006	10	6 (0.9)	10	6.2 (0.9)		0.41%	-0.21[-1.09,0.67]
Irvin 1996	11	3.3 (0.7)	11	3.7 (1.4)		0.44%	-0.35[-1.19,0.5]
Jacobson 1978	7	2.5 (0.9)	6	3.5 (0.5)		0.23%	-1.17[-2.39,0.04]
Karst 2007	19	45.2 (10.8)	10	56.5 (9.1)		0.46%	-1.07[-1.89,-0.25]
Karunakaran 1997	58	6.2 (1.2)	57	5.9 (0.6)		1.28%	0.31[-0.05,0.68]
Kendall 1979	11	7.5 (2.3)	11	8.2 (3)		0.44%	-0.23[-1.07,0.61]
Killeen 2004	24	1 (2.5)	35	1.9 (3.5)		0.88%	-0.28[-0.81,0.24]
Kilmann 1987	4	-33 (47)	4	-35 (47)		0.19%	0.04[-1.35,1.42]
Kober 2002	20	66.7 (10)	21	64.4 (13.3)		0.71%	0.19[-0.42,0.8]
Kotani 2001	23	15 (4.5)	24	18 (6)		0.76%	-0.55[-1.14,0.03]
Lander 1993	172	28.5 (29.3)	168	32.3 (33.4)		1.82%	-0.12[-0.33,0.09]
Leibing 2002	40	3.2 (1.8)	39	4.3 (1.9)		1.04%	-0.59[-1.04,-0.14]
Licciardone 2003	19	2.5 (1.7)	15	3.5 (2.7)		0.6%	-0.49[-1.17,0.2]
Limoges 2004	30	2.3 (1)	30	2.2 (1)		0.91%	0.04[-0.47,0.55]
Lin 2002	25	30.2 (14.4)	25	38.1 (16)		0.8%	-0.51[-1.07,0.05]
Lincoln 2003	42	14.4 (10)	38	16.7 (10)		1.07%	-0.23[-0.67,0.21]
Linde 2005	76	-2.2 (2.7)	64	-0.8 (2.2)		1.37%	-0.56[-0.9,-0.22]
Lindholm 1996	227	6.8 (0.5)	226	6.8 (0.5)		1.92%	0.15[-0.04,0.33]
Liossi 2003	20	4.3 (0.6)	20	4.6 (0.6)		0.69%	-0.49[-1.12,0.14]
Longo 1988	10	3.6 (0.6)	9	3.6 (0.4)		0.4%	0[-0.9,0.9]

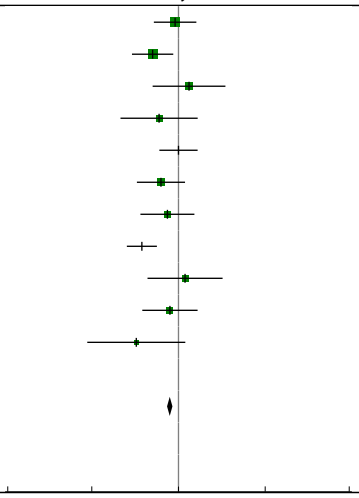


Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Lorr 1961	42	58.3 (9.9)	38	57.5 (9.9)		1.07%	0.08[-0.36,0.52]
Macaluso 1995	30	-3.3 (3.8)	30	-1.8 (3.3)		0.9%	-0.41[-0.93,0.1]
Markland 1993	7	37.3 (11.8)	7	36.9 (11.9)		0.31%	0.03[-1.01,1.08]
Matros 2006	23	76 (36.3)	21	72 (28.3)		0.75%	0.12[-0.47,0.71]
McLachlan 1991	8	6.3 (12.3)	12	5.7 (17.4)		0.4%	0.04[-0.86,0.93]
Melchart 2005	57	10.8 (8.3)	63	16.3 (7.4)		1.27%	-0.7[-1.07,-0.33]
Moffet 1996	22	24 (18.6)	27	34.6 (23.2)		0.78%	-0.49[-1.06,0.08]
Moreland 2006	50	-2 (1.3)	99	-2.1 (1.7)		1.36%	0.06[-0.28,0.4]
Morey 2006	38	-16.5 (9.3)	42	-14.7 (9.5)		1.07%	-0.19[-0.63,0.25]
Morton 1993	13	22.1 (16.4)	13	24.5 (16.4)		0.51%	-0.14[-0.91,0.63]
Murphy 1982	6	-16.5 (9.3)	11	-0.8 (6.4)		0.22%	-1.99[-3.24,-0.74]
Nandi 1976	10	53.2 (11.2)	8	57.5 (13.8)		0.37%	-0.33[-1.27,0.61]
Nawrocki 1997	40	9.5 (6)	42	17 (4.8)		0.96%	-1.37[-1.85,-0.89]
Nicassio 1974	7	117.3 (133.7)	9	99.3 (35.3)		0.34%	0.19[-0.8,1.18]
Nocella 1982	10	0.8 (0.9)	10	0.8 (0.7)		0.41%	-0.02[-0.9,0.85]
O'Brien 1996	53	6.7 (5.6)	54	7.5 (5.1)		1.24%	-0.15[-0.53,0.23]
Parker 1995	49	4 (1.9)	45	3.8 (2.2)		1.17%	0.1[-0.31,0.5]
Parker 2003	13	16.2 (7.5)	14	14.2 (7.5)		0.52%	0.26[-0.5,1.02]
Quahagen 1995	28	-108.3 (14.8)	25	-104.8 (13.9)		0.84%	-0.24[-0.78,0.3]
Ristikankare 1999	61	40.3 (21.5)	61	36 (21.5)		1.31%	0.2[-0.16,0.55]
Robinson 2001	13	3.9 (3.5)	10	4.3 (3.7)		0.46%	-0.11[-0.93,0.72]
Roongpisuthip 1999	18	-3.3 (4.2)	19	-2.9 (3.1)		0.66%	-0.11[-0.75,0.54]
Roscoe 2002	27	5.9 (5.2)	27	6.6 (3.6)		0.85%	-0.15[-0.69,0.38]
Roscoe 2005	31	2.4 (1.3)	33	2.8 (1.3)		0.94%	-0.3[-0.8,0.19]
Rosen 1976	9	6.9 (2)	5	8.3 (1.9)		0.27%	-0.67[-1.8,0.46]
Rossi 1982	6	107 (17)	6	108 (20)		0.27%	-0.05[-1.18,1.08]
Rowbotham 1996	35	-4.4 (8.7)	35	1.9 (8.7)		0.96%	-0.72[-1.2,-0.23]
Rybarczyk 1990	25	7.1 (2.2)	24	7.5 (2.8)		0.8%	-0.16[-0.73,0.4]
Röschke 2000	24	23 (16.2)	24	26 (16)		0.79%	-0.18[-0.75,0.38]
Rösler 2003	13	5.9 (3.4)	14	6 (3)		0.52%	-0.02[-0.78,0.73]
Sanders 1990	6	2 (0.4)	6	2.1 (0.3)		0.27%	-0.13[-1.26,1]
Seer 1980	14	92.5 (9.8)	13	104.5 (11)		0.46%	-1.12[-1.94,-0.3]
Senediak 1985	11	47.5 (8.4)	10	47.9 (7.5)		0.43%	-0.04[-0.9,0.81]
Shen 2000	33	40.7 (12.4)	34	43.7 (11.3)		0.97%	-0.25[-0.73,0.23]
Sinaiko 1991	60	66.5 (9.7)	27	64.1 (13.9)		1.03%	0.21[-0.24,0.67]
Sipich 1974	10	8 (14)	10	32.5 (14)		0.3%	-1.68[-2.73,-0.63]
Spanos 1995	13	21.4 (9.7)	12	19.1 (10.3)		0.49%	0.22[-0.56,1.01]
Sprott 1993	10	7.9 (3)	10	7.4 (3)		0.41%	0.16[-0.72,1.04]
Stabholz 1991	10	1.4 (0.5)	10	1.8 (0.6)		0.39%	-0.69[-1.6,0.22]
Steinsbekk 2004	102	44.5 (58.9)	74	53 (45.2)		1.5%	-0.16[-0.46,0.14]
Stewart 1991	25	-14.3 (5.5)	25	-12.8 (5.2)		0.81%	-0.28[-0.83,0.28]
Straub 2001	5	-5.8 (0.3)	5	-6 (0.7)		0.22%	0.27[-0.98,1.52]
Sumaya 2001	10	15.4 (2.7)	10	14.9 (1.8)		0.41%	0.21[-0.67,1.09]
Tan 1982	12	1.3 (0.6)	12	1.7 (0.8)		0.46%	-0.55[-1.36,0.27]
Tashjian 2006	19	3.4 (2.2)	24	3.3 (1.8)		0.73%	0.05[-0.55,0.65]
Theroux 1993	17	3.2 (0.7)	15	2.9 (0.6)		0.58%	0.48[-0.22,1.19]
Thomas 2002a	78	-0.9 (3)	78	-0.1 (2.9)		1.45%	-0.27[-0.59,0.04]
Thomas 2002b	114	-1.2 (3.5)	119	-1.6 (3.3)		1.65%	0.12[-0.14,0.37]
Tremeau 1992	39	-0.9 (1.3)	25	-1.1 (1.4)		0.92%	0.14[-0.36,0.65]
Tritrakarn 2000	41	49 (16)	41	61 (17)		1.05%	-0.72[-1.17,-0.27]



Favours placebo — Favours no-treatment

Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Tsay 2003	32	9.2 (4.4)	32	9.6 (4)		0.95%	-0.08[-0.57,0.41]
Tsay 2004	35	4.7 (1.5)	36	5.7 (1.8)		0.98%	-0.6[-1.07,-0.12]
Tuomilehto 1980	11	9 (1.4)	11	8.7 (1.6)		0.44%	0.24[-0.6,1.08]
Turner 1979	10	44.2 (41.3)	10	59.8 (22.9)		0.4%	-0.45[-1.34,0.44]
Vlaeyen 1996	39	0.4 (1.8)	40	0.4 (1.8)		1.07%	0[-0.44,0.44]
Wang 1997	25	10.7 (7.3)	26	13.4 (5.8)		0.81%	-0.4[-0.96,0.15]
Werntoft 2001	20	5.9 (2.4)	20	6.5 (2.2)		0.7%	-0.26[-0.88,0.37]
Witt 2005	73	35.8 (16.2)	67	49.6 (16.3)		1.34%	-0.84[-1.19,-0.5]
Wojciechowski 1984	9	264 (122)	12	238 (190)		0.42%	0.15[-0.71,1.02]
Woods 2005	19	1.2 (1.3)	19	1.5 (1.1)		0.67%	-0.2[-0.83,0.44]
Yates 1988	7	-1.4 (2.5)	7	0.7 (1.4)		0.27%	-0.97[-2.1,0.16]
Total * **	**4257**		**4229**			**100%**	**-0.2[-0.26,-0.14]**
Heterogeneity: Tau^2=0.04; Chi^2=217.87, df=129(P<0.0001); I^2=40.79%							
Test for overall effect: Z=6.35(P<0.0001)							

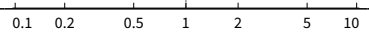


Comparison 7. Effect modification subgroup analysis: type of placebo interventions

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 Psychological placebos	9	298	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.75, 1.04]
2 Physical placebos	11	2536	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.81, 1.01]
3 Pharmacological placebos	24	3207	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.89, 1.05]
4 Psychological placebos	53	2546	Std. Mean Difference (IV, Random, 95% CI)	-0.22 [-0.31, -0.12]
5 Physical placebos	61	3922	Std. Mean Difference (IV, Random, 95% CI)	-0.31 [-0.41, -0.22]
6 Pharmacological placebos	44	4045	Std. Mean Difference (IV, Random, 95% CI)	-0.10 [-0.20, -0.01]

Analysis 7.1. Comparison 7 Effect modification subgroup analysis: type of placebo interventions, Outcome 1 Psychological placebos.

Study or subgroup	Placebo n/N	No-treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Carter 2003	13/28	20/29		7.68%	0.67[0.42,1.07]
Elliott 1978	6/18	6/6		4.78%	0.37[0.19,0.71]
Guglielmi 1982	12/12	11/12		14.7%	1.09[0.87,1.36]
Hyman 1986	9/15	15/15		8.83%	0.61[0.4,0.93]
Roughan 1981	9/12	9/14		6.87%	1.17[0.7,1.94]



Study or subgroup	Placebo n/N	No-treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Scharff 2002	11/12	12/12		14.7%	0.92[0.74,1.15]
Tan 1986	8/10	8/9		9.54%	0.9[0.61,1.32]
Tarrier 1998	22/26	25/28		15.29%	0.95[0.77,1.17]
Williams 1988	19/20	19/20		17.6%	1[0.87,1.15]
Total (95% CI)	**153**	**145**		**100%**	**0.88[0.75,1.04]**
Total events: 109 (Placebo), 125 (No-treatment)					
Heterogeneity: Tau^2=0.03; Chi^2=22.18, df=8(P=0); I^2=63.93%					
Test for overall effect: Z=1.54(P=0.12)					

Favours placebo 0.1 0.2 0.5 1 2 5 10 Favours no-treatment

Analysis 7.2. Comparison 7 Effect modification subgroup analysis: type of placebo interventions, Outcome 2 Physical placebos.

Study or subgroup	Placebo n/N	No-treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Alkaissi 1999	9/20	11/20		2.7%	0.82[0.44,1.53]
Alkaissi 2002	77/139	82/136		12.28%	0.92[0.75,1.12]
Aune 1998	11/26	9/14		2.95%	0.66[0.36,1.19]
Corver 2006	227/279	360/416		19.36%	0.94[0.88,1.01]
Dundee 1986	17/25	17/25		6%	1[0.68,1.46]
Faas 1993	107/162	108/155		14.98%	0.95[0.81,1.1]
Fanti 2003	8/10	9/10		6.18%	0.89[0.61,1.29]
McMillan 1994	14/26	24/46		4.65%	1.03[0.66,1.62]
Molsberger 2002	38/58	30/53		8.18%	1.16[0.86,1.56]
Scharf 2006	179/365	224/316		16.4%	0.69[0.61,0.78]
Tarcin 2004	58/158	27/77		6.32%	1.05[0.73,1.51]
Total (95% CI)	**1268**	**1268**		**100%**	**0.91[0.81,1.01]**
Total events: 745 (Placebo), 901 (No-treatment)					
Heterogeneity: Tau^2=0.02; Chi^2=24.73, df=10(P=0.01); I^2=59.57%					
Test for overall effect: Z=1.77(P=0.08)					

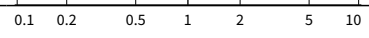
Favours placebo 0.1 0.2 0.5 1 2 5 10 Favours no-treatment

Analysis 7.3. Comparison 7 Effect modification subgroup analysis: type of placebo interventions, Outcome 3 Pharmacological placebos.

Study or subgroup	Placebo n/N	No-treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Adriaanse 1995	50/328	38/326		3.4%	1.31[0.88,1.94]
Berg 1983	9/11	9/15		2.29%	1.36[0.83,2.24]
Blackman 1964	6/12	6/12		0.97%	1[0.45,2.23]
De Sanctis 2001	9/10	8/9		4.87%	1.01[0.74,1.38]
Double 1993	3/22	3/22		0.29%	1[0.23,4.42]
Frank 1990	14/26	14/26		2.25%	1[0.6,1.65]
Harrison 1975	24/28	25/30		7.52%	1.03[0.83,1.28]
Heinzl 1981	70/130	92/132		8.54%	0.77[0.64,0.94]

Favours placebo 0.1 0.2 0.5 1 2 5 10 Favours no-treatment

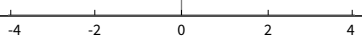
Study or subgroup	Placebo n/N	No-treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Hutton 1991	5/24	16/30		0.87%	0.39[0.17,0.91]
Jacobs 1971	9/15	12/39		1.53%	1.95[1.04,3.65]
Kerr 2003	28/33	32/36		8.99%	0.95[0.79,1.15]
Killen 1990	226/309	219/309		13.48%	1.03[0.94,1.14]
Klerman 1974	17/25	16/25		3.33%	1.06[0.71,1.58]
Malcolm 1980	40/63	44/58		6.91%	0.84[0.66,1.06]
Najnigier 1997	21/30	24/30		5.23%	0.88[0.65,1.17]
Rabkin 1990	14/27	12/23		2.03%	0.99[0.58,1.7]
Schallreuter 2002	3/10	4/10		0.44%	0.75[0.22,2.52]
Stransky 1989	1/5	1/4		0.11%	0.8[0.07,9.18]
Thomas 1987	47/100	50/100		5.45%	0.94[0.71,1.25]
Tyler 1946	89/260	106/303		7.23%	0.98[0.78,1.23]
Walton 1993	19/24	21/30		4.84%	1.13[0.83,1.54]
Watzl 1986	15/34	7/36		1.06%	2.27[1.06,4.88]
Whittaker 1963	3/13	7/13		0.52%	0.43[0.14,1.3]
Wilson 1980	31/40	10/10		7.84%	0.8[0.65,0.99]
Total (95% CI)	**1579**	**1628**		**100%**	**0.97[0.89,1.05]**
Total events: 753 (Placebo), 776 (No-treatment)					
Heterogeneity: Tau^2=0.01; Chi^2=33.64, df=23(P=0.07); I^2=31.63%					
Test for overall effect: Z=0.76(P=0.45)					



Favours placebo — Favours no-treatment

Analysis 7.4. Comparison 7 Effect modification subgroup analysis: type of placebo interventions, Outcome 4 Psychological placebos.

Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Abikoff 2004	35	-91.4 (18.9)	34	-89.5 (22.8)		3.14%	-0.09[-0.56,0.38]
Anderson 1999	30	-2.7 (0.8)	27	-2.7 (0.8)		2.71%	0.08[-0.44,0.6]
Ascher 1979	8	50.6 (44.1)	9	62.4 (25.3)		0.95%	-0.32[-1.28,0.64]
Blanchard 1990a	13	8.3 (13.6)	11	22.5 (25.1)		1.23%	-0.7[-1.53,0.13]
Blanchard 1990b	18	11.9 (23.9)	24	20.7 (34.8)		2.08%	-0.28[-0.9,0.33]
Block 1980	16	22.4 (6.6)	8	24.7 (9.2)		1.18%	-0.3[-1.15,0.56]
Bosley 1989	13	86 (10)	14	89 (10)		1.45%	-0.29[-1.05,0.47]
Bramston 1985	12	-78 (14.2)	12	-72 (13.8)		1.29%	-0.41[-1.22,0.4]
Canino 1994	4	99 (2.7)	9	95.6 (7.6)		0.63%	0.48[-0.72,1.67]
Cupal 2001	10	2.7 (1)	10	2.7 (1.3)		1.12%	0[-0.88,0.88]
Davidson 1980	10	1.8 (0.9)	10	2.9 (1.3)		1%	-0.94[-1.88,-0.01]
Ditto 2003	200	0.5 (0.4)	189	0.5 (0.4)		7.94%	-0.02[-0.22,0.17]
Ditto 2006	140	0.4 (0.4)	155	0.5 (0.4)		7.18%	-0.06[-0.28,0.17]
Espie 1989	14	63.5 (30.6)	13	96.5 (63.5)		1.39%	-0.65[-1.43,0.13]
Etringer 1982	13	-11.4 (4)	12	-10.1 (3.7)		1.35%	-0.33[-1.12,0.46]
Foster 2004	6	-3.6 (0.6)	12	-2.6 (1.1)		0.81%	-0.98[-2.02,0.06]
Frankel 1978	7	93 (5)	8	95 (3)		0.83%	-0.47[-1.5,0.57]
Fuchs 1977	10	14.3 (7)	10	21.4 (7)		0.99%	-0.97[-1.91,-0.03]
Hall 1974	23	-0.5 (7.8)	22	0.9 (7.8)		2.25%	-0.17[-0.76,0.41]
Hanson 1976	11	-0.9 (3.8)	10	-0.3 (2.2)		1.16%	-0.19[-1.05,0.67]
Hawkins 1995	10	37.4 (8.5)	10	52.1 (9.3)		0.83%	-1.58[-2.61,-0.55]

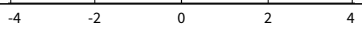


Favours placebo — Favours no-treatment

Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Hovell 2003	98	-155.4 (69.9)	96	-151 (73.8)		5.96%	-0.06[-0.34,0.22]
Irvin 1996	11	3.3 (0.7)	11	3.7 (1.4)		1.2%	-0.35[-1.19,0.5]
Jacobson 1978	7	2.5 (0.9)	6	3.5 (0.5)		0.61%	-1.17[-2.39,0.04]
Kendall 1979	11	7.5 (2.3)	11	8.2 (3)		1.21%	-0.23[-1.07,0.61]
Kilmann 1987	4	-33 (47)	4	-35 (47)		0.48%	0.04[-1.35,1.42]
Lick 1975	9	60.6 (32.7)	9	92.2 (22.1)		0.87%	-1.08[-2.09,-0.07]
Lick 1977	10	66 (25)	10	63 (32)		1.12%	0.1[-0.78,0.98]
Lincoln 2003	42	14.4 (10)	38	16.7 (10)		3.47%	-0.23[-0.67,0.21]
Liossi 2003	20	4.3 (0.6)	20	4.6 (0.6)		1.99%	-0.49[-1.12,0.14]
Longo 1988	10	3.6 (0.6)	9	3.6 (0.4)		1.07%	0[-0.9,0.9]
Markland 1993	7	37.3 (11.8)	7	36.9 (11.9)		0.81%	0.03[-1.01,1.08]
Moreland 2006	50	-2 (1.3)	99	-2.1 (1.7)		4.85%	0.06[-0.28,0.4]
Morey 2006	38	-16.5 (9.3)	42	-14.7 (9.5)		3.48%	-0.19[-0.63,0.25]
Murphy 1982	6	-16.5 (9.3)	11	-0.8 (6.4)		0.58%	-1.99[-3.24,-0.74]
Nicassio 1974	7	117.3 (133.7)	9	99.3 (35.3)		0.9%	0.19[-0.8,1.18]
Nocella 1982	10	0.8 (0.9)	10	0.8 (0.7)		1.12%	-0.02[-0.9,0.85]
Parker 1995	49	4 (1.9)	45	3.8 (2.2)		3.89%	0.1[-0.31,0.5]
Parker 2003	13	16.2 (7.5)	14	14.2 (7.5)		1.45%	0.26[-0.5,1.02]
Quahagen 1995	28	-108.3 (14.8)	25	-104.8 (13.9)		2.55%	-0.24[-0.78,0.3]
Reading 1982	18	1.6 (1.3)	20	2.3 (2)		1.92%	-0.4[-1.05,0.24]
Rosen 1976	9	6.9 (2)	5	8.3 (1.9)		0.7%	-0.67[-1.8,0.46]
Rybarczyk 1990	25	7.1 (2.2)	24	7.5 (2.8)		2.41%	-0.16[-0.73,0.4]
Seer 1980	14	92.5 (9.8)	13	104.5 (11)		1.26%	-1.12[-1.94,-0.3]
Senediak 1985	11	47.5 (8.4)	10	47.9 (7.5)		1.17%	-0.04[-0.9,0.81]
Sipich 1974	10	8 (14)	10	32.5 (14)		0.8%	-1.68[-2.73,-0.63]
Spanos 1995	13	21.4 (9.7)	12	19.1 (10.3)		1.36%	0.22[-0.56,1.01]
Stewart 1991	25	-14.3 (5.5)	25	-12.8 (5.2)		2.43%	-0.28[-0.83,0.28]
Tan 1982	12	1.3 (0.6)	12	1.7 (0.8)		1.27%	-0.55[-1.36,0.27]
Thomas 1999	14	13.4 (10.3)	26	16.5 (9.7)		1.87%	-0.31[-0.96,0.35]
Turner 1979	10	44.2 (41.3)	10	59.8 (22.9)		1.09%	-0.45[-1.34,0.44]
Vlaeyen 1996	39	0.4 (1.8)	40	0.4 (1.8)		3.46%	0[-0.44,0.44]
Wojciechowski 1984	9	264 (122)	12	238 (190)		1.15%	0.15[-0.71,1.02]
Total ***	**1242**		**1304**			**100%**	**-0.22[-0.31,-0.12]**

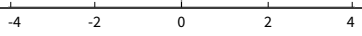
Heterogeneity: Tau^2=0.02; Chi^2=64.12, df=52(P=0.12); I^2=18.9%

Test for overall effect: Z=4.36(P<0.0001)

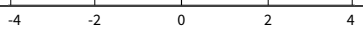


Analysis 7.5. Comparison 7 Effect modification subgroup analysis: type of placebo interventions, Outcome 5 Physical placebos.

Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Alfano 2001	24	6.2 (2.8)	14	6.6 (2.7)		1.34%	-0.14[-0.8,0.52]
Allen 1998	11	-2.9 (7.9)	11	-6.1 (10.9)		0.94%	0.32[-0.52,1.17]
Allen 2006	45	12 (9.6)	44	19 (9.6)		2.2%	-0.72[-1.15,-0.29]
Benedetti 1997	106	0.3 (0.1)	115	0.3 (0.1)		3.12%	-0.17[-0.43,0.1]

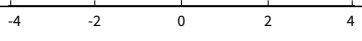


Study or subgroup	Placebo		No-treatment		Std. Mean Difference	Weight	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
Brinkhaus 2006	70	-23.6 (31)	74	-6.9 (22)		2.71%	-0.62[-0.96,-0.29]
Cabrini 2006	16	61.7 (24)	16	66.6 (28)		1.25%	-0.18[-0.88,0.51]
Chenard 1991	12	29 (19)	16	30 (19)		1.12%	-0.05[-0.8,0.7]
Conn 1986	13	28.2 (18.4)	14	44.4 (15.7)		1.01%	-0.92[-1.72,-0.12]
Coyne 1995	21	0.7 (0.7)	21	0.6 (0.7)		1.5%	0.13[-0.47,0.74]
Defrin 2005	9	7.3 (0.8)	8	7.6 (0.7)		0.76%	-0.39[-1.35,0.58]
Dibble 2007	49	3.1 (2.9)	51	3.5 (3.1)		2.39%	-0.12[-0.51,0.27]
Erdogmus 2007	40	-27.4 (19.7)	40	-20.3 (19.7)		2.14%	-0.36[-0.8,0.08]
Forster 1994	15	3.2 (2.8)	15	4.6 (2.2)		1.16%	-0.54[-1.27,0.19]
Foster 2007	112	6.5 (4.8)	105	6.8 (4.5)		3.11%	-0.06[-0.33,0.21]
Hargreaves 1989	25	4.5 (2.5)	25	4.9 (2.4)		1.67%	-0.16[-0.72,0.39]
Hashish 1986	25	16 (11.7)	50	30 (18.9)		1.89%	-0.82[-1.32,-0.32]
Hashish 1988	25	42 (25)	25	60 (23)		1.6%	-0.74[-1.31,-0.16]
Helms 1987	11	103 (91)	11	79 (99)		0.94%	0.24[-0.6,1.08]
Hong 1993	16	-1.1 (0.2)	21	-1 (0.1)		1.33%	-0.53[-1.19,0.13]
Hruby 2006	49	1.2 (2.1)	51	0.9 (1.5)		2.39%	0.21[-0.19,0.6]
Hyland 2006	10	6 (0.9)	10	6.2 (0.9)		0.88%	-0.21[-1.09,0.67]
Kaptchuk 2008	88	-4.3 (1.4)	87	-3.8 (1)		2.91%	-0.41[-0.71,-0.11]
Karst 2007	19	45.2 (10.8)	10	56.5 (9.1)		0.98%	-1.07[-1.89,-0.25]
Kober 2002	20	66.7 (10)	21	64.4 (13.3)		1.47%	0.19[-0.42,0.8]
Kokol 2005	16	9.5 (10.5)	10	7.3 (6.6)		1.03%	0.23[-0.56,1.02]
Kotani 2001	23	15 (4.5)	24	18 (6)		1.57%	-0.55[-1.14,0.03]
Lander 1993	172	28.5 (29.3)	168	32.3 (33.4)		3.43%	-0.12[-0.33,0.09]
Leibing 2002	40	3.2 (1.8)	39	4.3 (1.9)		2.1%	-0.59[-1.04,-0.14]
Licciardone 2003	19	2.5 (1.7)	15	3.5 (2.7)		1.26%	-0.49[-1.17,0.2]
Limoges 2004	30	2.3 (1)	30	2.2 (1)		1.86%	0.04[-0.47,0.55]
Lin 2002	25	30.2 (14.4)	25	38.1 (16)		1.64%	-0.51[-1.07,0.05]
Linde 2005	76	-2.2 (2.7)	64	-0.8 (2.2)		2.68%	-0.56[-0.9,-0.22]
Matros 2006	23	76 (36.3)	21	72 (28.3)		1.54%	0.12[-0.47,0.71]
Medici 2002	23	-0.2 (0.3)	18	-0.1 (0.3)		1.45%	-0.31[-0.93,0.32]
Melchart 2005	57	10.8 (8.3)	63	16.3 (7.4)		2.51%	-0.7[-1.07,-0.33]
Moffet 1996	22	24 (18.6)	27	34.6 (23.2)		1.61%	-0.49[-1.06,0.08]
Morton 1993	13	22.1 (16.4)	13	24.5 (16.4)		1.07%	-0.14[-0.91,0.63]
Nawrocki 1997	40	9.5 (6)	42	17 (4.8)		1.95%	-1.37[-1.85,-0.89]
O'Brien 1996	53	6.7 (5.6)	54	7.5 (5.1)		2.46%	-0.15[-0.53,0.23]
Robinson 2001	13	3.9 (3.5)	10	4.3 (3.7)		0.97%	-0.11[-0.93,0.72]
Roscoe 2002	27	5.9 (5.2)	27	6.6 (3.6)		1.75%	-0.15[-0.69,0.38]
Roscoe 2005	31	2.4 (1.3)	33	2.8 (1.3)		1.91%	-0.3[-0.8,0.19]
Röschke 2000	24	23 (16.2)	24	26 (16)		1.63%	-0.18[-0.75,0.38]
Rösler 2003	13	5.9 (3.4)	14	6 (3)		1.11%	-0.02[-0.78,0.73]
Sanders 1990	6	2 (0.4)	6	2.1 (0.3)		0.58%	-0.13[-1.26,1]
Shen 2000	33	40.7 (12.4)	34	43.7 (11.3)		1.97%	-0.25[-0.73,0.23]
Sprott 1993	10	7.9 (3)	10	7.4 (3)		0.88%	0.16[-0.72,1.04]
Stabholz 1991	10	1.4 (0.5)	10	1.8 (0.6)		0.83%	-0.69[-1.6,0.22]
Straub 2001	5	-5.8 (0.3)	5	-6 (0.7)		0.49%	0.27[-0.98,1.52]
Sumaya 2001	10	15.4 (2.7)	10	14.9 (1.8)		0.88%	0.21[-0.67,1.09]
Theroux 1993	17	3.2 (0.7)	15	2.9 (0.6)		1.22%	0.48[-0.22,1.19]
Tremeau 1992	39	-0.9 (1.3)	25	-1.1 (1.4)		1.87%	0.14[-0.36,0.65]
Tritrakarn 2000	41	49 (16)	41	61 (17)		2.12%	-0.72[-1.17,-0.27]
Tsay 2003	32	9.2 (4.4)	32	9.6 (4)		1.93%	-0.08[-0.57,0.41]
Tsay 2004	35	4.7 (1.5)	36	5.7 (1.8)		1.99%	-0.6[-1.07,-0.12]
Wang 1997	25	10.7 (7.3)	26	13.4 (5.8)		1.67%	-0.4[-0.96,0.15]



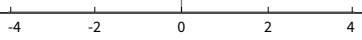
Favours placebo Favours no-treatment

Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Weingaertner 1971	15	1.1 (1.3)	15	1.2 (1.6)		1.19%	-0.1[-0.81,0.62]
Werntoft 2001	20	5.9 (2.4)	20	6.5 (2.2)		1.45%	-0.26[-0.88,0.37]
Witt 2005	73	35.8 (16.2)	67	49.6 (16.3)		2.64%	-0.84[-1.19,-0.5]
Woods 2005	19	1.2 (1.3)	19	1.5 (1.1)		1.4%	-0.2[-0.83,0.44]
Yates 1988	7	-1.4 (2.5)	7	0.7 (1.4)		0.58%	-0.97[-2.1,0.16]
Total ***	**1968**		**1954**			**100%**	**-0.31[-0.41,-0.22]**
Heterogeneity: Tau²=0.05; Chi²=108.97, df=60(P=0); I²=44.94%							
Test for overall effect: Z=6.64(P<0.0001)							

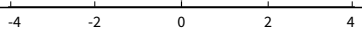


Analysis 7.6. Comparison 7 Effect modification subgroup analysis: type of placebo interventions, Outcome 6 Pharmacological placebos.

Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Andersen 1990	18	35 (27.2)	16	25 (23.6)		1.47%	0.38[-0.3,1.06]
Antivalle 1990	11	-1.6 (5.6)	10	-3.9 (7.3)		1%	0.34[-0.52,1.21]
Antonio 1999	6	79.7 (12.2)	6	72.6 (11.2)		0.59%	0.56[-0.6,1.72]
Asmar 1996	34	-0.2 (7.7)	34	0.7 (6.5)		2.44%	-0.12[-0.6,0.35]
Benedetti 1995	13	-2 (1.2)	11	-0.8 (1)		0.99%	-1.07[-1.94,-0.2]
Biro 1997	29	3.6 (2.5)	29	3.3 (2.1)		2.2%	0.13[-0.39,0.64]
Blades 2001	40	-16 (6)	40	-16 (6)		2.69%	0[-0.44,0.44]
Bova 1999	34	3.8 (2.2)	36	4.1 (2.3)		2.48%	-0.14[-0.61,0.33]
Carbajal 1999	25	7.2 (2.8)	25	6.9 (2.6)		1.99%	0.1[-0.45,0.66]
Classen 1983	15	11.3 (8.3)	15	14.4 (6.1)		1.33%	-0.41[-1.14,0.31]
Colker 1999	7	82.7 (18)	4	77.7 (10.5)		0.53%	0.29[-0.95,1.53]
Costello 2006	48	33 (25)	42	31 (25)		2.88%	0.08[-0.33,0.49]
Crosby 1994	26	13.6 (1.3)	33	13.5 (1.3)		2.21%	0.08[-0.44,0.59]
Etter 2002	269	20.6 (10)	389	25.4 (12.6)		5.54%	-0.41[-0.57,-0.26]
Fisher 2006	12	3.8 (1.9)	15	4.1 (2.5)		1.23%	-0.13[-0.89,0.63]
Frega 1994	21	20 (16)	21	23 (16)		1.75%	-0.18[-0.79,0.42]
Godfrey 1973	44	34.9 (16.7)	44	46.9 (16.2)		2.74%	-0.72[-1.15,-0.29]
Goodenough 1997	39	1.1 (1.6)	39	1.6 (1.9)		2.64%	-0.28[-0.73,0.16]
Gracely 1983	17	-2.9 (5.4)	12	0.2 (5.5)		1.25%	-0.54[-1.3,0.21]
GRECHO 1989	150	94.4 (40.7)	150	95.4 (33)		4.75%	-0.03[-0.25,0.2]
Hossmann 1981	12	94.2 (4.8)	12	95.1 (4.8)		1.13%	-0.18[-0.98,0.62]
Karunakaran 1997	58	6.2 (1.2)	57	5.9 (0.6)		3.26%	0.31[-0.05,0.68]
Killeen 2004	24	1 (2.5)	35	1.9 (3.5)		2.16%	-0.28[-0.81,0.24]
Lee 2005	27	-21.4 (25.9)	27	-5.9 (9.2)		1.99%	-0.79[-1.34,-0.23]
Levine 1984	12	-0.3 (0.7)	24	0.4 (2.5)		1.42%	-0.31[-1.01,0.38]
Lindholm 1996	227	6.8 (0.5)	226	6.8 (0.5)		5.23%	0.15[-0.04,0.33]
Lorr 1961	42	58.3 (9.9)	38	57.5 (9.9)		2.69%	0.08[-0.36,0.52]
Macaluso 1995	30	-3.3 (3.8)	30	-1.8 (3.3)		2.22%	-0.41[-0.93,0.1]
May 1988	24	-1.2 (0.5)	24	-1.2 (0.5)		1.93%	-0.02[-0.59,0.54]
McLachlan 1991	8	6.3 (12.3)	12	5.7 (17.4)		0.94%	0.04[-0.86,0.93]
Nandi 1976	10	53.2 (11.2)	8	57.5 (13.8)		0.87%	-0.33[-1.27,0.61]
Pelham 1992	38	-8.7 (1.7)	38	-8.5 (1.6)		2.61%	-0.12[-0.57,0.33]
Rawling 2001	89	5.3 (4.7)	96	5.6 (4.9)		4.05%	-0.06[-0.35,0.23]



Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Ristikankare 1999	61	40.3 (21.5)	61	36 (21.5)		3.37%	0.2[-0.16,0.55]
Roongpisuthip 1999	18	-3.3 (4.2)	19	-2.9 (3.1)		1.6%	-0.11[-0.75,0.54]
Rossi 1982	6	107 (17)	6	108 (20)		0.62%	-0.05[-1.18,1.08]
Rowbotham 1996	35	-4.4 (8.7)	35	1.9 (8.7)		2.38%	-0.72[-1.2,-0.23]
Sinaiko 1991	60	66.5 (9.7)	27	64.1 (13.9)		2.57%	0.21[-0.24,0.67]
Steinsbekk 2004	102	44.5 (58.9)	74	53 (45.2)		3.93%	-0.16[-0.46,0.14]
Tashjian 2006	19	3.4 (2.2)	24	3.3 (1.8)		1.77%	0.05[-0.55,0.65]
Thomas 2002a	78	-0.9 (3)	78	-0.1 (2.9)		3.77%	-0.27[-0.59,0.04]
Thomas 2002b	114	-1.2 (3.5)	119	-1.6 (3.3)		4.39%	0.12[-0.14,0.37]
Tuomilehto 1980	11	9 (1.4)	11	8.7 (1.6)		1.05%	0.24[-0.6,1.08]
Wilcock 2008	15	-6.4 (5.1)	15	-6.7 (5.9)		1.36%	0.05[-0.66,0.77]
Total * **	**1978**		**2067**			**100%**	**-0.1[-0.2,-0.01]**
Heterogeneity: Tau^2=0.03; Chi^2=75.3, df=43(P=0); I^2=42.89%							
Test for overall effect: Z=2.16(P=0.03)							



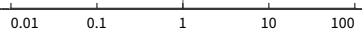
Favours Placebo — Favours no-treatment

Comparison 8. Effect modification subgroup analysis: patient information

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Binary outcomes: patients not informed that the trial involved placebo	7	1085	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.83, 1.12]
2 Binary outcomes: patients informed that the trial involved placebo (or not stated)	37	4956	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.87, 0.99]
3 Continuous outcomes: patients not informed that the trial involved placebo	23	1692	Std. Mean Difference (IV, Random, 95% CI)	-0.39 [-0.53, -0.26]
4 Continuous outcomes: patients informed that the trial involved placebo (or not stated)	135	8821	Std. Mean Difference (IV, Random, 95% CI)	-0.19 [-0.25, -0.13]

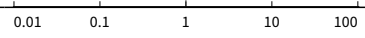
Analysis 8.1. Comparison 8 Effect modification subgroup analysis: patient information, Outcome 1 Binary outcomes: patients not informed that the trial involved placebo.

Study or subgroup	Placebo n/N	No-treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Carter 2003	13/28	20/29		8.54%	0.67[0.42,1.07]
Guglielmi 1982	12/12	11/12		21.82%	1.09[0.87,1.36]
Malcolm 1980	40/63	44/58		20.71%	0.84[0.66,1.06]
Rabkin 1990	14/27	12/23		6.86%	0.99[0.58,1.7]
Thomas 1987	47/100	50/100		16.9%	0.94[0.71,1.25]
Tyler 1946	89/260	106/303		21.51%	0.98[0.78,1.23]
Watzl 1986	15/34	7/36		3.66%	2.27[1.06,4.88]



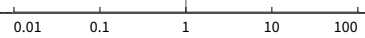
Favours placebo — Favours no-treatment

Study or subgroup	Placebo n/N	No-treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total (95% CI)	**524**	**561**		**100%**	**0.96[0.83,1.12]**
Total events: 230 (Placebo), 250 (No-treatment)					
Heterogeneity: Tau^2=0.01; Chi^2=9.6, df=6(P=0.14); I^2=37.53%					
Test for overall effect: Z=0.49(P=0.63)					

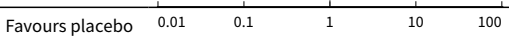


Analysis 8.2. Comparison 8 Effect modification subgroup analysis: patient information, Outcome 2 Binary outcomes: patients informed that the trial involved placebo (or not stated).

Study or subgroup	Placebo n/N	No-treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Adriaanse 1995	50/328	38/326		1.99%	1.31[0.88,1.94]
Alkaissi 1999	9/20	11/20		0.92%	0.82[0.44,1.53]
Alkaissi 2002	77/139	82/136		4.5%	0.92[0.75,1.12]
Aune 1998	11/26	9/14		1.01%	0.66[0.36,1.19]
Berg 1983	9/11	9/15		1.36%	1.36[0.83,2.24]
Blackman 1964	6/12	6/12		0.59%	1[0.45,2.23]
Corver 2006	227/279	360/416		7.53%	0.94[0.88,1.01]
De Sanctis 2001	9/10	8/9		2.79%	1.01[0.74,1.38]
Double 1993	3/22	3/22		0.18%	1[0.23,4.42]
Dundee 1986	17/25	17/25		2.09%	1[0.68,1.46]
Elliott 1978	6/18	6/6		0.84%	0.37[0.19,0.71]
Faas 1993	107/162	108/155		5.61%	0.95[0.81,1.1]
Fanti 2003	8/10	9/10		2.16%	0.89[0.61,1.29]
Frank 1990	14/26	14/26		1.34%	1[0.6,1.65]
Harrison 1975	24/28	25/30		4.15%	1.03[0.83,1.28]
Heinzl 1981	70/130	92/132		4.65%	0.77[0.64,0.94]
Hutton 1991	5/24	16/30		0.53%	0.39[0.17,0.91]
Hyman 1986	9/15	15/15		1.83%	0.61[0.4,0.93]
Jacobs 1971	9/15	12/39		0.92%	1.95[1.04,3.65]
Kerr 2003	28/33	32/36		4.86%	0.95[0.79,1.15]
Killen 1990	226/309	219/309		6.88%	1.03[0.94,1.14]
Klerman 1974	17/25	16/25		1.95%	1.06[0.71,1.58]
McMillan 1994	14/26	24/46		1.61%	1.03[0.66,1.62]
Molsberger 2002	38/58	30/53		2.9%	1.16[0.86,1.56]
Najnigier 1997	21/30	24/30		2.98%	0.88[0.65,1.17]
Roughan 1981	9/12	9/14		1.32%	1.17[0.7,1.94]
Schallreuter 2002	3/10	4/10		0.27%	0.75[0.22,2.52]
Scharf 2006	179/365	224/316		6.22%	0.69[0.61,0.78]
Scharff 2002	11/12	12/12		4.07%	0.92[0.74,1.15]
Stransky 1989	1/5	1/4		0.07%	0.8[0.07,9.18]
Tan 1986	8/10	8/9		2.04%	0.9[0.61,1.32]
Tarcin 2004	58/158	27/77		2.21%	1.05[0.73,1.51]
Tarrier 1998	22/26	25/28		4.38%	0.95[0.77,1.17]
Walton 1993	19/24	21/30		2.77%	1.13[0.83,1.54]
Whittaker 1963	3/13	7/13		0.32%	0.43[0.14,1.3]
Williams 1988	19/20	19/20		5.84%	1[0.87,1.15]
Wilson 1980	31/40	10/10		4.31%	0.8[0.65,0.99]

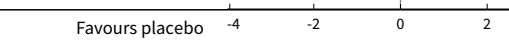


Study or subgroup	Placebo n/N	No-treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total (95% CI)	**2476**	**2480**		**100%**	**0.93[0.87,0.99]**
Total events: 1377 (Placebo), 1552 (No-treatment)					
Heterogeneity: Tau^2=0.01; Chi^2=69.12, df=36(P=0); I^2=47.92%					
Test for overall effect: Z=2.24(P=0.03)					



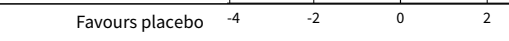
Analysis 8.3. Comparison 8 Effect modification subgroup analysis: patient information, Outcome 3 Continuous outcomes: patients not informed that the trial involved placebo.

Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Allen 2006	45	12 (9.6)	44	19 (9.6)		5.25%	-0.72[-1.15,-0.29]
Antivalle 1990	11	-1.6 (5.6)	10	-3.9 (7.3)		2.03%	0.34[-0.52,1.21]
Asmar 1996	34	-0.2 (7.7)	34	0.7 (6.5)		4.7%	-0.12[-0.6,0.35]
Brinkhaus 2006	70	-23.6 (31)	74	-6.9 (22)		6.6%	-0.62[-0.96,-0.29]
Etringer 1982	13	-11.4 (4)	12	-10.1 (3.7)		2.34%	-0.33[-1.12,0.46]
Foster 2007	112	6.5 (4.8)	105	6.8 (4.5)		7.73%	-0.06[-0.33,0.21]
Godfrey 1973	44	34.9 (16.7)	44	46.9 (16.2)		5.22%	-0.72[-1.15,-0.29]
Goodenough 1997	39	1.1 (1.6)	39	1.6 (1.9)		5.05%	-0.28[-0.73,0.16]
Hall 1974	23	-0.5 (7.8)	22	0.9 (7.8)		3.63%	-0.17[-0.76,0.41]
Hanson 1976	11	-0.9 (3.8)	10	-0.3 (2.2)		2.05%	-0.19[-1.05,0.67]
Hossmann 1981	12	94.2 (4.8)	12	95.1 (4.8)		2.29%	-0.18[-0.98,0.62]
Karst 2007	19	45.2 (10.8)	10	56.5 (9.1)		2.21%	-1.07[-1.89,-0.25]
Lee 2005	27	-21.4 (25.9)	27	-5.9 (9.2)		3.89%	-0.79[-1.34,-0.23]
Licciardone 2003	19	2.5 (1.7)	15	3.5 (2.7)		2.89%	-0.49[-1.17,0.2]
Lick 1977	10	66 (25)	10	63 (32)		1.98%	0.1[-0.78,0.98]
Linde 2005	76	-2.2 (2.7)	64	-0.8 (2.2)		6.53%	-0.56[-0.9,-0.22]
Melchart 2005	57	10.8 (8.3)	63	16.3 (7.4)		6.08%	-0.7[-1.07,-0.33]
Pelham 1992	38	-8.7 (1.7)	38	-8.5 (1.6)		5%	-0.12[-0.57,0.33]
Roscoe 2005	31	2.4 (1.3)	33	2.8 (1.3)		4.51%	-0.3[-0.8,0.19]
Rybarczyk 1990	25	7.1 (2.2)	24	7.5 (2.8)		3.84%	-0.16[-0.73,0.4]
Shen 2000	33	40.7 (12.4)	34	43.7 (11.3)		4.64%	-0.25[-0.73,0.23]
Vlaeyen 1996	39	0.4 (1.8)	40	0.4 (1.8)		5.11%	0[-0.44,0.44]
Witt 2005	73	35.8 (16.2)	67	49.6 (16.3)		6.42%	-0.84[-1.19,-0.5]
Total ***	**861**		**831**			**100%**	**-0.39[-0.53,-0.26]**
Heterogeneity: Tau^2=0.04; Chi^2=38.91, df=22(P=0.01); I^2=43.46%							
Test for overall effect: Z=5.66(P<0.0001)							

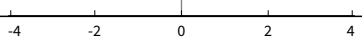


Analysis 8.4. Comparison 8 Effect modification subgroup analysis: patient information, Outcome 4 Continuous outcomes: patients informed that the trial involved placebo (or not stated).

Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Abikoff 2004	35	-91.4 (18.9)	34	-89.5 (22.8)		0.99%	-0.09[-0.56,0.38]
Alfano 2001	24	6.2 (2.8)	14	6.6 (2.7)		0.62%	-0.14[-0.8,0.52]



Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Allen 1998	11	-2.9 (7.9)	11	-6.1 (10.9)		0.42%	0.32[-0.52,1.17]
Andersen 1990	18	35 (27.2)	16	25 (23.6)		0.6%	0.38[-0.3,1.06]
Anderson 1999	30	-2.7 (0.8)	27	-2.7 (0.8)		0.87%	0.08[-0.44,0.6]
Antonio 1999	6	79.7 (12.2)	6	72.6 (11.2)		0.24%	0.56[-0.6,1.72]
Ascher 1979	8	50.6 (44.1)	9	62.4 (25.3)		0.34%	-0.32[-1.28,0.64]
Benedetti 1995	13	-2 (1.2)	11	-0.8 (1)		0.4%	-1.07[-1.94,-0.2]
Benedetti 1997	106	0.3 (0.1)	115	0.3 (0.1)		1.71%	-0.17[-0.43,0.1]
Biro 1997	29	3.6 (2.5)	29	3.3 (2.1)		0.88%	0.13[-0.39,0.64]
Blades 2001	40	-16 (6)	40	-16 (6)		1.08%	0[-0.44,0.44]
Blanchard 1990a	13	8.3 (13.6)	11	22.5 (25.1)		0.43%	-0.7[-1.53,0.13]
Blanchard 1990b	18	11.9 (23.9)	24	20.7 (34.8)		0.69%	-0.28[-0.9,0.33]
Block 1980	16	22.4 (6.6)	8	24.7 (9.2)		0.41%	-0.3[-1.15,0.56]
Bosley 1989	13	86 (10)	14	89 (10)		0.5%	-0.29[-1.05,0.47]
Bova 1999	34	3.8 (2.2)	36	4.1 (2.3)		1%	-0.14[-0.61,0.33]
Bramston 1985	12	-78 (14.2)	12	-72 (13.8)		0.45%	-0.41[-1.22,0.4]
Cabrini 2006	16	61.7 (24)	16	66.6 (28)		0.58%	-0.18[-0.88,0.51]
Canino 1994	4	99 (2.7)	9	95.6 (7.6)		0.23%	0.48[-0.72,1.67]
Carbajal 1999	25	7.2 (2.8)	25	6.9 (2.6)		0.8%	0.1[-0.45,0.66]
Chenard 1991	12	29 (19)	16	30 (19)		0.51%	-0.05[-0.8,0.7]
Classen 1983	15	11.3 (8.3)	15	14.4 (6.1)		0.54%	-0.41[-1.14,0.31]
Colker 1999	7	82.7 (18)	4	77.7 (10.5)		0.21%	0.29[-0.95,1.53]
Conn 1986	13	28.2 (18.4)	14	44.4 (15.7)		0.46%	-0.92[-1.72,-0.12]
Costello 2006	48	33 (25)	42	31 (25)		1.15%	0.08[-0.33,0.49]
Coyne 1995	21	0.7 (0.7)	21	0.6 (0.7)		0.71%	0.13[-0.47,0.74]
Crosby 1994	26	13.6 (1.3)	33	13.5 (1.3)		0.89%	0.08[-0.44,0.59]
Cupal 2001	10	2.7 (1)	10	2.7 (1.3)		0.39%	0[-0.88,0.88]
Davidson 1980	10	1.8 (0.9)	10	2.9 (1.3)		0.35%	-0.94[-1.88,-0.01]
Defrin 2005	9	7.3 (0.8)	8	7.6 (0.7)		0.34%	-0.39[-1.35,0.58]
Dibble 2007	49	3.1 (2.9)	51	3.5 (3.1)		1.22%	-0.12[-0.51,0.27]
Ditto 2003	200	0.5 (0.4)	189	0.5 (0.4)		2%	-0.02[-0.22,0.17]
Ditto 2006	140	0.4 (0.4)	155	0.5 (0.4)		1.86%	-0.06[-0.28,0.17]
Erdogmus 2007	40	-27.4 (19.7)	40	-20.3 (19.7)		1.07%	-0.36[-0.8,0.08]
Espie 1989	14	63.5 (30.6)	13	96.5 (63.5)		0.48%	-0.65[-1.43,0.13]
Etter 2002	269	20.6 (10)	389	25.4 (12.6)		2.18%	-0.41[-0.57,-0.26]
Fisher 2006	12	3.8 (1.9)	15	4.1 (2.5)		0.5%	-0.13[-0.89,0.63]
Forster 1994	15	3.2 (2.8)	15	4.6 (2.2)		0.53%	-0.54[-1.27,0.19]
Foster 2004	6	-3.6 (0.6)	12	-2.6 (1.1)		0.29%	-0.98[-2.02,0.06]
Frankel 1978	7	93 (5)	8	95 (3)		0.3%	-0.47[-1.5,0.57]
Frega 1994	21	20 (16)	21	23 (16)		0.71%	-0.18[-0.79,0.42]
Fuchs 1977	10	14.3 (7)	10	21.4 (7)		0.35%	-0.97[-1.91,-0.03]
Gracely 1983	17	-2.9 (5.4)	12	0.2 (5.5)		0.51%	-0.54[-1.3,0.21]
GRECHO 1989	150	94.4 (40.7)	150	95.4 (33)		1.87%	-0.03[-0.25,0.2]
Hargreaves 1989	25	4.5 (2.5)	25	4.9 (2.4)		0.8%	-0.16[-0.72,0.39]
Hashish 1986	25	16 (11.7)	50	30 (18.9)		0.92%	-0.82[-1.32,-0.32]
Hashish 1988	25	42 (25)	25	60 (23)		0.76%	-0.74[-1.31,-0.16]
Hawkins 1995	10	37.4 (8.5)	10	52.1 (9.3)		0.3%	-1.58[-2.61,-0.55]
Helms 1987	11	103 (91)	11	79 (99)		0.42%	0.24[-0.6,1.08]
Hong 1993	16	-1.1 (0.2)	21	-1 (0.1)		0.62%	-0.53[-1.19,0.13]
Hovell 2003	98	-155.4 (69.9)	96	-151 (73.8)		1.64%	-0.06[-0.34,0.22]
Hruby 2006	49	1.2 (2.1)	51	0.9 (1.5)		1.22%	0.21[-0.19,0.6]
Hyland 2006	10	6 (0.9)	10	6.2 (0.9)		0.39%	-0.21[-1.09,0.67]



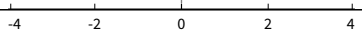
Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Irvin 1996	11	3.3 (0.7)	11	3.7 (1.4)		0.42%	-0.35[-1.19,0.5]
Jacobson 1978	7	2.5 (0.9)	6	3.5 (0.5)		0.22%	-1.17[-2.39,0.04]
Kaptchuk 2008	88	-4.3 (1.4)	87	-3.8 (1)		1.56%	-0.41[-0.71,-0.11]
Karunakaran 1997	58	6.2 (1.2)	57	5.9 (0.6)		1.3%	0.31[-0.05,0.68]
Kendall 1979	11	7.5 (2.3)	11	8.2 (3)		0.43%	-0.23[-1.07,0.61]
Killeen 2004	24	1 (2.5)	35	1.9 (3.5)		0.87%	-0.28[-0.81,0.24]
Kilmann 1987	4	-33 (47)	4	-35 (47)		0.17%	0.04[-1.35,1.42]
Kober 2002	20	66.7 (10)	21	64.4 (13.3)		0.69%	0.19[-0.42,0.8]
Kokol 2005	16	9.5 (10.5)	10	7.3 (6.6)		0.47%	0.23[-0.56,1.02]
Kotani 2001	23	15 (4.5)	24	18 (6)		0.75%	-0.55[-1.14,0.03]
Lander 1993	172	28.5 (29.3)	168	32.3 (33.4)		1.93%	-0.12[-0.33,0.09]
Leibing 2002	40	3.2 (1.8)	39	4.3 (1.9)		1.04%	-0.59[-1.04,-0.14]
Levine 1984	12	-0.3 (0.7)	24	0.4 (2.5)		0.57%	-0.31[-1.01,0.38]
Lick 1975	9	60.6 (32.7)	9	92.2 (22.1)		0.31%	-1.08[-2.09,-0.07]
Limoges 2004	30	2.3 (1)	30	2.2 (1)		0.91%	0.04[-0.47,0.55]
Lin 2002	25	30.2 (14.4)	25	38.1 (16)		0.78%	-0.51[-1.07,0.05]
Lincoln 2003	42	14.4 (10)	38	16.7 (10)		1.07%	-0.23[-0.67,0.21]
Lindholm 1996	227	6.8 (0.5)	226	6.8 (0.5)		2.06%	0.15[-0.04,0.33]
Liossi 2003	20	4.3 (0.6)	20	4.6 (0.6)		0.67%	-0.49[-1.12,0.14]
Longo 1988	10	3.6 (0.6)	9	3.6 (0.4)		0.38%	0[-0.9,0.9]
Lorr 1961	42	58.3 (9.9)	38	57.5 (9.9)		1.08%	0.08[-0.36,0.52]
Macaluso 1995	30	-3.3 (3.8)	30	-1.8 (3.3)		0.89%	-0.41[-0.93,0.1]
Markland 1993	7	37.3 (11.8)	7	36.9 (11.9)		0.29%	0.03[-1.01,1.08]
Matros 2006	23	76 (36.3)	21	72 (28.3)		0.73%	0.12[-0.47,0.71]
May 1988	24	-1.2 (0.5)	24	-1.2 (0.5)		0.78%	-0.02[-0.59,0.54]
McLachlan 1991	8	6.3 (12.3)	12	5.7 (17.4)		0.38%	0.04[-0.86,0.93]
Medici 2002	23	-0.2 (0.3)	18	-0.1 (0.3)		0.68%	-0.31[-0.93,0.32]
Moffet 1996	22	24 (18.6)	27	34.6 (23.2)		0.77%	-0.49[-1.06,0.08]
Moreland 2006	50	-2 (1.3)	99	-2.1 (1.7)		1.4%	0.06[-0.28,0.4]
Morey 2006	38	-16.5 (9.3)	42	-14.7 (9.5)		1.08%	-0.19[-0.63,0.25]
Morton 1993	13	22.1 (16.4)	13	24.5 (16.4)		0.49%	-0.14[-0.91,0.63]
Murphy 1982	6	-16.5 (9.3)	11	-0.8 (6.4)		0.21%	-1.99[-3.24,-0.74]
Nandi 1976	10	53.2 (11.2)	8	57.5 (13.8)		0.35%	-0.33[-1.27,0.61]
Nawrocki 1997	40	9.5 (6)	42	17 (4.8)		0.96%	-1.37[-1.85,-0.89]
Nicassio 1974	7	117.3 (133.7)	9	99.3 (35.3)		0.32%	0.19[-0.8,1.18]
Nocella 1982	10	0.8 (0.9)	10	0.8 (0.7)		0.39%	-0.02[-0.9,0.85]
O'Brien 1996	53	6.7 (5.6)	54	7.5 (5.1)		1.26%	-0.15[-0.53,0.23]
Parker 1995	49	4 (1.9)	45	3.8 (2.2)		1.18%	0.1[-0.31,0.5]
Parker 2003	13	16.2 (7.5)	14	14.2 (7.5)		0.5%	0.26[-0.5,1.02]
Quahagen 1995	28	-108.3 (14.8)	25	-104.8 (13.9)		0.83%	-0.24[-0.78,0.3]
Rawling 2001	89	5.3 (4.7)	96	5.6 (4.9)		1.61%	-0.06[-0.35,0.23]
Reading 1982	18	1.6 (1.3)	20	2.3 (2)		0.65%	-0.4[-1.05,0.24]
Ristikankare 1999	61	40.3 (21.5)	61	36 (21.5)		1.35%	0.2[-0.16,0.55]
Robinson 2001	13	3.9 (3.5)	10	4.3 (3.7)		0.44%	-0.11[-0.93,0.72]
Roongpisuthip 1999	18	-3.3 (4.2)	19	-2.9 (3.1)		0.64%	-0.11[-0.75,0.54]
Roscoe 2002	27	5.9 (5.2)	27	6.6 (3.6)		0.84%	-0.15[-0.69,0.38]
Rosen 1976	9	6.9 (2)	5	8.3 (1.9)		0.25%	-0.67[-1.8,0.46]
Rossi 1982	6	107 (17)	6	108 (20)		0.25%	-0.05[-1.18,1.08]
Rowbotham 1996	35	-4.4 (8.7)	35	1.9 (8.7)		0.96%	-0.72[-1.2,-0.23]
Röschke 2000	24	23 (16.2)	24	26 (16)		0.78%	-0.18[-0.75,0.38]

Favours placebo -4 -2 0 2 4 Favours no-treatment

Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Rösler 2003	13	5.9 (3.4)	14	6 (3)		0.51%	-0.02[-0.78,0.73]
Sanders 1990	6	2 (0.4)	6	2.1 (0.3)		0.25%	-0.13[-1.26,1]
Seer 1980	14	92.5 (9.8)	13	104.5 (11)		0.44%	-1.12[-1.94,-0.3]
Senediak 1985	11	47.5 (8.4)	10	47.9 (7.5)		0.41%	-0.04[-0.9,0.81]
Sinaiko 1991	60	66.5 (9.7)	27	64.1 (13.9)		1.03%	0.21[-0.24,0.67]
Sipich 1974	10	8 (14)	10	32.5 (14)		0.29%	-1.68[-2.73,-0.63]
Spanos 1995	13	21.4 (9.7)	12	19.1 (10.3)		0.47%	0.22[-0.56,1.01]
Sprott 1993	10	7.9 (3)	10	7.4 (3)		0.39%	0.16[-0.72,1.04]
Stabholz 1991	10	1.4 (0.5)	10	1.8 (0.6)		0.37%	-0.69[-1.6,0.22]
Steinsbekk 2004	102	44.5 (58.9)	74	53 (45.2)		1.56%	-0.16[-0.46,0.14]
Stewart 1991	25	-14.3 (5.5)	25	-12.8 (5.2)		0.8%	-0.28[-0.83,0.28]
Straub 2001	5	-5.8 (0.3)	5	-6 (0.7)		0.21%	0.27[-0.98,1.52]
Sumaya 2001	10	15.4 (2.7)	10	14.9 (1.8)		0.39%	0.21[-0.67,1.09]
Tan 1982	12	1.3 (0.6)	12	1.7 (0.8)		0.44%	-0.55[-1.36,0.27]
Tashjian 2006	19	3.4 (2.2)	24	3.3 (1.8)		0.71%	0.05[-0.55,0.65]
Theroux 1993	17	3.2 (0.7)	15	2.9 (0.6)		0.56%	0.48[-0.22,1.19]
Thomas 1999	14	13.4 (10.3)	26	16.5 (9.7)		0.63%	-0.31[-0.96,0.35]
Thomas 2002a	78	-0.9 (3)	78	-0.1 (2.9)		1.5%	-0.27[-0.59,0.04]
Thomas 2002b	114	-1.2 (3.5)	119	-1.6 (3.3)		1.74%	0.12[-0.14,0.37]
Tremeau 1992	39	-0.9 (1.3)	25	-1.1 (1.4)		0.91%	0.14[-0.36,0.65]
Tritrakarn 2000	41	49 (16)	41	61 (17)		1.05%	-0.72[-1.17,-0.27]
Tsay 2003	32	9.2 (4.4)	32	9.6 (4)		0.94%	-0.08[-0.57,0.41]
Tsay 2004	35	4.7 (1.5)	36	5.7 (1.8)		0.98%	-0.6[-1.07,-0.12]
Tuomilehto 1980	11	9 (1.4)	11	8.7 (1.6)		0.42%	0.24[-0.6,1.08]
Turner 1979	10	44.2 (41.3)	10	59.8 (22.9)		0.38%	-0.45[-1.34,0.44]
Wang 1997	25	10.7 (7.3)	26	13.4 (5.8)		0.8%	-0.4[-0.96,0.15]
Weingaertner 1971	15	1.1 (1.3)	15	1.2 (1.6)		0.55%	-0.1[-0.81,0.62]
Werntoft 2001	20	5.9 (2.4)	20	6.5 (2.2)		0.68%	-0.26[-0.88,0.37]
Wilcock 2008	15	-6.4 (5.1)	15	-6.7 (5.9)		0.55%	0.05[-0.66,0.77]
Wojciechowski 1984	9	264 (122)	12	238 (190)		0.4%	0.15[-0.71,1.02]
Woods 2005	19	1.2 (1.3)	19	1.5 (1.1)		0.66%	-0.2[-0.83,0.44]
Yates 1988	7	-1.4 (2.5)	7	0.7 (1.4)		0.25%	-0.97[-2.1,0.16]
Total ***	**4327**		**4494**			**100%**	**-0.19[-0.25,-0.13]**

Heterogeneity: Tau²=0.04; Chi²=210.53, df=134(P<0.0001); I²=36.35%

Test for overall effect: Z=6.16(P<0.0001)



Favours placebo — Favours no-treatment

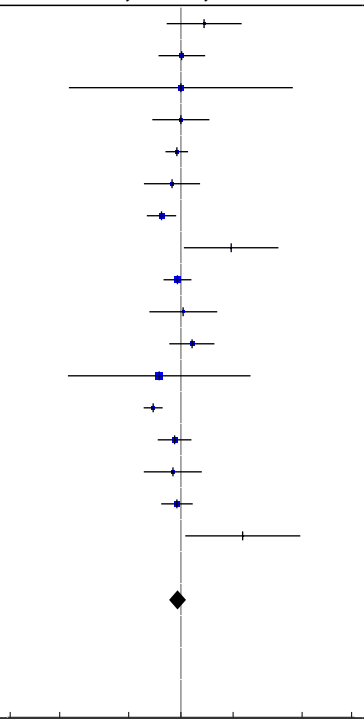
Comparison 9. Effect modification subgroup analysis: placebo as add-on treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Add-on treatment: yes	17	1912	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.85, 1.07]
2 Add-on treatment: no or not stated	27	4129	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.89, 1.00]
3 Add-on treatment: yes	71	5423	Std. Mean Difference (IV, Random, 95% CI)	-0.23 [-0.31, -0.15]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Add-on treatment: no or not stated	87	5090	Std. Mean Difference (IV, Random, 95% CI)	-0.22 [-0.30, -0.14]

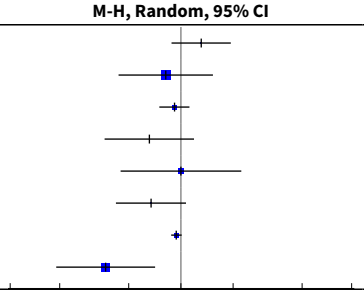
Analysis 9.1. Comparison 9 Effect modification subgroup analysis: placebo as add-on treatment, Outcome 1 Add-on treatment: yes.

Study or subgroup	Placebo n/N	No-treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Berg 1983	9/11	9/15		3.64%	1.36[0.83,2.24]
De Sanctis 2001	9/10	8/9		6.49%	1.01[0.74,1.38]
Double 1993	3/22	3/22		0.55%	1[0.23,4.42]
Dundee 1986	17/25	17/25		5.19%	1[0.68,1.46]
Faas 1993	107/162	108/155		10.4%	0.95[0.81,1.1]
Fanti 2003	8/10	9/10		5.32%	0.89[0.61,1.29]
Heinzl 1981	70/130	92/132		9.26%	0.77[0.64,0.94]
Jacobs 1971	9/15	12/39		2.57%	1.95[1.04,3.65]
Kerr 2003	28/33	32/36		9.53%	0.95[0.79,1.15]
McMillan 1994	14/26	24/46		4.18%	1.03[0.66,1.62]
Molsberger 2002	38/58	30/53		6.68%	1.16[0.86,1.56]
Schallreuter 2002	3/10	4/10		0.8%	0.75[0.22,2.52]
Scharf 2006	179/365	224/316		11.04%	0.69[0.61,0.78]
Scharff 2002	11/12	12/12		8.49%	0.92[0.74,1.15]
Tan 1986	8/10	8/9		5.09%	0.9[0.61,1.32]
Tarrier 1998	22/26	25/28		8.91%	0.95[0.77,1.17]
Watzl 1986	15/34	7/36		1.85%	2.27[1.06,4.88]
Total (95% CI)	**959**	**953**		**100%**	**0.96[0.85,1.07]**
Total events: 550 (Placebo), 624 (No-treatment)					
Heterogeneity: Tau^2=0.03; Chi^2=38.43, df=16(P=0); I^2=58.36%					
Test for overall effect: Z=0.78(P=0.43)					



Analysis 9.2. Comparison 9 Effect modification subgroup analysis: placebo as add-on treatment, Outcome 2 Add-on treatment: no or not stated.

Study or subgroup	Placebo n/N	No-treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Adriaanse 1995	50/328	38/326		2.23%	1.31[0.88,1.94]
Alkaissi 1999	9/20	11/20		0.95%	0.82[0.44,1.53]
Alkaissi 2002	77/139	82/136		6.27%	0.92[0.75,1.12]
Aune 1998	11/26	9/14		1.05%	0.66[0.36,1.19]
Blackman 1964	6/12	6/12		0.59%	1[0.45,2.23]
Carter 2003	13/28	20/29		1.64%	0.67[0.42,1.07]
Corver 2006	227/279	360/416		14.85%	0.94[0.88,1.01]
Elliott 1978	6/18	6/6		0.87%	0.37[0.19,0.71]



Study or subgroup	Placebo n/N	No-treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Frank 1990	14/26	14/26		1.43%	1[0.6,1.65]
Guglielmi 1982	12/12	11/12		5.44%	1.09[0.87,1.36]
Harrison 1975	24/28	25/30		5.59%	1.03[0.83,1.28]
Hutton 1991	5/24	16/30		0.53%	0.39[0.17,0.91]
Hyman 1986	9/15	15/15		2.03%	0.61[0.4,0.93]
Killen 1990	226/309	219/309		12.46%	1.03[0.94,1.14]
Klerman 1974	17/25	16/25		2.18%	1.06[0.71,1.58]
Malcolm 1980	40/63	44/58		5.04%	0.84[0.66,1.06]
Najnigier 1997	21/30	24/30		3.62%	0.88[0.65,1.17]
Rabkin 1990	14/27	12/23		1.28%	0.99[0.58,1.7]
Roughan 1981	9/12	9/14		1.4%	1.17[0.7,1.94]
Stransky 1989	1/5	1/4		0.07%	0.8[0.07,9.18]
Tarcin 2004	58/158	27/77		2.52%	1.05[0.73,1.51]
Thomas 1987	47/100	50/100		3.8%	0.94[0.71,1.25]
Tyler 1946	89/260	106/303		5.33%	0.98[0.78,1.23]
Walton 1993	19/24	21/30		3.31%	1.13[0.83,1.54]
Whittaker 1963	3/13	7/13		0.31%	0.43[0.14,1.3]
Williams 1988	19/20	19/20		9.34%	1[0.87,1.15]
Wilson 1980	31/40	10/10		5.89%	0.8[0.65,0.99]
Total (95% CI)	**2041**	**2088**		**100%**	**0.94[0.89,1]**
Total events: 1057 (Placebo), 1178 (No-treatment)					
Heterogeneity: Tau^2=0.01; Chi^2=36.36, df=26(P=0.09); I^2=28.49%					
Test for overall effect: Z=1.85(P=0.06)					

Analysis 9.3. Comparison 9 Effect modification subgroup analysis: placebo as add-on treatment, Outcome 3 Add-on treatment: yes.

Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Abikoff 2004	35	-91.4 (18.9)	34	-89.5 (22.8)		1.67%	-0.09[-0.56,0.38]
Anderson 1999	30	-2.7 (0.8)	27	-2.7 (0.8)		1.5%	0.08[-0.44,0.6]
Antonio 1999	6	79.7 (12.2)	6	72.6 (11.2)		0.44%	0.56[-0.6,1.72]
Biro 1997	29	3.6 (2.5)	29	3.3 (2.1)		1.51%	0.13[-0.39,0.64]
Blanchard 1990a	13	8.3 (13.6)	11	22.5 (25.1)		0.77%	-0.7[-1.53,0.13]
Blanchard 1990b	18	11.9 (23.9)	24	20.7 (34.8)		1.21%	-0.28[-0.9,0.33]
Bosley 1989	13	86 (10)	14	89 (10)		0.89%	-0.29[-1.05,0.47]
Brinkhaus 2006	70	-23.6 (31)	74	-6.9 (22)		2.32%	-0.62[-0.96,-0.29]
Cabrini 2006	16	61.7 (24)	16	66.6 (28)		1.02%	-0.18[-0.88,0.51]
Colker 1999	7	82.7 (18)	4	77.7 (10.5)		0.39%	0.29[-0.95,1.53]
Conn 1986	13	28.2 (18.4)	14	44.4 (15.7)		0.82%	-0.92[-1.72,-0.12]
Cupal 2001	10	2.7 (1)	10	2.7 (1.3)		0.71%	0[-0.88,0.88]
Defrin 2005	9	7.3 (0.8)	8	7.6 (0.7)		0.61%	-0.39[-1.35,0.58]
Dibble 2007	49	3.1 (2.9)	51	3.5 (3.1)		2.02%	-0.12[-0.51,0.27]
Erdogmus 2007	40	-27.4 (19.7)	40	-20.3 (19.7)		1.8%	-0.36[-0.8,0.08]
Espie 1989	14	63.5 (30.6)	13	96.5 (63.5)		0.86%	-0.65[-1.43,0.13]
Etter 2002	269	20.6 (10)	389	25.4 (12.6)		3.31%	-0.41[-0.57,-0.26]
Forster 1994	15	3.2 (2.8)	15	4.6 (2.2)		0.94%	-0.54[-1.27,0.19]

Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Foster 2004	6	-3.6 (0.6)	12	-2.6 (1.1)		0.53%	-0.98[-2.02,0.06]
Foster 2007	112	6.5 (4.8)	105	6.8 (4.5)		2.7%	-0.06[-0.33,0.21]
GRECHO 1989	150	94.4 (40.7)	150	95.4 (33)		2.93%	-0.03[-0.25,0.2]
Hall 1974	23	-0.5 (7.8)	22	0.9 (7.8)		1.29%	-0.17[-0.76,0.41]
Hanson 1976	11	-0.9 (3.8)	10	-0.3 (2.2)		0.73%	-0.19[-1.05,0.67]
Hargreaves 1989	25	4.5 (2.5)	25	4.9 (2.4)		1.38%	-0.16[-0.72,0.39]
Hashish 1986	25	16 (11.7)	50	30 (18.9)		1.57%	-0.82[-1.32,-0.32]
Hashish 1988	25	42 (25)	25	60 (23)		1.32%	-0.74[-1.31,-0.16]
Hawkins 1995	10	37.4 (8.5)	10	52.1 (9.3)		0.54%	-1.58[-2.61,-0.55]
Hovell 2003	98	-155.4 (69.9)	96	-151 (73.8)		2.61%	-0.06[-0.34,0.22]
Hruby 2006	49	1.2 (2.1)	51	0.9 (1.5)		2.02%	0.21[-0.19,0.6]
Karunakaran 1997	58	6.2 (1.2)	57	5.9 (0.6)		2.14%	0.31[-0.05,0.68]
Killeen 2004	24	1 (2.5)	35	1.9 (3.5)		1.49%	-0.28[-0.81,0.24]
Kokol 2005	16	9.5 (10.5)	10	7.3 (6.6)		0.83%	0.23[-0.56,1.02]
Kotani 2001	23	15 (4.5)	24	18 (6)		1.29%	-0.55[-1.14,0.03]
Licciardone 2003	19	2.5 (1.7)	15	3.5 (2.7)		1.03%	-0.49[-1.17,0.2]
Lick 1977	10	66 (25)	10	63 (32)		0.71%	0.1[-0.78,0.98]
Lin 2002	25	30.2 (14.4)	25	38.1 (16)		1.35%	-0.51[-1.07,0.05]
Linde 2005	76	-2.2 (2.7)	64	-0.8 (2.2)		2.29%	-0.56[-0.9,-0.22]
Lindholm 1996	227	6.8 (0.5)	226	6.8 (0.5)		3.17%	0.15[-0.04,0.33]
Liossi 2003	20	4.3 (0.6)	20	4.6 (0.6)		1.17%	-0.49[-1.12,0.14]
Lorr 1961	42	58.3 (9.9)	38	57.5 (9.9)		1.81%	0.08[-0.36,0.52]
Matros 2006	23	76 (36.3)	21	72 (28.3)		1.27%	0.12[-0.47,0.71]
Medici 2002	23	-0.2 (0.3)	18	-0.1 (0.3)		1.19%	-0.31[-0.93,0.32]
Melchart 2005	57	10.8 (8.3)	63	16.3 (7.4)		2.14%	-0.7[-1.07,-0.33]
Moreland 2006	50	-2 (1.3)	99	-2.1 (1.7)		2.29%	0.06[-0.28,0.4]
O'Brien 1996	53	6.7 (5.6)	54	7.5 (5.1)		2.09%	-0.15[-0.53,0.23]
Parker 1995	49	4 (1.9)	45	3.8 (2.2)		1.96%	0.1[-0.31,0.5]
Parker 2003	13	16.2 (7.5)	14	14.2 (7.5)		0.89%	0.26[-0.5,1.02]
Pelham 1992	38	-8.7 (1.7)	38	-8.5 (1.6)		1.76%	-0.12[-0.57,0.33]
Rawling 2001	89	5.3 (4.7)	96	5.6 (4.9)		2.57%	-0.06[-0.35,0.23]
Reading 1982	18	1.6 (1.3)	20	2.3 (2)		1.13%	-0.4[-1.05,0.24]
Robinson 2001	13	3.9 (3.5)	10	4.3 (3.7)		0.78%	-0.11[-0.93,0.72]
Roongpisuthip 1999	18	-3.3 (4.2)	19	-2.9 (3.1)		1.13%	-0.11[-0.75,0.54]
Roscoe 2002	27	5.9 (5.2)	27	6.6 (3.6)		1.45%	-0.15[-0.69,0.38]
Roscoe 2005	31	2.4 (1.3)	33	2.8 (1.3)		1.59%	-0.3[-0.8,0.19]
Rowbotham 1996	35	-4.4 (8.7)	35	1.9 (8.7)		1.63%	-0.72[-1.2,-0.23]
Röschke 2000	24	23 (16.2)	24	26 (16)		1.34%	-0.18[-0.75,0.38]
Rösler 2003	13	5.9 (3.4)	14	6 (3)		0.9%	-0.02[-0.78,0.73]
Shen 2000	33	40.7 (12.4)	34	43.7 (11.3)		1.64%	-0.25[-0.73,0.23]
Sprott 1993	10	7.9 (3)	10	7.4 (3)		0.71%	0.16[-0.72,1.04]
Stabholz 1991	10	1.4 (0.5)	10	1.8 (0.6)		0.67%	-0.69[-1.6,0.22]
Tashjian 2006	19	3.4 (2.2)	24	3.3 (1.8)		1.24%	0.05[-0.55,0.65]
Tsay 2003	32	9.2 (4.4)	32	9.6 (4)		1.61%	-0.08[-0.57,0.41]
Tsay 2004	35	4.7 (1.5)	36	5.7 (1.8)		1.66%	-0.6[-1.07,-0.12]
Tuomilehto 1980	11	9 (1.4)	11	8.7 (1.6)		0.76%	0.24[-0.6,1.08]
Turner 1979	10	44.2 (41.3)	10	59.8 (22.9)		0.69%	-0.45[-1.34,0.44]
Wang 1997	25	10.7 (7.3)	26	13.4 (5.8)		1.38%	-0.4[-0.96,0.15]
Weingaertner 1971	15	1.1 (1.3)	15	1.2 (1.6)		0.97%	-0.1[-0.81,0.62]
Wilcock 2008	15	-6.4 (5.1)	15	-6.7 (5.9)		0.97%	0.05[-0.66,0.77]
Witt 2005	73	35.8 (16.2)	67	49.6 (16.3)		2.25%	-0.84[-1.19,-0.5]

Favours placebo -4 -2 0 2 4 Favours no-treatment

Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Woods 2005	19	1.2 (1.3)	19	1.5 (1.1)		1.15%	-0.2[-0.83,0.44]
Yates 1988	7	-1.4 (2.5)	7	0.7 (1.4)		0.46%	-0.97[-2.1,0.16]
Total ***	**2618**		**2805**			**100%**	**-0.23[-0.31,-0.15]**
Heterogeneity: Tau²=0.05; Chi²=128.68, df=70(P<0.0001); I²=45.6%							
Test for overall effect: Z=5.53(P<0.0001)							

Favours placebo -4 -2 0 2 4 Favours no-treatment

Analysis 9.4. Comparison 9 Effect modification subgroup analysis: placebo as add-on treatment, Outcome 4 Add-on treatment: no or not stated.

Study or subgroup	Placebo N	Placebo Mean(SD)	no-treatment N	no-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Alfano 2001	24	6.2 (2.8)	14	6.6 (2.7)		1.04%	-0.14[-0.8,0.52]
Allen 1998	11	-2.9 (7.9)	11	-6.1 (10.9)		0.72%	0.32[-0.52,1.17]
Allen 2006	45	12 (9.6)	44	19 (9.6)		1.77%	-0.72[-1.15,-0.29]
Andersen 1990	18	35 (27.2)	16	25 (23.6)		1%	0.38[-0.3,1.06]
Antivalle 1990	11	-1.6 (5.6)	10	-3.9 (7.3)		0.69%	0.34[-0.52,1.21]
Ascher 1979	8	50.6 (44.1)	9	62.4 (25.3)		0.58%	-0.32[-1.28,0.64]
Asmar 1996	34	-0.2 (7.7)	34	0.7 (6.5)		1.58%	-0.12[-0.6,0.35]
Benedetti 1995	13	-2 (1.2)	11	-0.8 (1)		0.68%	-1.07[-1.94,-0.2]
Benedetti 1997	106	0.3 (0.1)	115	0.3 (0.1)		2.6%	-0.17[-0.43,0.1]
Blades 2001	40	-16 (6)	40	-16 (6)		1.73%	0[-0.44,0.44]
Block 1980	16	22.4 (6.6)	8	24.7 (9.2)		0.7%	-0.3[-1.15,0.56]
Bova 1999	34	3.8 (2.2)	36	4.1 (2.3)		1.61%	-0.14[-0.61,0.33]
Bramston 1985	12	-78 (14.2)	12	-72 (13.8)		0.76%	-0.41[-1.22,0.4]
Canino 1994	4	99 (2.7)	9	95.6 (7.6)		0.39%	0.48[-0.72,1.67]
Carbajal 1999	25	7.2 (2.8)	25	6.9 (2.6)		1.32%	0.1[-0.45,0.66]
Chenard 1991	12	29 (19)	16	30 (19)		0.86%	-0.05[-0.8,0.7]
Classen 1983	15	11.3 (8.3)	15	14.4 (6.1)		0.91%	-0.41[-1.14,0.31]
Costello 2006	48	33 (25)	42	31 (25)		1.83%	0.08[-0.33,0.49]
Coyne 1995	21	0.7 (0.7)	21	0.6 (0.7)		1.17%	0.13[-0.47,0.74]
Crosby 1994	26	13.6 (1.3)	33	13.5 (1.3)		1.45%	0.08[-0.44,0.59]
Davidson 1980	10	1.8 (0.9)	10	2.9 (1.3)		0.61%	-0.94[-1.88,-0.01]
Ditto 2003	200	0.5 (0.4)	189	0.5 (0.4)		2.97%	-0.02[-0.22,0.17]
Ditto 2006	140	0.4 (0.4)	155	0.5 (0.4)		2.8%	-0.06[-0.28,0.17]
Etringer 1982	13	-11.4 (4)	12	-10.1 (3.7)		0.79%	-0.33[-1.12,0.46]
Fisher 2006	12	3.8 (1.9)	15	4.1 (2.5)		0.84%	-0.13[-0.89,0.63]
Frankel 1978	7	93 (5)	8	95 (3)		0.51%	-0.47[-1.5,0.57]
Frega 1994	21	20 (16)	21	23 (16)		1.17%	-0.18[-0.79,0.42]
Fuchs 1977	10	14.3 (7)	10	21.4 (7)		0.6%	-0.97[-1.91,-0.03]
Godfrey 1973	44	34.9 (16.7)	44	46.9 (16.2)		1.76%	-0.72[-1.15,-0.29]
Goodenough 1997	39	1.1 (1.6)	39	1.6 (1.9)		1.7%	-0.28[-0.73,0.16]
Gracely 1983	17	-2.9 (5.4)	12	0.2 (5.5)		0.85%	-0.54[-1.3,0.21]
Helms 1987	11	103 (91)	11	79 (99)		0.72%	0.24[-0.6,1.08]
Hong 1993	16	-1.1 (0.2)	21	-1 (0.1)		1.03%	-0.53[-1.19,0.13]
Hossmann 1981	12	94.2 (4.8)	12	95.1 (4.8)		0.78%	-0.18[-0.98,0.62]
Hyland 2006	10	6 (0.9)	10	6.2 (0.9)		0.67%	-0.21[-1.09,0.67]
Irvin 1996	11	3.3 (0.7)	11	3.7 (1.4)		0.72%	-0.35[-1.19,0.5]

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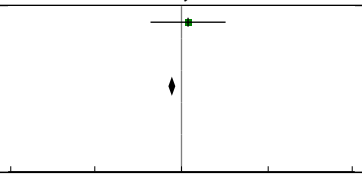
Study or subgroup	Placebo N	Placebo Mean(SD)	no-treatment N	no-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Jacobson 1978	7	2.5 (0.9)	6	3.5 (0.5)		0.38%	-1.17[-2.39,0.04]
Kaptchuk 2008	88	-4.3 (1.4)	87	-3.8 (1)		2.4%	-0.41[-0.71,-0.11]
Karst 2007	19	45.2 (10.8)	10	56.5 (9.1)		0.75%	-1.07[-1.89,-0.25]
Kendall 1979	11	7.5 (2.3)	11	8.2 (3)		0.72%	-0.23[-1.07,0.61]
Kilmann 1987	4	-33 (47)	4	-35 (47)		0.3%	0.04[-1.35,1.42]
Kober 2002	20	66.7 (10)	21	64.4 (13.3)		1.15%	0.19[-0.42,0.8]
Lander 1993	172	28.5 (29.3)	168	32.3 (33.4)		2.89%	-0.12[-0.33,0.09]
Lee 2005	27	-21.4 (25.9)	27	-5.9 (9.2)		1.32%	-0.79[-1.34,-0.23]
Leibing 2002	40	3.2 (1.8)	39	4.3 (1.9)		1.68%	-0.59[-1.04,-0.14]
Levine 1984	12	-0.3 (0.7)	24	0.4 (2.5)		0.96%	-0.31[-1.01,0.38]
Lick 1975	9	60.6 (32.7)	9	92.2 (22.1)		0.54%	-1.08[-2.09,-0.07]
Limoges 2004	30	2.3 (1)	30	2.2 (1)		1.47%	0.04[-0.47,0.55]
Lincoln 2003	42	14.4 (10)	38	16.7 (10)		1.72%	-0.23[-0.67,0.21]
Longo 1988	10	3.6 (0.6)	9	3.6 (0.4)		0.64%	0[-0.9,0.9]
Macaluso 1995	30	-3.3 (3.8)	30	-1.8 (3.3)		1.46%	-0.41[-0.93,0.1]
Markland 1993	7	37.3 (11.8)	7	36.9 (11.9)		0.5%	0.03[-1.01,1.08]
May 1988	24	-1.2 (0.5)	24	-1.2 (0.5)		1.28%	-0.02[-0.59,0.54]
McLachlan 1991	8	6.3 (12.3)	12	5.7 (17.4)		0.65%	0.04[-0.86,0.93]
Moffet 1996	22	24 (18.6)	27	34.6 (23.2)		1.27%	-0.49[-1.06,0.08]
Morey 2006	38	-16.5 (9.3)	42	-14.7 (9.5)		1.73%	-0.19[-0.63,0.25]
Morton 1993	13	22.1 (16.4)	13	24.5 (16.4)		0.83%	-0.14[-0.91,0.63]
Murphy 1982	6	-16.5 (9.3)	11	-0.8 (6.4)		0.36%	-1.99[-3.24,-0.74]
Nandi 1976	10	53.2 (11.2)	8	57.5 (13.8)		0.6%	-0.33[-1.27,0.61]
Nawrocki 1997	40	9.5 (6)	42	17 (4.8)		1.56%	-1.37[-1.85,-0.89]
Nicassio 1974	7	117.3 (133.7)	9	99.3 (35.3)		0.55%	0.19[-0.8,1.18]
Nocella 1982	10	0.8 (0.9)	10	0.8 (0.7)		0.67%	-0.02[-0.9,0.85]
Quahagen 1995	28	-108.3 (14.8)	25	-104.8 (13.9)		1.36%	-0.24[-0.78,0.3]
Ristikankare 1999	61	40.3 (21.5)	61	36 (21.5)		2.11%	0.2[-0.16,0.55]
Rosen 1976	9	6.9 (2)	5	8.3 (1.9)		0.44%	-0.67[-1.8,0.46]
Rossi 1982	6	107 (17)	6	108 (20)		0.44%	-0.05[-1.18,1.08]
Rybarczyk 1990	25	7.1 (2.2)	24	7.5 (2.8)		1.3%	-0.16[-0.73,0.4]
Sanders 1990	6	2 (0.4)	6	2.1 (0.3)		0.44%	-0.13[-1.26,1]
Seer 1980	14	92.5 (9.8)	13	104.5 (11)		0.75%	-1.12[-1.94,-0.3]
Senediak 1985	11	47.5 (8.4)	10	47.9 (7.5)		0.7%	-0.04[-0.9,0.81]
Sinaiko 1991	60	66.5 (9.7)	27	64.1 (13.9)		1.66%	0.21[-0.24,0.67]
Sipich 1974	10	8 (14)	10	32.5 (14)		0.5%	-1.68[-2.73,-0.63]
Spanos 1995	13	21.4 (9.7)	12	19.1 (10.3)		0.8%	0.22[-0.56,1.01]
Steinsbekk 2004	102	44.5 (58.9)	74	53 (45.2)		2.4%	-0.16[-0.46,0.14]
Stewart 1991	25	-14.3 (5.5)	25	-12.8 (5.2)		1.31%	-0.28[-0.83,0.28]
Straub 2001	5	-5.8 (0.3)	5	-6 (0.7)		0.37%	0.27[-0.98,1.52]
Sumaya 2001	10	15.4 (2.7)	10	14.9 (1.8)		0.67%	0.21[-0.67,1.09]
Tan 1982	12	1.3 (0.6)	12	1.7 (0.8)		0.75%	-0.55[-1.36,0.27]
Theroux 1993	17	3.2 (0.7)	15	2.9 (0.6)		0.94%	0.48[-0.22,1.19]
Thomas 1999	14	13.4 (10.3)	26	16.5 (9.7)		1.06%	-0.31[-0.96,0.35]
Thomas 2002a	78	-0.9 (3)	78	-0.1 (2.9)		2.32%	-0.27[-0.59,0.04]
Thomas 2002b	114	-1.2 (3.5)	119	-1.6 (3.3)		2.64%	0.12[-0.14,0.37]
Tremeau 1992	39	-0.9 (1.3)	25	-1.1 (1.4)		1.49%	0.14[-0.36,0.65]
Tritrakarn 2000	41	49 (16)	41	61 (17)		1.7%	-0.72[-1.17,-0.27]
Vlaeyen 1996	39	0.4 (1.8)	40	0.4 (1.8)		1.72%	0[-0.44,0.44]
Werntoft 2001	20	5.9 (2.4)	20	6.5 (2.2)		1.13%	-0.26[-0.88,0.37]

Favours placebo -4 -2 0 2 4 Favours no-treatment

Study or subgroup	Placebo N	Placebo Mean(SD)	no-treatment N	no-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Wojciechowski 1984	9	264 (122)	12	238 (190)		0.69%	0.15[-0.71,1.02]
Total ***	**2570**		**2520**			**100%**	**-0.22[-0.3,-0.14]**
Heterogeneity: Tau²=0.05; Chi²=140.54, df=86(P=0); I²=38.81%							
Test for overall effect: Z=5.46(P<0.0001)							

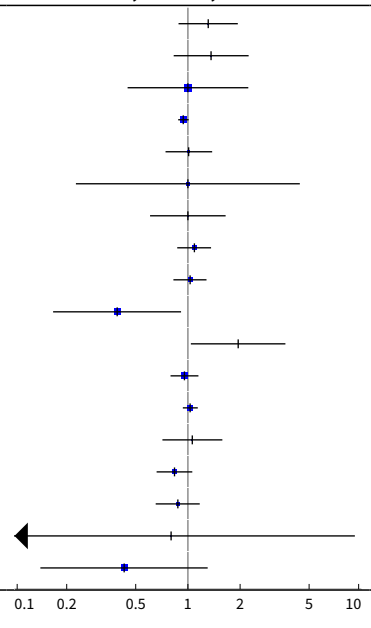


Comparison 10. Risk of bias subgroup analysis: blinding of placebo treatment providers

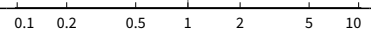
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Placebo intervention provider blinded: yes	19	2707	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.91, 1.05]
2 Placebo intervention provider blinded: no or not stated	25	3334	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.83, 0.99]
3 Placebo intervention provider blinded: yes	42	3069	Std. Mean Difference (IV, Random, 95% CI)	-0.15 [-0.27, -0.02]
4 Placebo intervention provider blinded: no or not stated	116	7444	Std. Mean Difference (IV, Random, 95% CI)	-0.26 [-0.32, -0.19]

Analysis 10.1. Comparison 10 Risk of bias subgroup analysis: blinding of placebo treatment providers, Outcome 1 Placebo intervention provider blinded: yes.

Study or subgroup	Placebo n/N	No-treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Adriaanse 1995	50/328	38/326		2.88%	1.31[0.88,1.94]
Berg 1983	9/11	9/15		1.87%	1.36[0.83,2.24]
Blackman 1964	6/12	6/12		0.76%	1[0.45,2.23]
Corver 2006	227/279	360/416		21.69%	0.94[0.88,1.01]
De Sanctis 2001	9/10	8/9		4.35%	1.01[0.74,1.38]
Double 1993	3/22	3/22		0.22%	1[0.23,4.42]
Frank 1990	14/26	14/26		1.83%	1[0.6,1.65]
Guglielmi 1982	12/12	11/12		7.24%	1.09[0.87,1.36]
Harrison 1975	24/28	25/30		7.45%	1.03[0.83,1.28]
Hutton 1991	5/24	16/30		0.67%	0.39[0.17,0.91]
Jacobs 1971	9/15	12/39		1.21%	1.95[1.04,3.65]
Kerr 2003	28/33	32/36		9.49%	0.95[0.79,1.15]
Killen 1990	226/309	219/309		17.76%	1.03[0.94,1.14]
Klerman 1974	17/25	16/25		2.81%	1.06[0.71,1.58]
Malcolm 1980	40/63	44/58		6.68%	0.84[0.66,1.06]
Najnigier 1997	21/30	24/30		4.73%	0.88[0.65,1.17]
Stransky 1989	1/5	1/4		0.08%	0.8[0.07,9.18]
Whittaker 1963	3/13	7/13		0.4%	0.43[0.14,1.3]



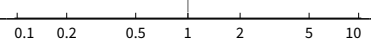
Study or subgroup	Placebo n/N	No-treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Wilson 1980	31/40	10/10		7.87%	0.8[0.65,0.99]
Total (95% CI)	**1285**	**1422**		**100%**	**0.97[0.91,1.05]**
Total events: 735 (Placebo), 855 (No-treatment)					
Heterogeneity: Tau^2=0; Chi^2=24.5, df=18(P=0.14); I^2=26.53%					
Test for overall effect: Z=0.7(P=0.48)					



Favours placebo — Favours no-treatment

Analysis 10.2. Comparison 10 Risk of bias subgroup analysis: blinding of placebo treatment providers, Outcome 2 Placebo intervention provider blinded: no or not stated.

Study or subgroup	Placebo n/N	No-treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Alkaissi 1999	9/20	11/20		1.57%	0.82[0.44,1.53]
Alkaissi 2002	77/139	82/136		6.37%	0.92[0.75,1.12]
Aune 1998	11/26	9/14		1.71%	0.66[0.36,1.19]
Carter 2003	13/28	20/29		2.51%	0.67[0.42,1.07]
Dundee 1986	17/25	17/25		3.35%	1[0.68,1.46]
Elliott 1978	6/18	6/6		1.45%	0.37[0.19,0.71]
Faas 1993	107/162	108/155		7.55%	0.95[0.81,1.1]
Fanti 2003	8/10	9/10		3.44%	0.89[0.61,1.29]
Heinzl 1981	70/130	92/132		6.54%	0.77[0.64,0.94]
Hyman 1986	9/15	15/15		2.98%	0.61[0.4,0.93]
McMillan 1994	14/26	24/46		2.64%	1.03[0.66,1.62]
Molsberger 2002	38/58	30/53		4.45%	1.16[0.86,1.56]
Rabkin 1990	14/27	12/23		2.04%	0.99[0.58,1.7]
Roughan 1981	9/12	9/14		2.2%	1.17[0.7,1.94]
Schallreuter 2002	3/10	4/10		0.47%	0.75[0.22,2.52]
Scharf 2006	179/365	224/316		8.14%	0.69[0.61,0.78]
Scharff 2002	11/12	12/12		5.89%	0.92[0.74,1.15]
Tan 1986	8/10	8/9		3.28%	0.9[0.61,1.32]
Tarcin 2004	58/158	27/77		3.51%	1.05[0.73,1.51]
Tarrier 1998	22/26	25/28		6.24%	0.95[0.77,1.17]
Thomas 1987	47/100	50/100		4.7%	0.94[0.71,1.25]
Tyler 1946	89/260	106/303		5.81%	0.98[0.78,1.23]
Walton 1993	19/24	21/30		4.28%	1.13[0.83,1.54]
Watzl 1986	15/34	7/36		1.11%	2.27[1.06,4.88]
Williams 1988	19/20	19/20		7.77%	1[0.87,1.15]
Total (95% CI)	**1715**	**1619**		**100%**	**0.9[0.83,0.99]**
Total events: 872 (Placebo), 947 (No-treatment)					
Heterogeneity: Tau^2=0.02; Chi^2=48.53, df=24(P=0); I^2=50.54%					
Test for overall effect: Z=2.3(P=0.02)					



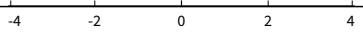
Favours placebo — Favours no-treatment

Analysis 10.3. Comparison 10 Risk of bias subgroup analysis: blinding of placebo treatment providers, Outcome 3 Placebo intervention provider blinded: yes.

Study or subgroup	Placebo		No-treatment		Std. Mean Difference	Weight	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
Allen 1998	11	-2.9 (7.9)	11	-6.1 (10.9)		1.48%	0.32[-0.52,1.17]
Allen 2006	45	12 (9.6)	44	19 (9.6)		3.03%	-0.72[-1.15,-0.29]
Andersen 1990	18	35 (27.2)	16	25 (23.6)		1.95%	0.38[-0.3,1.06]
Antonio 1999	6	79.7 (12.2)	6	72.6 (11.2)		0.91%	0.56[-0.6,1.72]
Benedetti 1995	13	-2 (1.2)	11	-0.8 (1)		1.42%	-1.07[-1.94,-0.2]
Blades 2001	40	-16 (6)	40	-16 (6)		2.98%	0[-0.44,0.44]
Classen 1983	15	11.3 (8.3)	15	14.4 (6.1)		1.8%	-0.41[-1.14,0.31]
Colker 1999	7	82.7 (18)	4	77.7 (10.5)		0.82%	0.29[-0.95,1.53]
Costello 2006	48	33 (25)	42	31 (25)		3.11%	0.08[-0.33,0.49]
Crosby 1994	26	13.6 (1.3)	33	13.5 (1.3)		2.61%	0.08[-0.44,0.59]
Dibble 2007	49	3.1 (2.9)	51	3.5 (3.1)		3.23%	-0.12[-0.51,0.27]
Fisher 2006	12	3.8 (1.9)	15	4.1 (2.5)		1.69%	-0.13[-0.89,0.63]
Frega 1994	21	20 (16)	21	23 (16)		2.22%	-0.18[-0.79,0.42]
Gracely 1983	17	-2.9 (5.4)	12	0.2 (5.5)		1.71%	-0.54[-1.3,0.21]
GRECHO 1989	150	94.4 (40.7)	150	95.4 (33)		4.13%	-0.03[-0.25,0.2]
Hashish 1986	25	16 (11.7)	50	30 (18.9)		2.68%	-0.82[-1.32,-0.32]
Karunakaran 1997	58	6.2 (1.2)	57	5.9 (0.6)		3.36%	0.31[-0.05,0.68]
Kober 2002	20	66.7 (10)	21	64.4 (13.3)		2.19%	0.19[-0.42,0.8]
Kokol 2005	16	9.5 (10.5)	10	7.3 (6.6)		1.6%	0.23[-0.56,1.02]
Levine 1984	12	-0.3 (0.7)	24	0.4 (2.5)		1.89%	-0.31[-1.01,0.38]
Lindholm 1996	227	6.8 (0.5)	226	6.8 (0.5)		4.34%	0.15[-0.04,0.33]
Lorr 1961	42	58.3 (9.9)	38	57.5 (9.9)		2.98%	0.08[-0.36,0.52]
Macaluso 1995	30	-3.3 (3.8)	30	-1.8 (3.3)		2.62%	-0.41[-0.93,0.1]
May 1988	24	-1.2 (0.5)	24	-1.2 (0.5)		2.38%	-0.02[-0.59,0.54]
Moffet 1996	22	24 (18.6)	27	34.6 (23.2)		2.36%	-0.49[-1.06,0.08]
Nawrocki 1997	40	9.5 (6)	42	17 (4.8)		2.76%	-1.37[-1.85,-0.89]
Pelham 1992	38	-8.7 (1.7)	38	-8.5 (1.6)		2.92%	-0.12[-0.57,0.33]
Rawling 2001	89	5.3 (4.7)	96	5.6 (4.9)		3.8%	-0.06[-0.35,0.23]
Ristikankare 1999	61	40.3 (21.5)	61	36 (21.5)		3.43%	0.2[-0.16,0.55]
Roongpisuthip 1999	18	-3.3 (4.2)	19	-2.9 (3.1)		2.07%	-0.11[-0.75,0.54]
Rosen 1976	9	6.9 (2)	5	8.3 (1.9)		0.95%	-0.67[-1.8,0.46]
Rowbotham 1996	35	-4.4 (8.7)	35	1.9 (8.7)		2.75%	-0.72[-1.2,-0.23]
Sinaiko 1991	60	66.5 (9.7)	27	64.1 (13.9)		2.9%	0.21[-0.24,0.67]
Stabholz 1991	10	1.4 (0.5)	10	1.8 (0.6)		1.33%	-0.69[-1.6,0.22]
Steinsbekk 2004	102	44.5 (58.9)	74	53 (45.2)		3.74%	-0.16[-0.46,0.14]
Tashjian 2006	19	3.4 (2.2)	24	3.3 (1.8)		2.23%	0.05[-0.55,0.65]
Theroux 1993	17	3.2 (0.7)	15	2.9 (0.6)		1.86%	0.48[-0.22,1.19]
Tritrakarn 2000	41	49 (16)	41	61 (17)		2.94%	-0.72[-1.17,-0.27]
Tuomilehto 1980	11	9 (1.4)	11	8.7 (1.6)		1.48%	0.24[-0.6,1.08]
Wilcock 2008	15	-6.4 (5.1)	15	-6.7 (5.9)		1.83%	0.05[-0.66,0.77]
Wojciechowski 1984	9	264 (122)	12	238 (190)		1.42%	0.15[-0.71,1.02]
Woods 2005	19	1.2 (1.3)	19	1.5 (1.1)		2.1%	-0.2[-0.83,0.44]
Total * **	**1547**		**1522**			**100%**	**-0.15[-0.27,-0.02]**

Heterogeneity: Tau^2=0.08; Chi^2=98.58, df=41(P<0.0001); I^2=58.41%

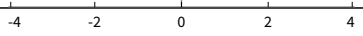
Test for overall effect: Z=2.35(P=0.02)



Favours placebo — Favours no-treatment

Analysis 10.4. Comparison 10 Risk of bias subgroup analysis: blinding of placebo treatment providers, Outcome 4 Placebo intervention provider blinded: no or not stated.

Study or subgroup	Placebo		No-treatment		Std. Mean Difference	Weight	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
Abikoff 2004	35	-91.4 (18.9)	34	-89.5 (22.8)		1.14%	-0.09[-0.56,0.38]
Alfano 2001	24	6.2 (2.8)	14	6.6 (2.7)		0.69%	-0.14[-0.8,0.52]
Anderson 1999	30	-2.7 (0.8)	27	-2.7 (0.8)		1%	0.08[-0.44,0.6]
Antivalle 1990	11	-1.6 (5.6)	10	-3.9 (7.3)		0.43%	0.34[-0.52,1.21]
Ascher 1979	8	50.6 (44.1)	9	62.4 (25.3)		0.36%	-0.32[-1.28,0.64]
Asmar 1996	34	-0.2 (7.7)	34	0.7 (6.5)		1.13%	-0.12[-0.6,0.35]
Benedetti 1997	106	0.3 (0.1)	115	0.3 (0.1)		2.18%	-0.17[-0.43,0.1]
Biro 1997	29	3.6 (2.5)	29	3.3 (2.1)		1.01%	0.13[-0.39,0.64]
Blanchard 1990a	13	8.3 (13.6)	11	22.5 (25.1)		0.47%	-0.7[-1.53,0.13]
Blanchard 1990b	18	11.9 (23.9)	24	20.7 (34.8)		0.77%	-0.28[-0.9,0.33]
Block 1980	16	22.4 (6.6)	8	24.7 (9.2)		0.44%	-0.3[-1.15,0.56]
Bosley 1989	13	86 (10)	14	89 (10)		0.54%	-0.29[-1.05,0.47]
Bova 1999	34	3.8 (2.2)	36	4.1 (2.3)		1.15%	-0.14[-0.61,0.33]
Bramston 1985	12	-78 (14.2)	12	-72 (13.8)		0.49%	-0.41[-1.22,0.4]
Brinkhaus 2006	70	-23.6 (31)	74	-6.9 (22)		1.75%	-0.62[-0.96,-0.29]
Cabrini 2006	16	61.7 (24)	16	66.6 (28)		0.63%	-0.18[-0.88,0.51]
Canino 1994	4	99 (2.7)	9	95.6 (7.6)		0.24%	0.48[-0.72,1.67]
Carbajal 1999	25	7.2 (2.8)	25	6.9 (2.6)		0.9%	0.1[-0.45,0.66]
Chenard 1991	12	29 (19)	16	30 (19)		0.56%	-0.05[-0.8,0.7]
Conn 1986	13	28.2 (18.4)	14	44.4 (15.7)		0.5%	-0.92[-1.72,-0.12]
Coyne 1995	21	0.7 (0.7)	21	0.6 (0.7)		0.79%	0.13[-0.47,0.74]
Cupal 2001	10	2.7 (1)	10	2.7 (1.3)		0.42%	0[-0.88,0.88]
Davidson 1980	10	1.8 (0.9)	10	2.9 (1.3)		0.38%	-0.94[-1.88,-0.01]
Defrin 2005	9	7.3 (0.8)	8	7.6 (0.7)		0.36%	-0.39[-1.35,0.58]
Ditto 2003	200	0.5 (0.4)	189	0.5 (0.4)		2.66%	-0.02[-0.22,0.17]
Ditto 2006	140	0.4 (0.4)	155	0.5 (0.4)		2.44%	-0.06[-0.28,0.17]
Erdogmus 2007	40	-27.4 (19.7)	40	-20.3 (19.7)		1.25%	-0.36[-0.8,0.08]
Espie 1989	14	63.5 (30.6)	13	96.5 (63.5)		0.52%	-0.65[-1.43,0.13]
Etringer 1982	13	-11.4 (4)	12	-10.1 (3.7)		0.51%	-0.33[-1.12,0.46]
Etter 2002	269	20.6 (10)	389	25.4 (12.6)		2.98%	-0.41[-0.57,-0.26]
Forster 1994	15	3.2 (2.8)	15	4.6 (2.2)		0.58%	-0.54[-1.27,0.19]
Foster 2004	6	-3.6 (0.6)	12	-2.6 (1.1)		0.31%	-0.98[-2.02,0.06]
Foster 2007	112	6.5 (4.8)	105	6.8 (4.5)		2.17%	-0.06[-0.33,0.21]
Frankel 1978	7	93 (5)	8	95 (3)		0.32%	-0.47[-1.5,0.57]
Fuchs 1977	10	14.3 (7)	10	21.4 (7)		0.38%	-0.97[-1.91,-0.03]
Godfrey 1973	44	34.9 (16.7)	44	46.9 (16.2)		1.29%	-0.72[-1.15,-0.29]
Goodenough 1997	39	1.1 (1.6)	39	1.6 (1.9)		1.23%	-0.28[-0.73,0.16]
Hall 1974	23	-0.5 (7.8)	22	0.9 (7.8)		0.83%	-0.17[-0.76,0.41]
Hanson 1976	11	-0.9 (3.8)	10	-0.3 (2.2)		0.44%	-0.19[-1.05,0.67]
Hargreaves 1989	25	4.5 (2.5)	25	4.9 (2.4)		0.9%	-0.16[-0.72,0.39]
Hashish 1988	25	42 (25)	25	60 (23)		0.86%	-0.74[-1.31,-0.16]
Hawkins 1995	10	37.4 (8.5)	10	52.1 (9.3)		0.32%	-1.58[-2.61,-0.55]
Helms 1987	11	103 (91)	11	79 (99)		0.46%	0.24[-0.6,1.08]
Hong 1993	16	-1.1 (0.2)	21	-1 (0.1)		0.68%	-0.53[-1.19,0.13]
Hossmann 1981	12	94.2 (4.8)	12	95.1 (4.8)		0.5%	-0.18[-0.98,0.62]
Hovell 2003	98	-155.4 (69.9)	96	-151 (73.8)		2.07%	-0.06[-0.34,0.22]
Hruby 2006	49	1.2 (2.1)	51	0.9 (1.5)		1.45%	0.21[-0.19,0.6]
Hyland 2006	10	6 (0.9)	10	6.2 (0.9)		0.42%	-0.21[-1.09,0.67]



Favours placebo — Favours no-treatment

Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Irvin 1996	11	3.3 (0.7)	11	3.7 (1.4)		0.45%	-0.35[-1.19,0.5]
Jacobson 1978	7	2.5 (0.9)	6	3.5 (0.5)		0.23%	-1.17[-2.39,0.04]
Kaptchuk 2008	88	-4.3 (1.4)	87	-3.8 (1)		1.95%	-0.41[-0.71,-0.11]
Karst 2007	19	45.2 (10.8)	10	56.5 (9.1)		0.48%	-1.07[-1.89,-0.25]
Kendall 1979	11	7.5 (2.3)	11	8.2 (3)		0.46%	-0.23[-1.07,0.61]
Killeen 2004	24	1 (2.5)	35	1.9 (3.5)		0.99%	-0.28[-0.81,0.24]
Kilmann 1987	4	-33 (47)	4	-35 (47)		0.18%	0.04[-1.35,1.42]
Kotani 2001	23	15 (4.5)	24	18 (6)		0.84%	-0.55[-1.14,0.03]
Lander 1993	172	28.5 (29.3)	168	32.3 (33.4)		2.56%	-0.12[-0.33,0.09]
Lee 2005	27	-21.4 (25.9)	27	-5.9 (9.2)		0.9%	-0.79[-1.34,-0.23]
Leibing 2002	40	3.2 (1.8)	39	4.3 (1.9)		1.22%	-0.59[-1.04,-0.14]
Licciardone 2003	19	2.5 (1.7)	15	3.5 (2.7)		0.64%	-0.49[-1.17,0.2]
Lick 1975	9	60.6 (32.7)	9	92.2 (22.1)		0.33%	-1.08[-2.09,-0.07]
Lick 1977	10	66 (25)	10	63 (32)		0.42%	0.1[-0.78,0.98]
Limoges 2004	30	2.3 (1)	30	2.2 (1)		1.04%	0.04[-0.47,0.55]
Lin 2002	25	30.2 (14.4)	25	38.1 (16)		0.88%	-0.51[-1.07,0.05]
Lincoln 2003	42	14.4 (10)	38	16.7 (10)		1.26%	-0.23[-0.67,0.21]
Linde 2005	76	-2.2 (2.7)	64	-0.8 (2.2)		1.72%	-0.56[-0.9,-0.22]
Liossi 2003	20	4.3 (0.6)	20	4.6 (0.6)		0.74%	-0.49[-1.12,0.14]
Longo 1988	10	3.6 (0.6)	9	3.6 (0.4)		0.4%	0[-0.9,0.9]
Markland 1993	7	37.3 (11.8)	7	36.9 (11.9)		0.31%	0.03[-1.01,1.08]
Matros 2006	23	76 (36.3)	21	72 (28.3)		0.82%	0.12[-0.47,0.71]
McLachlan 1991	8	6.3 (12.3)	12	5.7 (17.4)		0.41%	0.04[-0.86,0.93]
Medici 2002	23	-0.2 (0.3)	18	-0.1 (0.3)		0.76%	-0.31[-0.93,0.32]
Melchart 2005	57	10.8 (8.3)	63	16.3 (7.4)		1.56%	-0.7[-1.07,-0.33]
Moreland 2006	50	-2 (1.3)	99	-2.1 (1.7)		1.72%	0.06[-0.28,0.4]
Morey 2006	38	-16.5 (9.3)	42	-14.7 (9.5)		1.26%	-0.19[-0.63,0.25]
Morton 1993	13	22.1 (16.4)	13	24.5 (16.4)		0.53%	-0.14[-0.91,0.63]
Murphy 1982	6	-16.5 (9.3)	11	-0.8 (6.4)		0.22%	-1.99[-3.24,-0.74]
Nandi 1976	10	53.2 (11.2)	8	57.5 (13.8)		0.38%	-0.33[-1.27,0.61]
Nicassio 1974	7	117.3 (133.7)	9	99.3 (35.3)		0.34%	0.19[-0.8,1.18]
Nocella 1982	10	0.8 (0.9)	10	0.8 (0.7)		0.42%	-0.02[-0.9,0.85]
O'Brien 1996	53	6.7 (5.6)	54	7.5 (5.1)		1.52%	-0.15[-0.53,0.23]
Parker 1995	49	4 (1.9)	45	3.8 (2.2)		1.4%	0.1[-0.31,0.5]
Parker 2003	13	16.2 (7.5)	14	14.2 (7.5)		0.55%	0.26[-0.5,1.02]
Quahagen 1995	28	-108.3 (14.8)	25	-104.8 (13.9)		0.94%	-0.24[-0.78,0.3]
Reading 1982	18	1.6 (1.3)	20	2.3 (2)		0.72%	-0.4[-1.05,0.24]
Robinson 2001	13	3.9 (3.5)	10	4.3 (3.7)		0.47%	-0.11[-0.93,0.72]
Roscoe 2002	27	5.9 (5.2)	27	6.6 (3.6)		0.96%	-0.15[-0.69,0.38]
Roscoe 2005	31	2.4 (1.3)	33	2.8 (1.3)		1.08%	-0.3[-0.8,0.19]
Rossi 1982	6	107 (17)	6	108 (20)		0.27%	-0.05[-1.18,1.08]
Rybarczyk 1990	25	7.1 (2.2)	24	7.5 (2.8)		0.89%	-0.16[-0.73,0.4]
Röschke 2000	24	23 (16.2)	24	26 (16)		0.87%	-0.18[-0.75,0.38]
Rösler 2003	13	5.9 (3.4)	14	6 (3)		0.55%	-0.02[-0.78,0.73]
Sanders 1990	6	2 (0.4)	6	2.1 (0.3)		0.27%	-0.13[-1.26,1]
Seer 1980	14	92.5 (9.8)	13	104.5 (11)		0.48%	-1.12[-1.94,-0.3]
Senediak 1985	11	47.5 (8.4)	10	47.9 (7.5)		0.44%	-0.04[-0.9,0.81]
Shen 2000	33	40.7 (12.4)	34	43.7 (11.3)		1.11%	-0.25[-0.73,0.23]
Sipich 1974	10	8 (14)	10	32.5 (14)		0.31%	-1.68[-2.73,-0.63]
Spanos 1995	13	21.4 (9.7)	12	19.1 (10.3)		0.51%	0.22[-0.56,1.01]

Favours placebo -4 -2 0 2 4 Favours no-treatment

Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Sprott 1993	10	7.9 (3)	10	7.4 (3)		0.42%	0.16[-0.72,1.04]
Stewart 1991	25	-14.3 (5.5)	25	-12.8 (5.2)		0.9%	-0.28[-0.83,0.28]
Straub 2001	5	-5.8 (0.3)	5	-6 (0.7)		0.22%	0.27[-0.98,1.52]
Sumaya 2001	10	15.4 (2.7)	10	14.9 (1.8)		0.42%	0.21[-0.67,1.09]
Tan 1982	12	1.3 (0.6)	12	1.7 (0.8)		0.48%	-0.55[-1.36,0.27]
Thomas 1999	14	13.4 (10.3)	26	16.5 (9.7)		0.7%	-0.31[-0.96,0.35]
Thomas 2002a	78	-0.9 (3)	78	-0.1 (2.9)		1.86%	-0.27[-0.59,0.04]
Thomas 2002b	114	-1.2 (3.5)	119	-1.6 (3.3)		2.23%	0.12[-0.14,0.37]
Tremeau 1992	39	-0.9 (1.3)	25	-1.1 (1.4)		1.05%	0.14[-0.36,0.65]
Tsay 2003	32	9.2 (4.4)	32	9.6 (4)		1.08%	-0.08[-0.57,0.41]
Tsay 2004	35	4.7 (1.5)	36	5.7 (1.8)		1.13%	-0.6[-1.07,-0.12]
Turner 1979	10	44.2 (41.3)	10	59.8 (22.9)		0.41%	-0.45[-1.34,0.44]
Vlaeyen 1996	39	0.4 (1.8)	40	0.4 (1.8)		1.25%	0[-0.44,0.44]
Wang 1997	25	10.7 (7.3)	26	13.4 (5.8)		0.9%	-0.4[-0.96,0.15]
Weingaertner 1971	15	1.1 (1.3)	15	1.2 (1.6)		0.6%	-0.1[-0.81,0.62]
Werntoft 2001	20	5.9 (2.4)	20	6.5 (2.2)		0.76%	-0.26[-0.88,0.37]
Witt 2005	73	35.8 (16.2)	67	49.6 (16.3)		1.68%	-0.84[-1.19,-0.5]
Yates 1988	7	-1.4 (2.5)	7	0.7 (1.4)		0.27%	-0.97[-2.1,0.16]
Total ***	**3641**		**3803**			**100%**	**-0.26[-0.32,-0.19]**

Heterogeneity: Tau^2=0.03; Chi^2=160.19, df=115(P=0); I^2=28.21%

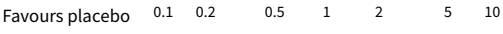
Test for overall effect: Z=8.25(P<0.0001)

Comparison 11. Risk of bias subgroup analysis: blinding of observer

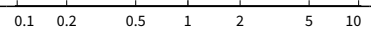
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Blinding of observer: yes	2	316	Risk Ratio (M-H, Random, 95% CI)	0.85 [0.68, 1.07]
2 Blinding of observer: not stated	11	1679	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.87, 1.06]
3 Blinding of observer: yes	20	669	Std. Mean Difference (IV, Random, 95% CI)	-0.23 [-0.42, -0.05]
4 Blinding of observer: not stated	29	1844	Std. Mean Difference (IV, Random, 95% CI)	-0.07 [-0.20, 0.06]

Analysis 11.1. Comparison 11 Risk of bias subgroup analysis: blinding of observer, Outcome 1 Blinding of observer: yes.

Study or subgroup	Placebo n/N	No-treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heinzl 1981	70/130	92/132		51.35%	0.77[0.64,0.94]
Tarrier 1998	22/26	25/28		48.65%	0.95[0.77,1.17]



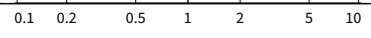
Study or subgroup	Placebo n/N	No-treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Total (95% CI)	**156**	**160**		**100%**	**0.85[0.68,1.07]**
Total events: 92 (Placebo), 117 (No-treatment)					
Heterogeneity: Tau^2=0.02; Chi^2=2.43, df=1(P=0.12); I^2=58.88%					
Test for overall effect: Z=1.4(P=0.16)					



Favours placebo — Favours no-treatment

Analysis 11.2. Comparison 11 Risk of bias subgroup analysis: blinding of observer, Outcome 2 Blinding of observer: not stated.

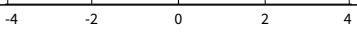
Study or subgroup	Placebo n/N	No-treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Adriaanse 1995	50/328	38/326		5.29%	1.31[0.88,1.94]
De Sanctis 2001	9/10	8/9		7.97%	1.01[0.74,1.38]
Double 1993	3/22	3/22		0.41%	1[0.23,4.42]
Fanti 2003	8/10	9/10		5.82%	0.89[0.61,1.29]
Harrison 1975	24/28	25/30		13.54%	1.03[0.83,1.28]
Hyman 1986	9/15	15/15		4.81%	0.61[0.4,0.93]
Kerr 2003	28/33	32/36		17.15%	0.95[0.79,1.15]
Killen 1990	226/309	219/309		31.49%	1.03[0.94,1.14]
Malcolm 1980	40/63	44/58		12.17%	0.84[0.66,1.06]
Schallreuter 2002	3/10	4/10		0.62%	0.75[0.22,2.52]
Whittaker 1963	3/13	7/13		0.73%	0.43[0.14,1.3]
Total (95% CI)	**841**	**838**		**100%**	**0.96[0.87,1.06]**
Total events: 403 (Placebo), 404 (No-treatment)					
Heterogeneity: Tau^2=0.01; Chi^2=12.77, df=10(P=0.24); I^2=21.67%					
Test for overall effect: Z=0.8(P=0.42)					



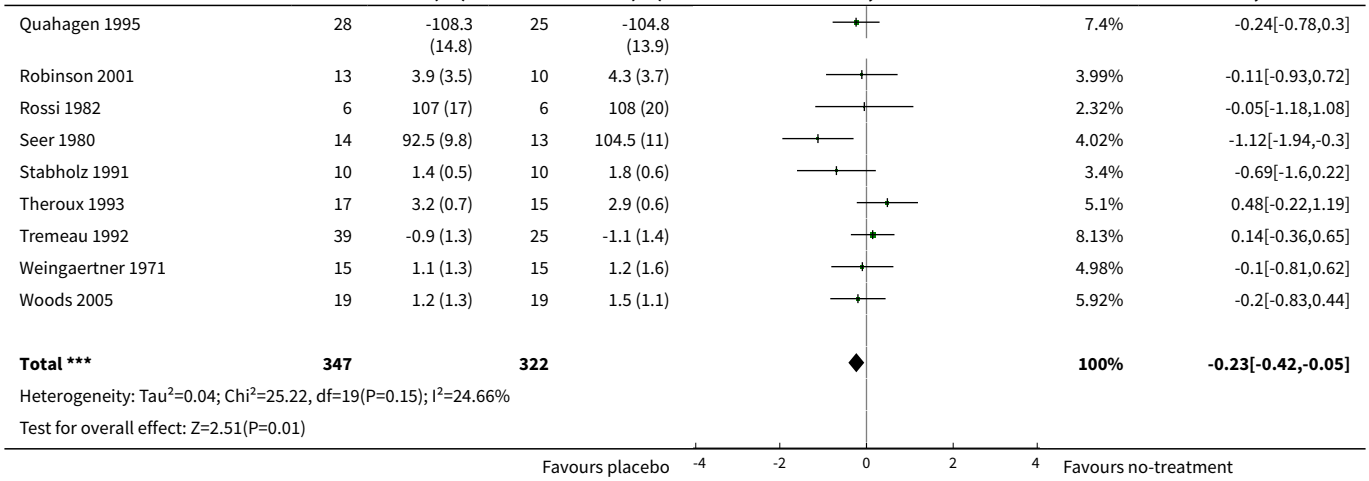
Favours placebo — Favours no-treatment

Analysis 11.3. Comparison 11 Risk of bias subgroup analysis: blinding of observer, Outcome 3 Blinding of observer: yes.

Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Allen 1998	11	-2.9 (7.9)	11	-6.1 (10.9)		3.85%	0.32[-0.52,1.17]
Allen 2006	45	12 (9.6)	44	19 (9.6)		9.75%	-0.72[-1.15,-0.29]
Bosley 1989	13	86 (10)	14	89 (10)		4.55%	-0.29[-1.05,0.47]
Bramston 1985	12	-78 (14.2)	12	-72 (13.8)		4.1%	-0.41[-1.22,0.4]
Etringer 1982	13	-11.4 (4)	12	-10.1 (3.7)		4.27%	-0.33[-1.12,0.46]
Frankel 1978	7	93 (5)	8	95 (3)		2.73%	-0.47[-1.5,0.57]
Kokol 2005	16	9.5 (10.5)	10	7.3 (6.6)		4.25%	0.23[-0.56,1.02]
Lee 2005	27	-21.4 (25.9)	27	-5.9 (9.2)		7.16%	-0.79[-1.34,-0.23]
May 1988	24	-1.2 (0.5)	24	-1.2 (0.5)		6.99%	-0.02[-0.59,0.54]
McLachlan 1991	8	6.3 (12.3)	12	5.7 (17.4)		3.49%	0.04[-0.86,0.93]
Nocella 1982	10	0.8 (0.9)	10	0.8 (0.7)		3.61%	-0.02[-0.9,0.85]



Favours placebo — Favours no-treatment

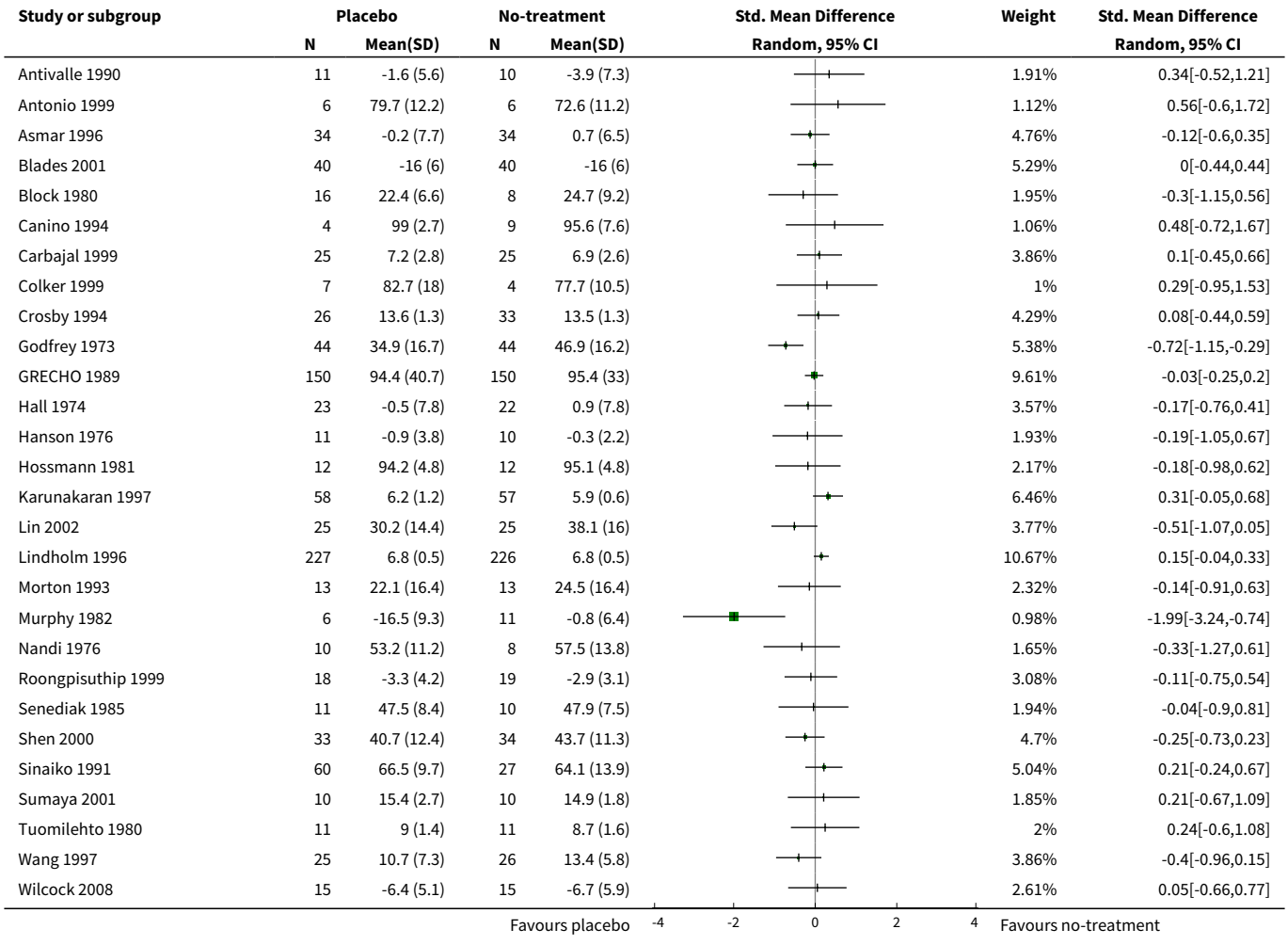


Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Quahagen 1995	28	-108.3 (14.8)	25	-104.8 (13.9)		7.4%	-0.24[-0.78,0.3]
Robinson 2001	13	3.9 (3.5)	10	4.3 (3.7)		3.99%	-0.11[-0.93,0.72]
Rossi 1982	6	107 (17)	6	108 (20)		2.32%	-0.05[-1.18,1.08]
Seer 1980	14	92.5 (9.8)	13	104.5 (11)		4.02%	-1.12[-1.94,-0.3]
Stabholz 1991	10	1.4 (0.5)	10	1.8 (0.6)		3.4%	-0.69[-1.6,0.22]
Theroux 1993	17	3.2 (0.7)	15	2.9 (0.6)		5.1%	0.48[-0.22,1.19]
Tremeau 1992	39	-0.9 (1.3)	25	-1.1 (1.4)		8.13%	0.14[-0.36,0.65]
Weingaertner 1971	15	1.1 (1.3)	15	1.2 (1.6)		4.98%	-0.1[-0.81,0.62]
Woods 2005	19	1.2 (1.3)	19	1.5 (1.1)		5.92%	-0.2[-0.83,0.44]
Total ***	**347**		**322**			**100%**	**-0.23[-0.42,-0.05]**

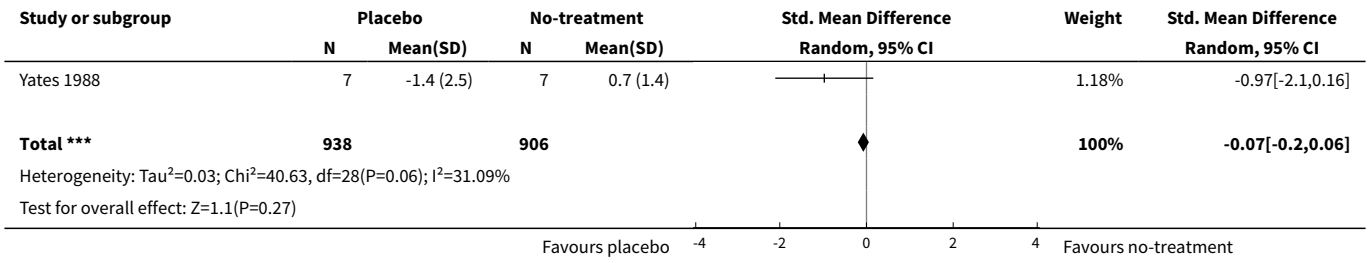
Heterogeneity: Tau^2=0.04; Chi^2=25.22, df=19(P=0.15); I^2=24.66%

Test for overall effect: Z=2.51(P=0.01)

Analysis 11.4. Comparison 11 Risk of bias subgroup analysis: blinding of observer, Outcome 4 Blinding of observer: not stated.



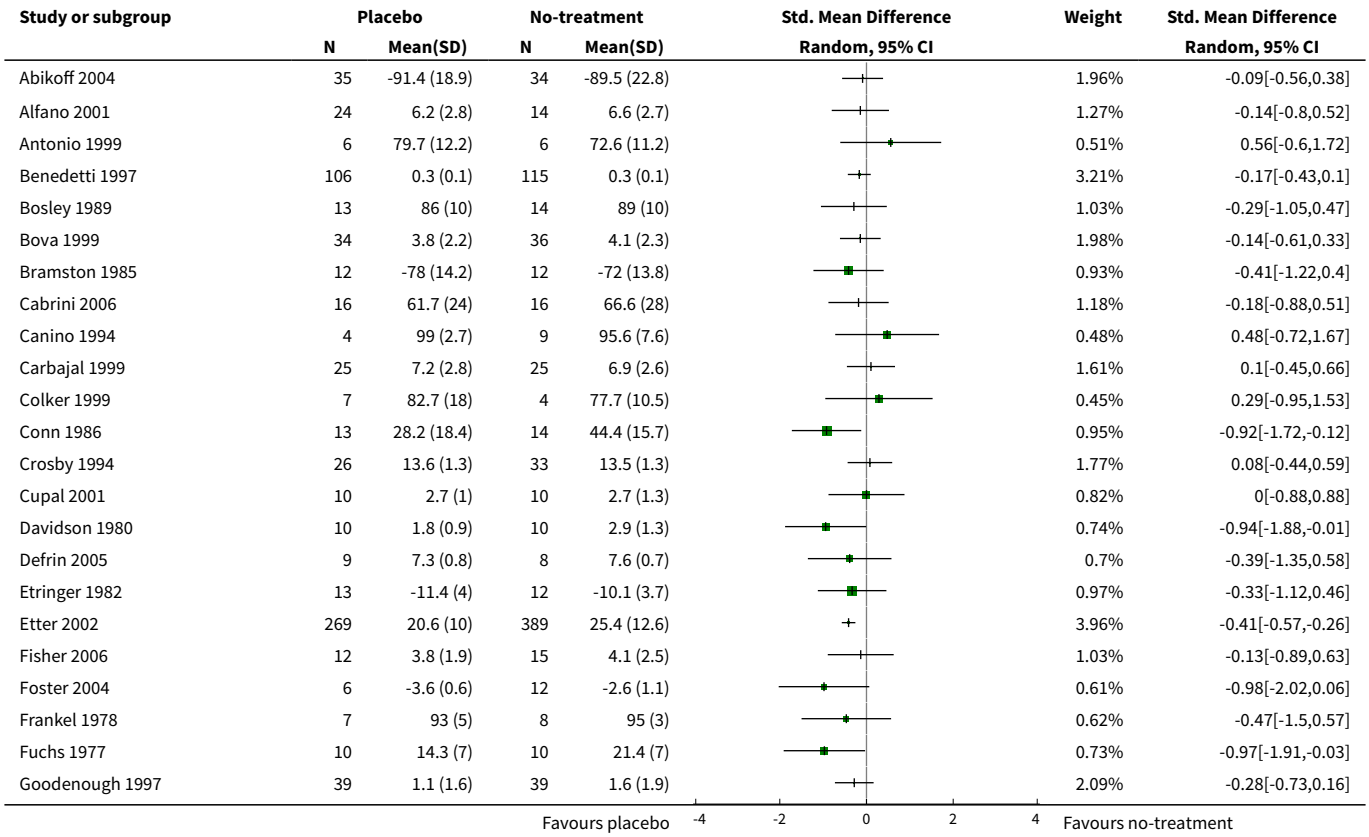
Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Antivalle 1990	11	-1.6 (5.6)	10	-3.9 (7.3)		1.91%	0.34[-0.52,1.21]
Antonio 1999	6	79.7 (12.2)	6	72.6 (11.2)		1.12%	0.56[-0.6,1.72]
Asmar 1996	34	-0.2 (7.7)	34	0.7 (6.5)		4.76%	-0.12[-0.6,0.35]
Blades 2001	40	-16 (6)	40	-16 (6)		5.29%	0[-0.44,0.44]
Block 1980	16	22.4 (6.6)	8	24.7 (9.2)		1.95%	-0.3[-1.15,0.56]
Canino 1994	4	99 (2.7)	9	95.6 (7.6)		1.06%	0.48[-0.72,1.67]
Carbajal 1999	25	7.2 (2.8)	25	6.9 (2.6)		3.86%	0.1[-0.45,0.66]
Colker 1999	7	82.7 (18)	4	77.7 (10.5)		1%	0.29[-0.95,1.53]
Crosby 1994	26	13.6 (1.3)	33	13.5 (1.3)		4.29%	0.08[-0.44,0.59]
Godfrey 1973	44	34.9 (16.7)	44	46.9 (16.2)		5.38%	-0.72[-1.15,-0.29]
GRECHO 1989	150	94.4 (40.7)	150	95.4 (33)		9.61%	-0.03[-0.25,0.2]
Hall 1974	23	-0.5 (7.8)	22	0.9 (7.8)		3.57%	-0.17[-0.76,0.41]
Hanson 1976	11	-0.9 (3.8)	10	-0.3 (2.2)		1.93%	-0.19[-1.05,0.67]
Hossmann 1981	12	94.2 (4.8)	12	95.1 (4.8)		2.17%	-0.18[-0.98,0.62]
Karunakaran 1997	58	6.2 (1.2)	57	5.9 (0.6)		6.46%	0.31[-0.05,0.68]
Lin 2002	25	30.2 (14.4)	25	38.1 (16)		3.77%	-0.51[-1.07,0.05]
Lindholm 1996	227	6.8 (0.5)	226	6.8 (0.5)		10.67%	0.15[-0.04,0.33]
Morton 1993	13	22.1 (16.4)	13	24.5 (16.4)		2.32%	-0.14[-0.91,0.63]
Murphy 1982	6	-16.5 (9.3)	11	-0.8 (6.4)		0.98%	-1.99[-3.24,-0.74]
Nandi 1976	10	53.2 (11.2)	8	57.5 (13.8)		1.65%	-0.33[-1.27,0.61]
Roongpisuthip 1999	18	-3.3 (4.2)	19	-2.9 (3.1)		3.08%	-0.11[-0.75,0.54]
Senediak 1985	11	47.5 (8.4)	10	47.9 (7.5)		1.94%	-0.04[-0.9,0.81]
Shen 2000	33	40.7 (12.4)	34	43.7 (11.3)		4.7%	-0.25[-0.73,0.23]
Sinaiko 1991	60	66.5 (9.7)	27	64.1 (13.9)		5.04%	0.21[-0.24,0.67]
Sumaya 2001	10	15.4 (2.7)	10	14.9 (1.8)		1.85%	0.21[-0.67,1.09]
Tuomilehto 1980	11	9 (1.4)	11	8.7 (1.6)		2%	0.24[-0.6,1.08]
Wang 1997	25	10.7 (7.3)	26	13.4 (5.8)		3.86%	-0.4[-0.96,0.15]
Wilcock 2008	15	-6.4 (5.1)	15	-6.7 (5.9)		2.61%	0.05[-0.66,0.77]



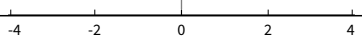
Comparison 12. Risk of bias subgroup analysis: variance inequality and skewness

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 No signs of unequal variance or skewness	72	4378	Std. Mean Difference (IV, Random, 95% CI)	-0.24 [-0.33, -0.15]
2 Signs of either unequal variance or skewness	52	4108	Std. Mean Difference (IV, Random, 95% CI)	-0.20 [-0.30, -0.11]

Analysis 12.1. Comparison 12 Risk of bias subgroup analysis: variance inequality and skewness, Outcome 1 No signs of unequal variance or skewness.



Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Hargreaves 1989	25	4.5 (2.5)	25	4.9 (2.4)		1.61%	-0.16[-0.72,0.39]
Hashish 1988	25	42 (25)	25	60 (23)		1.54%	-0.74[-1.31,-0.16]
Hawkins 1995	10	37.4 (8.5)	10	52.1 (9.3)		0.62%	-1.58[-2.61,-0.55]
Hossmann 1981	12	94.2 (4.8)	12	95.1 (4.8)		0.95%	-0.18[-0.98,0.62]
Hovell 2003	98	-155.4 (69.9)	96	-151 (73.8)		3.09%	-0.06[-0.34,0.22]
Hyland 2006	10	6 (0.9)	10	6.2 (0.9)		0.82%	-0.21[-1.09,0.67]
Irvin 1996	11	3.3 (0.7)	11	3.7 (1.4)		0.87%	-0.35[-1.19,0.5]
Jacobson 1978	7	2.5 (0.9)	6	3.5 (0.5)		0.47%	-1.17[-2.39,0.04]
Kaptchuk 2008	88	-4.3 (1.4)	87	-3.8 (1)		2.97%	-0.41[-0.71,-0.11]
Karst 2007	19	45.2 (10.8)	10	56.5 (9.1)		0.91%	-1.07[-1.89,-0.25]
Kober 2002	20	66.7 (10)	21	64.4 (13.3)		1.41%	0.19[-0.42,0.8]
Kotani 2001	23	15 (4.5)	24	18 (6)		1.51%	-0.55[-1.14,0.03]
Leibing 2002	40	3.2 (1.8)	39	4.3 (1.9)		2.06%	-0.59[-1.04,-0.14]
Lick 1977	10	66 (25)	10	63 (32)		0.82%	0.1[-0.78,0.98]
Limoges 2004	30	2.3 (1)	30	2.2 (1)		1.81%	0.04[-0.47,0.55]
Lin 2002	25	30.2 (14.4)	25	38.1 (16)		1.58%	-0.51[-1.07,0.05]
Lindholm 1996	227	6.8 (0.5)	226	6.8 (0.5)		3.78%	0.15[-0.04,0.33]
Liossi 2003	20	4.3 (0.6)	20	4.6 (0.6)		1.36%	-0.49[-1.12,0.14]
Longo 1988	10	3.6 (0.6)	9	3.6 (0.4)		0.79%	0[-0.9,0.9]
Lorr 1961	42	58.3 (9.9)	38	57.5 (9.9)		2.13%	0.08[-0.36,0.52]
Matros 2006	23	76 (36.3)	21	72 (28.3)		1.48%	0.12[-0.47,0.71]
Morey 2006	38	-16.5 (9.3)	42	-14.7 (9.5)		2.12%	-0.19[-0.63,0.25]
Nandi 1976	10	53.2 (11.2)	8	57.5 (13.8)		0.73%	-0.33[-1.27,0.61]
Parker 2003	13	16.2 (7.5)	14	14.2 (7.5)		1.03%	0.26[-0.5,1.02]
Pelham 1992	38	-8.7 (1.7)	38	-8.5 (1.6)		2.07%	-0.12[-0.57,0.33]
Quahagen 1995	28	-108.3 (14.8)	25	-104.8 (13.9)		1.66%	-0.24[-0.78,0.3]
Ristikankare 1999	61	40.3 (21.5)	61	36 (21.5)		2.6%	0.2[-0.16,0.55]
Roscoe 2002	27	5.9 (5.2)	27	6.6 (3.6)		1.69%	-0.15[-0.69,0.38]
Roscoe 2005	31	2.4 (1.3)	33	2.8 (1.3)		1.87%	-0.3[-0.8,0.19]
Rosen 1976	9	6.9 (2)	5	8.3 (1.9)		0.53%	-0.67[-1.8,0.46]
Rossi 1982	6	107 (17)	6	108 (20)		0.53%	-0.05[-1.18,1.08]
Rösler 2003	13	5.9 (3.4)	14	6 (3)		1.04%	-0.02[-0.78,0.73]
Sanders 1990	6	2 (0.4)	6	2.1 (0.3)		0.53%	-0.13[-1.26,1]
Seer 1980	14	92.5 (9.8)	13	104.5 (11)		0.91%	-1.12[-1.94,-0.3]
Senediak 1985	11	47.5 (8.4)	10	47.9 (7.5)		0.85%	-0.04[-0.9,0.81]
Shen 2000	33	40.7 (12.4)	34	43.7 (11.3)		1.92%	-0.25[-0.73,0.23]
Sinaiko 1991	60	66.5 (9.7)	27	64.1 (13.9)		2.04%	0.21[-0.24,0.67]
Spanos 1995	13	21.4 (9.7)	12	19.1 (10.3)		0.98%	0.22[-0.56,1.01]
Stabholz 1991	10	1.4 (0.5)	10	1.8 (0.6)		0.77%	-0.69[-1.6,0.22]
Stewart 1991	25	-14.3 (5.5)	25	-12.8 (5.2)		1.6%	-0.28[-0.83,0.28]
Straub 2001	5	-5.8 (0.3)	5	-6 (0.7)		0.45%	0.27[-0.98,1.52]
Sumaya 2001	10	15.4 (2.7)	10	14.9 (1.8)		0.82%	0.21[-0.67,1.09]
Tan 1982	12	1.3 (0.6)	12	1.7 (0.8)		0.92%	-0.55[-1.36,0.27]
Theroux 1993	17	3.2 (0.7)	15	2.9 (0.6)		1.15%	0.48[-0.22,1.19]
Tritrakarn 2000	41	49 (16)	41	61 (17)		2.08%	-0.72[-1.17,-0.27]
Tsay 2004	35	4.7 (1.5)	36	5.7 (1.8)		1.94%	-0.6[-1.07,-0.12]
Tuomilehto 1980	11	9 (1.4)	11	8.7 (1.6)		0.88%	0.24[-0.6,1.08]
Werntoft 2001	20	5.9 (2.4)	20	6.5 (2.2)		1.38%	-0.26[-0.88,0.37]
Witt 2005	73	35.8 (16.2)	67	49.6 (16.3)		2.66%	-0.84[-1.19,-0.5]



Favours placebo Favours no-treatment

Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Total ***	**2151**		**2227**			**100%**	**-0.24[-0.33,-0.15]**
Heterogeneity: Tau²=0.04; Chi²=115.6, df=71(P=0); I²=38.58%							
Test for overall effect: Z=5.31(P<0.0001)							

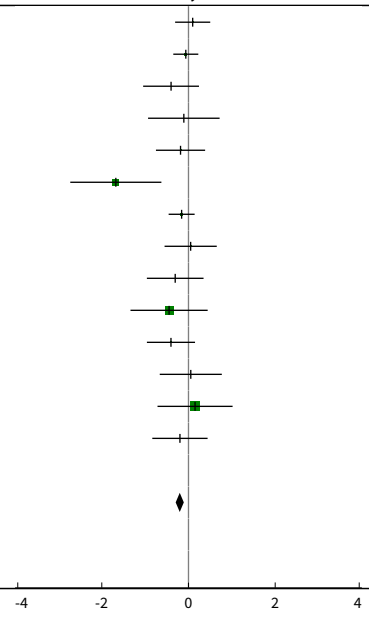
Favours placebo -4 -2 0 2 4 Favours no-treatment

Analysis 12.2. Comparison 12 Risk of bias subgroup analysis: variance inequality and skewness, Outcome 2 Signs of either unequal variance or skewness.

Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Allen 2006	45	12 (9.6)	44	19 (9.6)		2.48%	-0.72[-1.15,-0.29]
Andersen 1990	18	35 (27.2)	16	25 (23.6)		1.39%	0.38[-0.3,1.06]
Ascher 1979	8	50.6 (44.1)	9	62.4 (25.3)		0.81%	-0.32[-1.28,0.64]
Biro 1997	29	3.6 (2.5)	29	3.3 (2.1)		2.02%	0.13[-0.39,0.64]
Blanchard 1990a	13	8.3 (13.6)	11	22.5 (25.1)		1.02%	-0.7[-1.53,0.13]
Blanchard 1990b	18	11.9 (23.9)	24	20.7 (34.8)		1.61%	-0.28[-0.9,0.33]
Chenard 1991	12	29 (19)	16	30 (19)		1.21%	-0.05[-0.8,0.7]
Classen 1983	15	11.3 (8.3)	15	14.4 (6.1)		1.27%	-0.41[-1.14,0.31]
Costello 2006	48	33 (25)	42	31 (25)		2.57%	0.08[-0.33,0.49]
Coyne 1995	21	0.7 (0.7)	21	0.6 (0.7)		1.64%	0.13[-0.47,0.74]
Dibble 2007	49	3.1 (2.9)	51	3.5 (3.1)		2.71%	-0.12[-0.51,0.27]
Ditto 2003	200	0.5 (0.4)	189	0.5 (0.4)		4.16%	-0.02[-0.22,0.17]
Ditto 2006	140	0.4 (0.4)	155	0.5 (0.4)		3.93%	-0.06[-0.28,0.17]
Espie 1989	14	63.5 (30.6)	13	96.5 (63.5)		1.14%	-0.65[-1.43,0.13]
Forster 1994	15	3.2 (2.8)	15	4.6 (2.2)		1.25%	-0.54[-1.27,0.19]
Foster 2007	112	6.5 (4.8)	105	6.8 (4.5)		3.63%	-0.06[-0.33,0.21]
Frega 1994	21	20 (16)	21	23 (16)		1.64%	-0.18[-0.79,0.42]
Goodenough 1997	39	1.1 (1.6)	39	1.6 (1.9)		2.38%	-0.28[-0.73,0.16]
GRECHO 1989	150	94.4 (40.7)	150	95.4 (33)		3.95%	-0.03[-0.25,0.2]
Hashish 1986	25	16 (11.7)	50	30 (18.9)		2.1%	-0.82[-1.32,-0.32]
Helms 1987	11	103 (91)	11	79 (99)		1.01%	0.24[-0.6,1.08]
Hruby 2006	49	1.2 (2.1)	51	0.9 (1.5)		2.7%	0.21[-0.19,0.6]
Irvin 1996	11	3.3 (0.7)	11	3.7 (1.4)		1%	-0.35[-1.19,0.5]
Karunakaran 1997	58	6.2 (1.2)	57	5.9 (0.6)		2.87%	0.31[-0.05,0.68]
Killeen 2004	24	1 (2.5)	35	1.9 (3.5)		1.99%	-0.28[-0.81,0.24]
Kilmann 1987	4	-33 (47)	4	-35 (47)		0.42%	0.04[-1.35,1.42]
Kokol 2005	16	9.5 (10.5)	10	7.3 (6.6)		1.1%	0.23[-0.56,1.02]
Lander 1993	172	28.5 (29.3)	168	32.3 (33.4)		4.05%	-0.12[-0.33,0.09]
Lee 2005	27	-21.4 (25.9)	27	-5.9 (9.2)		1.84%	-0.79[-1.34,-0.23]
Licciardone 2003	19	2.5 (1.7)	15	3.5 (2.7)		1.37%	-0.49[-1.17,0.2]
Lincoln 2003	42	14.4 (10)	38	16.7 (10)		2.41%	-0.23[-0.67,0.21]
McLachlan 1991	8	6.3 (12.3)	12	5.7 (17.4)		0.91%	0.04[-0.86,0.93]
Melchart 2005	57	10.8 (8.3)	63	16.3 (7.4)		2.86%	-0.7[-1.07,-0.33]
Moffet 1996	22	24 (18.6)	27	34.6 (23.2)		1.77%	-0.49[-1.06,0.08]
Nawrocki 1997	40	9.5 (6)	42	17 (4.8)		2.18%	-1.37[-1.85,-0.89]
Nicassio 1974	7	117.3 (133.7)	9	99.3 (35.3)		0.77%	0.19[-0.8,1.18]
Nocella 1982	10	0.8 (0.9)	10	0.8 (0.7)		0.94%	-0.02[-0.9,0.85]
O'Brien 1996	53	6.7 (5.6)	54	7.5 (5.1)		2.79%	-0.15[-0.53,0.23]

Favours placebo -4 -2 0 2 4 Favours no-treatment

Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Parker 1995	49	4 (1.9)	45	3.8 (2.2)		2.63%	0.1[-0.31,0.5]
Rawling 2001	89	5.3 (4.7)	96	5.6 (4.9)		3.45%	-0.06[-0.35,0.23]
Reading 1982	18	1.6 (1.3)	20	2.3 (2)		1.51%	-0.4[-1.05,0.24]
Robinson 2001	13	3.9 (3.5)	10	4.3 (3.7)		1.04%	-0.11[-0.93,0.72]
Röschke 2000	24	23 (16.2)	24	26 (16)		1.79%	-0.18[-0.75,0.38]
Sipich 1974	10	8 (14)	10	32.5 (14)		0.69%	-1.68[-2.73,-0.63]
Steinsbekk 2004	102	44.5 (58.9)	74	53 (45.2)		3.37%	-0.16[-0.46,0.14]
Tashjian 2006	19	3.4 (2.2)	24	3.3 (1.8)		1.65%	0.05[-0.55,0.65]
Thomas 1999	14	13.4 (10.3)	26	16.5 (9.7)		1.47%	-0.31[-0.96,0.35]
Turner 1979	10	44.2 (41.3)	10	59.8 (22.9)		0.92%	-0.45[-1.34,0.44]
Wang 1997	25	10.7 (7.3)	26	13.4 (5.8)		1.84%	-0.4[-0.96,0.15]
Wilcock 2008	15	-6.4 (5.1)	15	-6.7 (5.9)		1.29%	0.05[-0.66,0.77]
Wojciechowski 1984	9	264 (122)	12	238 (190)		0.96%	0.15[-0.71,1.02]
Woods 2005	19	1.2 (1.3)	19	1.5 (1.1)		1.53%	-0.2[-0.83,0.44]
Total ***	**2038**		**2070**			**100%**	**-0.2[-0.3,-0.11]**
Heterogeneity: Tau^2=0.05; Chi^2=94.32, df=51(P=0); I^2=45.93%							
Test for overall effect: Z=4.2(P<0.0001)							

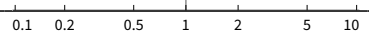


Comparison 13. Risk of bias subgroup analysis: selection of outcome

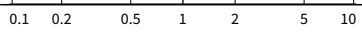
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Selection of outcome: primary trial outcome clearly indicated	31	4775	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.86, 1.00]
2 Selection of outcome: primary trial outcome not clearly indicated (or not selected)	13	1265	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.89, 1.01]
3 Selection of outcome: primary trial outcome clearly indicated	85	6028	Std. Mean Difference (IV, Random, 95% CI)	-0.26 [-0.34, -0.19]
4 Selection of outcome: primary trial outcome not clearly indicated (or not selected)	73	4485	Std. Mean Difference (IV, Random, 95% CI)	-0.17 [-0.25, -0.09]

Analysis 13.1. Comparison 13 Risk of bias subgroup analysis: selection of outcome, Outcome 1 Selection of outcome: primary trial outcome clearly indicated.

Study or subgroup	Placebo n/N	No-treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Adriaanse 1995	50/328	38/326		2.57%	1.31[0.88,1.94]
Alkaissi 2002	77/139	82/136		5.08%	0.92[0.75,1.12]
Aune 1998	11/26	9/14		1.37%	0.66[0.36,1.19]
Blackman 1964	6/12	6/12		0.82%	1[0.45,2.23]
Carter 2003	13/28	20/29		2.01%	0.67[0.42,1.07]



Study or subgroup	Placebo n/N	No-treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Double 1993	3/22	3/22		0.26%	1[0.23,4.42]
Dundee 1986	17/25	17/25		2.68%	1[0.68,1.46]
Elliott 1978	6/18	6/6		1.16%	0.37[0.19,0.71]
Faas 1993	107/162	108/155		6%	0.95[0.81,1.1]
Frank 1990	14/26	14/26		1.79%	1[0.6,1.65]
Harrison 1975	24/28	25/30		4.77%	1.03[0.83,1.28]
Heinzl 1981	70/130	92/132		5.21%	0.77[0.64,0.94]
Hyman 1986	9/15	15/15		2.38%	0.61[0.4,0.93]
Jacobs 1971	9/15	12/39		1.26%	1.95[1.04,3.65]
Kerr 2003	28/33	32/36		5.39%	0.95[0.79,1.15]
Killen 1990	226/309	219/309		6.94%	1.03[0.94,1.14]
Klerman 1974	17/25	16/25		2.52%	1.06[0.71,1.58]
Malcolm 1980	40/63	44/58		4.49%	0.84[0.66,1.06]
McMillan 1994	14/26	24/46		2.12%	1.03[0.66,1.62]
Molsberger 2002	38/58	30/53		3.56%	1.16[0.86,1.56]
Najnigier 1997	21/30	24/30		3.64%	0.88[0.65,1.17]
Rabkin 1990	14/27	12/23		1.63%	0.99[0.58,1.7]
Roughan 1981	9/12	9/14		1.76%	1.17[0.7,1.94]
Scharf 2006	179/365	224/316		6.47%	0.69[0.61,0.78]
Scharff 2002	9/11	11/12		3.24%	0.89[0.64,1.24]
Tarrier 1998	22/26	25/28		4.97%	0.95[0.77,1.17]
Thomas 1987	47/100	50/100		3.75%	0.94[0.71,1.25]
Tyler 1946	89/260	106/303		4.63%	0.98[0.78,1.23]
Watzl 1986	15/34	7/36		0.89%	2.27[1.06,4.88]
Whittaker 1963	3/13	7/13		0.45%	0.43[0.14,1.3]
Williams 1988	19/20	19/20		6.18%	1[0.87,1.15]
Total (95% CI)	**2386**	**2389**		**100%**	**0.93[0.86,1]**
Total events: 1206 (Placebo), 1306 (No-treatment)					
Heterogeneity: Tau²=0.02; Chi²=65.9, df=30(P=0); I²=54.47%					
Test for overall effect: Z=1.9(P=0.06)					



Favours placebo — Favours no-treatment

Analysis 13.2. Comparison 13 Risk of bias subgroup analysis: selection of outcome, Outcome 2 Selection of outcome: primary trial outcome not clearly indicated (or not selected).

Study or subgroup	Placebo n/N	No-treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Alkaissi 1999	9/20	11/20		1.05%	0.82[0.44,1.53]
Berg 1983	9/11	9/15		1.65%	1.36[0.83,2.24]
Corver 2006	227/279	360/416		62.63%	0.94[0.88,1.01]
De Sanctis 2001	9/10	8/9		4.21%	1.01[0.74,1.38]
Fanti 2003	8/10	9/10		2.93%	0.89[0.61,1.29]
Guglielmi 1982	12/12	11/12		7.88%	1.09[0.87,1.36]
Hutton 1991	5/24	16/30		0.57%	0.39[0.17,0.91]
Schallreuter 2002	3/10	4/10		0.28%	0.75[0.22,2.52]
Stransky 1989	1/5	1/4		0.07%	0.8[0.07,9.18]
Tan 1986	8/10	8/9		2.73%	0.9[0.61,1.32]
Tarcin 2004	58/158	27/77		3.03%	1.05[0.73,1.51]

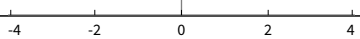
Favours placebo — Favours no-treatment

Study or subgroup	Placebo n/N	No-treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Walton 1993	19/24	21/30		4.17%	1.13[0.83,1.54]
Wilson 1980	31/40	10/10		8.8%	0.8[0.65,0.99]
Total (95% CI)	**613**	**652**		**100%**	**0.95[0.89,1.01]**
Total events: 399 (Placebo), 495 (No-treatment)					
Heterogeneity: Tau^2=0; Chi^2=12.31, df=12(P=0.42); I^2=2.5%					
Test for overall effect: Z=1.64(P=0.1)					

Favours placebo — Favours no-treatment

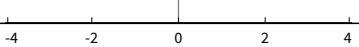
Analysis 13.3. Comparison 13 Risk of bias subgroup analysis: selection of outcome, Outcome 3 Selection of outcome: primary trial outcome clearly indicated.

Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Allen 2006	45	12 (9.6)	44	19 (9.6)		1.57%	-0.72[-1.15,-0.29]
Andersen 1990	18	35 (27.2)	16	25 (23.6)		0.92%	0.38[-0.3,1.06]
Antivalle 1990	11	-1.6 (5.6)	10	-3.9 (7.3)		0.65%	0.34[-0.52,1.21]
Antonio 1999	6	79.7 (12.2)	6	72.6 (11.2)		0.4%	0.56[-0.6,1.72]
Benedetti 1995	13	-2 (1.2)	11	-0.8 (1)		0.64%	-1.07[-1.94,-0.2]
Benedetti 1997	106	0.3 (0.1)	115	0.3 (0.1)		2.22%	-0.17[-0.43,0.1]
Blades 2001	40	-16 (6)	40	-16 (6)		1.54%	0[-0.44,0.44]
Block 1980	16	22.4 (6.6)	8	24.7 (9.2)		0.66%	-0.3[-1.15,0.56]
Bosley 1989	13	86 (10)	14	89 (10)		0.79%	-0.29[-1.05,0.47]
Bova 1999	34	3.8 (2.2)	36	4.1 (2.3)		1.44%	-0.14[-0.61,0.33]
Brinkhaus 2006	70	-23.6 (31)	74	-6.9 (22)		1.93%	-0.62[-0.96,-0.29]
Canino 1994	4	99 (2.7)	9	95.6 (7.6)		0.38%	0.48[-0.72,1.67]
Chenard 1991	12	29 (19)	16	30 (19)		0.81%	-0.05[-0.8,0.7]
Classen 1983	15	11.3 (8.3)	15	14.4 (6.1)		0.85%	-0.41[-1.14,0.31]
Conn 1986	13	28.2 (18.4)	14	44.4 (15.7)		0.73%	-0.92[-1.72,-0.12]
Crosby 1994	26	13.6 (1.3)	33	13.5 (1.3)		1.31%	0.08[-0.44,0.59]
Ditto 2003	200	0.5 (0.4)	189	0.5 (0.4)		2.48%	-0.02[-0.22,0.17]
Ditto 2006	140	0.4 (0.4)	155	0.5 (0.4)		2.36%	-0.06[-0.28,0.17]
Erdogmus 2007	40	-27.4 (19.7)	40	-20.3 (19.7)		1.53%	-0.36[-0.8,0.08]
Etringer 1982	13	-11.4 (4)	12	-10.1 (3.7)		0.74%	-0.33[-1.12,0.46]
Fisher 2006	12	3.8 (1.9)	15	4.1 (2.5)		0.79%	-0.13[-0.89,0.63]
Forster 1994	15	3.2 (2.8)	15	4.6 (2.2)		0.84%	-0.54[-1.27,0.19]
Foster 2007	112	6.5 (4.8)	105	6.8 (4.5)		2.21%	-0.06[-0.33,0.21]
Frankel 1978	7	93 (5)	8	95 (3)		0.49%	-0.47[-1.5,0.57]
Frega 1994	21	20 (16)	21	23 (16)		1.08%	-0.18[-0.79,0.42]
Fuchs 1977	10	14.3 (7)	10	21.4 (7)		0.57%	-0.97[-1.91,-0.03]
Godfrey 1973	44	34.9 (16.7)	44	46.9 (16.2)		1.57%	-0.72[-1.15,-0.29]
Goodenough 1997	39	1.1 (1.6)	39	1.6 (1.9)		1.52%	-0.28[-0.73,0.16]
Gracely 1983	17	-2.9 (5.4)	12	0.2 (5.5)		0.8%	-0.54[-1.3,0.21]
GRECHO 1989	150	94.4 (40.7)	150	95.4 (33)		2.37%	-0.03[-0.25,0.2]
Hanson 1976	11	-0.9 (3.8)	10	-0.3 (2.2)		0.66%	-0.19[-1.05,0.67]
Hargreaves 1989	25	4.5 (2.5)	25	4.9 (2.4)		1.2%	-0.16[-0.72,0.39]
Hashish 1988	25	42 (25)	25	60 (23)		1.15%	-0.74[-1.31,-0.16]
Hawkins 1995	10	37.4 (8.5)	10	52.1 (9.3)		0.49%	-1.58[-2.61,-0.55]
Helms 1987	11	103 (91)	11	79 (99)		0.68%	0.24[-0.6,1.08]



Favours placebo — Favours no-treatment

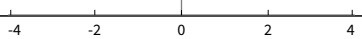
Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Hong 1993	16	-1.1 (0.2)	21	-1 (0.1)		0.96%	-0.53[-1.19,0.13]
Hovell 2003	98	-155.4 (69.9)	96	-151 (73.8)		2.14%	-0.06[-0.34,0.22]
Kaptchuk 2008	88	-4.3 (1.4)	87	-3.8 (1)		2.07%	-0.41[-0.71,-0.11]
Karunakaran 1997	58	6.2 (1.2)	57	5.9 (0.6)		1.8%	0.31[-0.05,0.68]
Kendall 1979	11	7.5 (2.3)	11	8.2 (3)		0.68%	-0.23[-1.07,0.61]
Killeen 2004	24	1 (2.5)	35	1.9 (3.5)		1.29%	-0.28[-0.81,0.24]
Leibing 2002	40	3.2 (1.8)	39	4.3 (1.9)		1.5%	-0.59[-1.04,-0.14]
Levine 1984	12	-0.3 (0.7)	24	0.4 (2.5)		0.89%	-0.31[-1.01,0.38]
Lincoln 2003	42	14.4 (10)	38	16.7 (10)		1.54%	-0.23[-0.67,0.21]
Linde 2005	76	-2.2 (2.7)	64	-0.8 (2.2)		1.91%	-0.56[-0.9,-0.22]
Macaluso 1995	30	-3.3 (3.8)	30	-1.8 (3.3)		1.32%	-0.41[-0.93,0.1]
Markland 1993	7	37.3 (11.8)	7	36.9 (11.9)		0.48%	0.03[-1.01,1.08]
Matros 2006	23	76 (36.3)	21	72 (28.3)		1.11%	0.12[-0.47,0.71]
May 1988	24	-1.2 (0.5)	24	-1.2 (0.5)		1.17%	-0.02[-0.59,0.54]
McLachlan 1991	8	6.3 (12.3)	12	5.7 (17.4)		0.61%	0.04[-0.86,0.93]
Medici 2002	23	-0.2 (0.3)	18	-0.1 (0.3)		1.04%	-0.31[-0.93,0.32]
Melchart 2005	57	10.8 (8.3)	63	16.3 (7.4)		1.79%	-0.7[-1.07,-0.33]
Moreland 2006	50	-2 (1.3)	99	-2.1 (1.7)		1.9%	0.06[-0.28,0.4]
Morey 2006	38	-16.5 (9.3)	42	-14.7 (9.5)		1.54%	-0.19[-0.63,0.25]
Morton 1993	13	22.1 (16.4)	13	24.5 (16.4)		0.77%	-0.14[-0.91,0.63]
Nandi 1976	10	53.2 (11.2)	8	57.5 (13.8)		0.57%	-0.33[-1.27,0.61]
Nawrocki 1997	40	9.5 (6)	42	17 (4.8)		1.4%	-1.37[-1.85,-0.89]
Nocella 1982	10	0.8 (0.9)	10	0.8 (0.7)		0.64%	-0.02[-0.9,0.85]
O'Brien 1996	53	6.7 (5.6)	54	7.5 (5.1)		1.75%	-0.15[-0.53,0.23]
Parker 2003	13	16.2 (7.5)	14	14.2 (7.5)		0.79%	0.26[-0.5,1.02]
Rawling 2001	89	5.3 (4.7)	96	5.6 (4.9)		2.11%	-0.06[-0.35,0.23]
Reading 1982	18	1.6 (1.3)	20	2.3 (2)		0.99%	-0.4[-1.05,0.24]
Roongpisuthip 1999	18	-3.3 (4.2)	19	-2.9 (3.1)		0.99%	-0.11[-0.75,0.54]
Roscoe 2002	27	5.9 (5.2)	27	6.6 (3.6)		1.25%	-0.15[-0.69,0.38]
Roscoe 2005	31	2.4 (1.3)	33	2.8 (1.3)		1.37%	-0.3[-0.8,0.19]
Rossi 1982	6	107 (17)	6	108 (20)		0.42%	-0.05[-1.18,1.08]
Rowbotham 1996	35	-4.4 (8.7)	35	1.9 (8.7)		1.4%	-0.72[-1.2,-0.23]
Rybarczyk 1990	25	7.1 (2.2)	24	7.5 (2.8)		1.18%	-0.16[-0.73,0.4]
Rösler 2003	13	5.9 (3.4)	14	6 (3)		0.8%	-0.02[-0.78,0.73]
Sanders 1990	6	2 (0.4)	6	2.1 (0.3)		0.42%	-0.13[-1.26,1]
Seer 1980	14	92.5 (9.8)	13	104.5 (11)		0.7%	-1.12[-1.94,-0.3]
Sipich 1974	10	8 (14)	10	32.5 (14)		0.47%	-1.68[-2.73,-0.63]
Spanos 1995	13	21.4 (9.7)	12	19.1 (10.3)		0.75%	0.22[-0.56,1.01]
Stewart 1991	25	-14.3 (5.5)	25	-12.8 (5.2)		1.19%	-0.28[-0.83,0.28]
Sumaya 2001	10	15.4 (2.7)	10	14.9 (1.8)		0.63%	0.21[-0.67,1.09]
Thomas 2002a	78	-0.9 (3)	78	-0.1 (2.9)		2%	-0.27[-0.59,0.04]
Thomas 2002b	114	-1.2 (3.5)	119	-1.6 (3.3)		2.25%	0.12[-0.14,0.37]
Tremeau 1992	39	-0.9 (1.3)	25	-1.1 (1.4)		1.34%	0.14[-0.36,0.65]
Tritrakarn 2000	41	49 (16)	41	61 (17)		1.51%	-0.72[-1.17,-0.27]
Tsay 2003	32	9.2 (4.4)	32	9.6 (4)		1.38%	-0.08[-0.57,0.41]
Werntoft 2001	20	5.9 (2.4)	20	6.5 (2.2)		1.04%	-0.26[-0.88,0.37]
Wilcock 2008	15	-6.4 (5.1)	15	-6.7 (5.9)		0.86%	0.05[-0.66,0.77]
Witt 2005	73	35.8 (16.2)	67	49.6 (16.3)		1.88%	-0.84[-1.19,-0.5]
Wojciechowski 1984	9	264 (122)	12	238 (190)		0.65%	0.15[-0.71,1.02]
Yates 1988	7	-1.4 (2.5)	7	0.7 (1.4)		0.42%	-0.97[-2.1,0.16]



Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Total ***	**2976**		**3052**			**100%**	**-0.26[-0.34,-0.19]**
Heterogeneity: Tau²=0.05; Chi²=162.39, df=84(P<0.0001); I²=48.27%							
Test for overall effect: Z=6.58(P<0.0001)							

Analysis 13.4. Comparison 13 Risk of bias subgroup analysis: selection of outcome, Outcome 4 Selection of outcome: primary trial outcome not clearly indicated (or not selected).

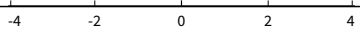
Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Abikoff 2004	35	-91.4 (18.9)	34	-89.5 (22.8)		1.92%	-0.09[-0.56,0.38]
Alfano 2001	24	6.2 (2.8)	14	6.6 (2.7)		1.19%	-0.14[-0.8,0.52]
Allen 1998	11	-2.9 (7.9)	11	-6.1 (10.9)		0.79%	0.32[-0.52,1.17]
Anderson 1999	30	-2.7 (0.8)	27	-2.7 (0.8)		1.69%	0.08[-0.44,0.6]
Ascher 1979	8	50.6 (44.1)	9	62.4 (25.3)		0.63%	-0.32[-1.28,0.64]
Asmar 1996	34	-0.2 (7.7)	34	0.7 (6.5)		1.9%	-0.12[-0.6,0.35]
Biro 1997	29	3.6 (2.5)	29	3.3 (2.1)		1.71%	0.13[-0.39,0.64]
Blanchard 1990a	13	8.3 (13.6)	11	22.5 (25.1)		0.81%	-0.7[-1.53,0.13]
Blanchard 1990b	18	11.9 (23.9)	24	20.7 (34.8)		1.32%	-0.28[-0.9,0.33]
Bramston 1985	12	-78 (14.2)	12	-72 (13.8)		0.85%	-0.41[-1.22,0.4]
Cabrini 2006	16	61.7 (24)	16	66.6 (28)		1.09%	-0.18[-0.88,0.51]
Carbajal 1999	25	7.2 (2.8)	25	6.9 (2.6)		1.54%	0.1[-0.45,0.66]
Colker 1999	7	82.7 (18)	4	77.7 (10.5)		0.4%	0.29[-0.95,1.53]
Costello 2006	48	33 (25)	42	31 (25)		2.26%	0.08[-0.33,0.49]
Coyne 1995	21	0.7 (0.7)	21	0.6 (0.7)		1.35%	0.13[-0.47,0.74]
Cupal 2001	10	2.7 (1)	10	2.7 (1.3)		0.74%	0[-0.88,0.88]
Davidson 1980	10	1.8 (0.9)	10	2.9 (1.3)		0.66%	-0.94[-1.88,-0.01]
Defrin 2005	9	7.3 (0.8)	8	7.6 (0.7)		0.63%	-0.39[-1.35,0.58]
Dibble 2007	49	3.1 (2.9)	51	3.5 (3.1)		2.4%	-0.12[-0.51,0.27]
Espie 1989	14	63.5 (30.6)	13	96.5 (63.5)		0.91%	-0.65[-1.43,0.13]
Etter 2002	269	20.6 (10)	389	25.4 (12.6)		4.56%	-0.41[-0.57,-0.26]
Foster 2004	6	-3.6 (0.6)	12	-2.6 (1.1)		0.54%	-0.98[-2.02,0.06]
Hall 1974	23	-0.5 (7.8)	22	0.9 (7.8)		1.42%	-0.17[-0.76,0.41]
Hashish 1986	25	16 (11.7)	50	30 (18.9)		1.79%	-0.82[-1.32,-0.32]
Hossmann 1981	12	94.2 (4.8)	12	95.1 (4.8)		0.86%	-0.18[-0.98,0.62]
Hruby 2006	49	1.2 (2.1)	51	0.9 (1.5)		2.4%	0.21[-0.19,0.6]
Hyland 2006	10	6 (0.9)	10	6.2 (0.9)		0.74%	-0.21[-1.09,0.67]
Irvin 1996	11	3.3 (0.7)	11	3.7 (1.4)		0.79%	-0.35[-1.19,0.5]
Jacobson 1978	7	2.5 (0.9)	6	3.5 (0.5)		0.41%	-1.17[-2.39,0.04]
Karst 2007	19	45.2 (10.8)	10	56.5 (9.1)		0.83%	-1.07[-1.89,-0.25]
Kilmann 1987	4	-33 (47)	4	-35 (47)		0.32%	0.04[-1.35,1.42]
Kober 2002	20	66.7 (10)	21	64.4 (13.3)		1.33%	0.19[-0.42,0.8]
Kokol 2005	16	9.5 (10.5)	10	7.3 (6.6)		0.88%	0.23[-0.56,1.02]
Kotani 2001	23	15 (4.5)	24	18 (6)		1.43%	-0.55[-1.14,0.03]
Lander 1993	172	28.5 (29.3)	168	32.3 (33.4)		3.99%	-0.12[-0.33,0.09]
Lee 2005	27	-21.4 (25.9)	27	-5.9 (9.2)		1.54%	-0.79[-1.34,-0.23]
Licciardone 2003	19	2.5 (1.7)	15	3.5 (2.7)		1.11%	-0.49[-1.17,0.2]
Lick 1975	9	60.6 (32.7)	9	92.2 (22.1)		0.58%	-1.08[-2.09,-0.07]
Lick 1977	10	66 (25)	10	63 (32)		0.74%	0.1[-0.78,0.98]



Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Limoges 2004	30	2.3 (1)	30	2.2 (1)		1.75%	0.04[-0.47,0.55]
Lin 2002	25	30.2 (14.4)	25	38.1 (16)		1.5%	-0.51[-1.07,0.05]
Lindholm 1996	227	6.8 (0.5)	226	6.8 (0.5)		4.28%	0.15[-0.04,0.33]
Liossi 2003	20	4.3 (0.6)	20	4.6 (0.6)		1.27%	-0.49[-1.12,0.14]
Longo 1988	10	3.6 (0.6)	9	3.6 (0.4)		0.71%	0[-0.9,0.9]
Lorr 1961	42	58.3 (9.9)	38	57.5 (9.9)		2.11%	0.08[-0.36,0.52]
Moffet 1996	22	24 (18.6)	27	34.6 (23.2)		1.47%	-0.49[-1.06,0.08]
Murphy 1982	6	-16.5 (9.3)	11	-0.8 (6.4)		0.39%	-1.99[-3.24,-0.74]
Nicassio 1974	7	117.3 (133.7)	9	99.3 (35.3)		0.6%	0.19[-0.8,1.18]
Parker 1995	49	4 (1.9)	45	3.8 (2.2)		2.32%	0.1[-0.31,0.5]
Pelham 1992	38	-8.7 (1.7)	38	-8.5 (1.6)		2.04%	-0.12[-0.57,0.33]
Quahagen 1995	28	-108.3 (14.8)	25	-104.8 (13.9)		1.59%	-0.24[-0.78,0.3]
Ristikankare 1999	61	40.3 (21.5)	61	36 (21.5)		2.67%	0.2[-0.16,0.55]
Robinson 2001	13	3.9 (3.5)	10	4.3 (3.7)		0.82%	-0.11[-0.93,0.72]
Rosen 1976	9	6.9 (2)	5	8.3 (1.9)		0.47%	-0.67[-1.8,0.46]
Röschke 2000	24	23 (16.2)	24	26 (16)		1.49%	-0.18[-0.75,0.38]
Senediak 1985	11	47.5 (8.4)	10	47.9 (7.5)		0.77%	-0.04[-0.9,0.81]
Shen 2000	33	40.7 (12.4)	34	43.7 (11.3)		1.88%	-0.25[-0.73,0.23]
Sinaiko 1991	60	66.5 (9.7)	27	64.1 (13.9)		2.01%	0.21[-0.24,0.67]
Sprott 1993	10	7.9 (3)	10	7.4 (3)		0.74%	0.16[-0.72,1.04]
Stabholz 1991	10	1.4 (0.5)	10	1.8 (0.6)		0.7%	-0.69[-1.6,0.22]
Steinsbekk 2004	102	44.5 (58.9)	74	53 (45.2)		3.14%	-0.16[-0.46,0.14]
Straub 2001	5	-5.8 (0.3)	5	-6 (0.7)		0.39%	0.27[-0.98,1.52]
Tan 1982	12	1.3 (0.6)	12	1.7 (0.8)		0.83%	-0.55[-1.36,0.27]
Tashjian 2006	19	3.4 (2.2)	24	3.3 (1.8)		1.37%	0.05[-0.55,0.65]
Theroux 1993	17	3.2 (0.7)	15	2.9 (0.6)		1.07%	0.48[-0.22,1.19]
Thomas 1999	14	13.4 (10.3)	26	16.5 (9.7)		1.2%	-0.31[-0.96,0.35]
Tsay 2004	35	4.7 (1.5)	36	5.7 (1.8)		1.9%	-0.6[-1.07,-0.12]
Tuomilehto 1980	11	9 (1.4)	11	8.7 (1.6)		0.8%	0.24[-0.6,1.08]
Turner 1979	10	44.2 (41.3)	10	59.8 (22.9)		0.72%	-0.45[-1.34,0.44]
Vlaeyen 1996	39	0.4 (1.8)	40	0.4 (1.8)		2.09%	0[-0.44,0.44]
Wang 1997	25	10.7 (7.3)	26	13.4 (5.8)		1.54%	-0.4[-0.96,0.15]
Weingaertner 1971	15	1.1 (1.3)	15	1.2 (1.6)		1.04%	-0.1[-0.81,0.62]
Woods 2005	19	1.2 (1.3)	19	1.5 (1.1)		1.25%	-0.2[-0.83,0.44]
Total ***	**2212**		**2273**			**100%**	**-0.17[-0.25,-0.09]**

Heterogeneity: Tau²=0.03; Chi²=104.21, df=72(P=0.01); I²=30.91%

Test for overall effect: Z=4.16(P<0.0001)



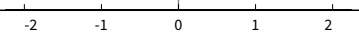
Comparison 14. Risk of bias subgroup analysis: format of outcome

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Outcome was final values	118	7866	Std. Mean Difference (IV, Random, 95% CI)	-0.21 [-0.28, -0.14]

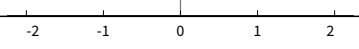
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
2 Outcome was change from baseline	40	2659	Std. Mean Difference (IV, Random, 95% CI)	-0.27 [-0.37, -0.16]

Analysis 14.1. Comparison 14 Risk of bias subgroup analysis: format of outcome, Outcome 1 Outcome was final values.

Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Alfano 2001	24	6.2 (2.8)	14	6.6 (2.7)		0.74%	-0.14[-0.8,0.52]
Allen 2006	45	12 (9.6)	44	19 (9.6)		1.24%	-0.72[-1.15,-0.29]
Andersen 1990	18	35 (27.2)	16	25 (23.6)		0.7%	0.38[-0.3,1.06]
Antonio 1999	6	79.7 (12.2)	6	72.6 (11.2)		0.3%	0.56[-0.6,1.72]
Ascher 1979	8	50.6 (44.1)	9	62.4 (25.3)		0.41%	-0.32[-1.28,0.64]
Benedetti 1997	106	0.3 (0.1)	115	0.3 (0.1)		1.8%	-0.17[-0.43,0.1]
Biro 1997	29	3.6 (2.5)	29	3.3 (2.1)		1.01%	0.13[-0.39,0.64]
Blanchard 1990a	13	8.3 (13.6)	11	22.5 (25.1)		0.52%	-0.7[-1.53,0.13]
Blanchard 1990b	18	11.9 (23.9)	24	20.7 (34.8)		0.81%	-0.28[-0.9,0.33]
Block 1980	16	22.4 (6.6)	8	24.7 (9.2)		0.5%	-0.3[-1.15,0.56]
Bosley 1989	13	86 (10)	14	89 (10)		0.6%	-0.29[-1.05,0.47]
Bova 1999	34	3.8 (2.2)	36	4.1 (2.3)		1.13%	-0.14[-0.61,0.33]
Cabrini 2006	16	61.7 (24)	16	66.6 (28)		0.68%	-0.18[-0.88,0.51]
Canino 1994	4	99 (2.7)	9	95.6 (7.6)		0.28%	0.48[-0.72,1.67]
Carbajal 1999	25	7.2 (2.8)	25	6.9 (2.6)		0.93%	0.1[-0.45,0.66]
Chenard 1991	12	29 (19)	16	30 (19)		0.61%	-0.05[-0.8,0.7]
Classen 1983	15	11.3 (8.3)	15	14.4 (6.1)		0.64%	-0.41[-1.14,0.31]
Colker 1999	7	82.7 (18)	4	77.7 (10.5)		0.26%	0.29[-0.95,1.53]
Conn 1986	13	28.2 (18.4)	14	44.4 (15.7)		0.55%	-0.92[-1.72,-0.12]
Costello 2006	48	33 (25)	42	31 (25)		1.28%	0.08[-0.33,0.49]
Coyne 1995	21	0.7 (0.7)	21	0.6 (0.7)		0.83%	0.13[-0.47,0.74]
Crosby 1994	26	13.6 (1.3)	33	13.5 (1.3)		1.02%	0.08[-0.44,0.59]
Cupal 2001	10	2.7 (1)	10	2.7 (1.3)		0.48%	0[-0.88,0.88]
Davidson 1980	10	1.8 (0.9)	10	2.9 (1.3)		0.43%	-0.94[-1.88,-0.01]
Defrin 2005	9	7.3 (0.8)	8	7.6 (0.7)		0.41%	-0.39[-1.35,0.58]
Dibble 2007	49	3.1 (2.9)	51	3.5 (3.1)		1.35%	-0.12[-0.51,0.27]
Ditto 2003	200	0.5 (0.4)	189	0.5 (0.4)		2.05%	-0.02[-0.22,0.17]
Ditto 2006	140	0.4 (0.4)	155	0.5 (0.4)		1.94%	-0.06[-0.28,0.17]
Espie 1989	14	63.5 (30.6)	13	96.5 (63.5)		0.58%	-0.65[-1.43,0.13]
Etter 2002	269	20.6 (10)	389	25.4 (12.6)		2.2%	-0.41[-0.57,-0.26]
Fisher 2006	12	3.8 (1.9)	15	4.1 (2.5)		0.6%	-0.13[-0.89,0.63]
Forster 1994	15	3.2 (2.8)	15	4.6 (2.2)		0.63%	-0.54[-1.27,0.19]
Foster 2007	112	6.5 (4.8)	105	6.8 (4.5)		1.8%	-0.06[-0.33,0.21]
Frankel 1978	7	93 (5)	8	95 (3)		0.36%	-0.47[-1.5,0.57]
Frega 1994	21	20 (16)	21	23 (16)		0.83%	-0.18[-0.79,0.42]
Fuchs 1977	10	14.3 (7)	10	21.4 (7)		0.43%	-0.97[-1.91,-0.03]
Goodenough 1997	39	1.1 (1.6)	39	1.6 (1.9)		1.19%	-0.28[-0.73,0.16]
GRECHO 1989	150	94.4 (40.7)	150	95.4 (33)		1.95%	-0.03[-0.25,0.2]
Hargreaves 1989	25	4.5 (2.5)	25	4.9 (2.4)		0.93%	-0.16[-0.72,0.39]



Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Hashish 1986	25	16 (11.7)	50	30 (18.9)		1.05%	-0.82[-1.32,-0.32]
Hashish 1988	25	42 (25)	25	60 (23)		0.89%	-0.74[-1.31,-0.16]
Hawkins 1995	10	37.4 (8.5)	10	52.1 (9.3)		0.36%	-1.58[-2.61,-0.55]
Helms 1987	11	103 (91)	11	79 (99)		0.51%	0.24[-0.6,1.08]
Hossmann 1981	12	94.2 (4.8)	12	95.1 (4.8)		0.55%	-0.18[-0.98,0.62]
Hruby 2006	49	1.2 (2.1)	51	0.9 (1.5)		1.35%	0.21[-0.19,0.6]
Hyland 2006	10	6 (0.9)	10	6.2 (0.9)		0.48%	-0.21[-1.09,0.67]
Irvin 1996	11	3.3 (0.7)	11	3.7 (1.4)		0.51%	-0.35[-1.19,0.5]
Jacobson 1978	7	2.5 (0.9)	6	3.5 (0.5)		0.27%	-1.17[-2.39,0.04]
Karst 2007	19	45.2 (10.8)	10	56.5 (9.1)		0.53%	-1.07[-1.89,-0.25]
Karunakaran 1997	58	6.2 (1.2)	57	5.9 (0.6)		1.43%	0.31[-0.05,0.68]
Kendall 1979	11	7.5 (2.3)	11	8.2 (3)		0.51%	-0.23[-1.07,0.61]
Killeen 2004	24	1 (2.5)	35	1.9 (3.5)		1%	-0.28[-0.81,0.24]
Kober 2002	20	66.7 (10)	21	64.4 (13.3)		0.81%	0.19[-0.42,0.8]
Kokol 2005	16	9.5 (10.5)	10	7.3 (6.6)		0.56%	0.23[-0.56,1.02]
Kotani 2001	23	15 (4.5)	24	18 (6)		0.87%	-0.55[-1.14,0.03]
Lander 1993	172	28.5 (29.3)	168	32.3 (33.4)		2%	-0.12[-0.33,0.09]
Leibing 2002	40	3.2 (1.8)	39	4.3 (1.9)		1.18%	-0.59[-1.04,-0.14]
Licciardone 2003	19	2.5 (1.7)	15	3.5 (2.7)		0.69%	-0.49[-1.17,0.2]
Lick 1975	9	60.6 (32.7)	9	92.2 (22.1)		0.38%	-1.08[-2.09,-0.07]
Lick 1977	10	66 (25)	10	63 (32)		0.48%	0.1[-0.78,0.98]
Limoges 2004	30	2.3 (1)	30	2.2 (1)		1.04%	0.04[-0.47,0.55]
Lin 2002	25	30.2 (14.4)	25	38.1 (16)		0.91%	-0.51[-1.07,0.05]
Lincoln 2003	42	14.4 (10)	38	16.7 (10)		1.21%	-0.23[-0.67,0.21]
Lindholm 1996	227	6.8 (0.5)	226	6.8 (0.5)		2.1%	0.15[-0.04,0.33]
Liossi 2003	20	4.3 (0.6)	20	4.6 (0.6)		0.78%	-0.49[-1.12,0.14]
Longo 1988	10	3.6 (0.6)	9	3.6 (0.4)		0.46%	0[-0.9,0.9]
Lorr 1961	42	58.3 (9.9)	38	57.5 (9.9)		1.21%	0.08[-0.36,0.52]
Markland 1993	7	37.3 (11.8)	7	36.9 (11.9)		0.35%	0.03[-1.01,1.08]
Matros 2006	23	76 (36.3)	21	72 (28.3)		0.85%	0.12[-0.47,0.71]
McLachlan 1991	8	6.3 (12.3)	12	5.7 (17.4)		0.46%	0.04[-0.86,0.93]
Melchart 2005	57	10.8 (8.3)	63	16.3 (7.4)		1.43%	-0.7[-1.07,-0.33]
Moffet 1996	22	24 (18.6)	27	34.6 (23.2)		0.89%	-0.49[-1.06,0.08]
Morton 1993	13	22.1 (16.4)	13	24.5 (16.4)		0.59%	-0.14[-0.91,0.63]
Nandi 1976	10	53.2 (11.2)	8	57.5 (13.8)		0.43%	-0.33[-1.27,0.61]
Nawrocki 1997	40	9.5 (6)	42	17 (4.8)		1.09%	-1.37[-1.85,-0.89]
Nicassio 1974	7	117.3 (133.7)	9	99.3 (35.3)		0.39%	0.19[-0.8,1.18]
Nocella 1982	10	0.8 (0.9)	10	0.8 (0.7)		0.48%	-0.02[-0.9,0.85]
O'Brien 1996	53	6.7 (5.6)	54	7.5 (5.1)		1.39%	-0.15[-0.53,0.23]
Parker 1995	49	4 (1.9)	45	3.8 (2.2)		1.31%	0.1[-0.31,0.5]
Parker 2003	13	16.2 (7.5)	14	14.2 (7.5)		0.6%	0.26[-0.5,1.02]
Rawling 2001	89	5.3 (4.7)	96	5.6 (4.9)		1.71%	-0.06[-0.35,0.23]
Reading 1982	18	1.6 (1.3)	20	2.3 (2)		0.76%	-0.4[-1.05,0.24]
Ristikankare 1999	61	40.3 (21.5)	61	36 (21.5)		1.47%	0.2[-0.16,0.55]
Robinson 2001	13	3.9 (3.5)	10	4.3 (3.7)		0.53%	-0.11[-0.93,0.72]
Roscoe 2002	27	5.9 (5.2)	27	6.6 (3.6)		0.97%	-0.15[-0.69,0.38]
Roscoe 2005	31	2.4 (1.3)	33	2.8 (1.3)		1.07%	-0.3[-0.8,0.19]
Rosen 1976	9	6.9 (2)	5	8.3 (1.9)		0.31%	-0.67[-1.8,0.46]
Rossi 1982	6	107 (17)	6	108 (20)		0.31%	-0.05[-1.18,1.08]
Rybarczyk 1990	25	7.1 (2.2)	24	7.5 (2.8)		0.91%	-0.16[-0.73,0.4]
Röschke 2000	24	23 (16.2)	24	26 (16)		0.9%	-0.18[-0.75,0.38]

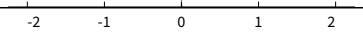


Favours placebo — Favours no-treatment

Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Rösler 2003	13	5.9 (3.4)	14	6 (3)		0.6%	-0.02[-0.78,0.73]
Sanders 1990	6	2 (0.4)	6	2.1 (0.3)		0.31%	-0.13[-1.26,1]
Seer 1980	14	92.5 (9.8)	13	104.5 (11)		0.53%	-1.12[-1.94,-0.3]
Senediak 1985	11	47.5 (8.4)	10	47.9 (7.5)		0.5%	-0.04[-0.9,0.81]
Shen 2000	33	40.7 (12.4)	34	43.7 (11.3)		1.1%	-0.25[-0.73,0.23]
Sinaiko 1991	60	66.5 (9.7)	27	64.1 (13.9)		1.17%	0.21[-0.24,0.67]
Sipich 1974	10	8 (14)	10	32.5 (14)		0.35%	-1.68[-2.73,-0.63]
Spanos 1995	13	21.4 (9.7)	12	19.1 (10.3)		0.57%	0.22[-0.56,1.01]
Sprott 1993	10	7.9 (3)	10	7.4 (3)		0.48%	0.16[-0.72,1.04]
Stabholz 1991	10	1.4 (0.5)	10	1.8 (0.6)		0.45%	-0.69[-1.6,0.22]
Steinsbekk 2004	102	44.5 (58.9)	74	53 (45.2)		1.67%	-0.16[-0.46,0.14]
Sumaya 2001	10	15.4 (2.7)	10	14.9 (1.8)		0.48%	0.21[-0.67,1.09]
Tan 1982	12	1.3 (0.6)	12	1.7 (0.8)		0.53%	-0.55[-1.36,0.27]
Tashjian 2006	19	3.4 (2.2)	24	3.3 (1.8)		0.83%	0.05[-0.55,0.65]
Theroux 1993	17	3.2 (0.7)	15	2.9 (0.6)		0.67%	0.48[-0.22,1.19]
Thomas 1999	14	13.4 (10.3)	26	16.5 (9.7)		0.75%	-0.31[-0.96,0.35]
Tritrakarn 2000	41	49 (16)	41	61 (17)		1.19%	-0.72[-1.17,-0.27]
Tsay 2003	32	9.2 (4.4)	32	9.6 (4)		1.08%	-0.08[-0.57,0.41]
Tsay 2004	35	4.7 (1.5)	36	5.7 (1.8)		1.11%	-0.6[-1.07,-0.12]
Tuomilehto 1980	11	9 (1.4)	11	8.7 (1.6)		0.51%	0.24[-0.6,1.08]
Turner 1979	10	44.2 (41.3)	10	59.8 (22.9)		0.47%	-0.45[-1.34,0.44]
Vlaeyen 1996	39	0.4 (1.8)	40	0.4 (1.8)		1.21%	0[-0.44,0.44]
Wang 1997	25	10.7 (7.3)	26	13.4 (5.8)		0.93%	-0.4[-0.96,0.15]
Weingaertner 1971	15	1.1 (1.3)	15	1.2 (1.6)		0.65%	-0.1[-0.81,0.62]
Werntoft 2001	20	5.9 (2.4)	20	6.5 (2.2)		0.8%	-0.26[-0.88,0.37]
Witt 2005	73	35.8 (16.2)	67	49.6 (16.3)		1.5%	-0.84[-1.19,-0.5]
Wojciechowski 1984	9	264 (122)	12	238 (190)		0.49%	0.15[-0.71,1.02]
Woods 2005	19	1.2 (1.3)	19	1.5 (1.1)		0.77%	-0.2[-0.83,0.44]
Total ***	**3884**		**3982**			**100%**	**-0.21[-0.28,-0.14]**

Heterogeneity: Tau^2=0.05; Chi^2=205.25, df=117(P<0.0001); I^2=43%

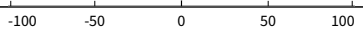
Test for overall effect: Z=6.14(P<0.0001)



Favours placebo — Favours no-treatment

Analysis 14.2. Comparison 14 Risk of bias subgroup analysis: format of outcome, Outcome 2 Outcome was change from baseline.

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Abikoff 2004	35	-91.4 (18.9)	34	-89.5 (22.8)		3%	-0.09[-0.56,0.38]
Allen 1998	11	-2.9 (7.9)	11	-6.1 (10.9)		1.3%	0.32[-0.52,1.17]
Anderson 1999	30	-2.7 (0.8)	27	-2.7 (0.8)		2.66%	0.08[-0.44,0.6]
Antivalle 1990	11	-1.6 (5.6)	10	-3.9 (7.3)		1.25%	0.34[-0.52,1.21]
Asmar 1996	34	-0.2 (7.7)	34	0.7 (6.5)		2.98%	-0.12[-0.6,0.35]
Benedetti 1995	13	-2 (1.2)	11	-0.8 (1)		1.23%	-1.07[-1.94,-0.2]
Blades 2001	40	-16 (6)	40	-16 (6)		3.28%	0[-0.44,0.44]
Bramston 1985	12	-78 (14.2)	12	-72 (13.8)		1.38%	-0.41[-1.22,0.4]
Brinkhaus 2006	70	-23.6 (31)	74	-6.9 (22)		4.29%	-0.62[-0.96,-0.29]
Erdogmus 2007	40	-27.4 (19.7)	40	-20.3 (19.7)		3.25%	-0.36[-0.8,0.08]

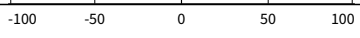


Favours experimental — Favours control

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Etringer 1982	13	-11.4 (4)	12	-10.1 (3.7)		1.44%	-0.33[-1.12,0.46]
Foster 2004	6	-3.6 (0.6)	12	-2.6 (1.1)		0.9%	-0.98[-2.02,0.06]
Godfrey 1973	44	34.9 (16.7)	44	46.9 (16.2)		3.33%	-0.72[-1.15,-0.29]
Gracely 1983	17	-2.9 (5.4)	12	0.2 (5.5)		1.55%	-0.54[-1.3,0.21]
Hall 1974	23	-0.5 (7.8)	22	0.9 (7.8)		2.27%	-0.17[-0.76,0.41]
Hanson 1976	11	-0.9 (3.8)	10	-0.3 (2.2)		1.26%	-0.19[-1.05,0.67]
Hong 1993	16	-1.1 (0.2)	21	-1 (0.1)		1.9%	-0.53[-1.19,0.13]
Hovell 2003	98	-155.4 (69.9)	96	-151 (73.8)		4.91%	-0.06[-0.34,0.22]
Kaptchuk 2008	88	-4.3 (1.4)	87	-3.8 (1)		4.69%	-0.41[-0.71,-0.11]
Kilmann 1987	4	-33 (47)	4	-35 (47)		0.54%	0.04[-1.35,1.42]
Lee 2005	27	-21.4 (25.9)	27	-5.9 (9.2)		2.44%	-0.79[-1.34,-0.23]
Levine 1984	12	-0.3 (0.7)	24	0.4 (2.5)		1.76%	-0.31[-1.01,0.38]
Linde 2005	76	-2.2 (2.7)	76	-0.8 (2.2)		4.41%	-0.57[-0.89,-0.24]
Macaluso 1995	30	-3.3 (3.8)	30	-1.8 (3.3)		2.72%	-0.41[-0.93,0.1]
May 1988	24	-1.2 (0.5)	24	-1.2 (0.5)		2.38%	-0.02[-0.59,0.54]
Medici 2002	23	-0.2 (0.3)	18	-0.1 (0.3)		2.09%	-0.31[-0.93,0.32]
Moreland 2006	50	-2 (1.3)	99	-2.1 (1.7)		4.23%	0.06[-0.28,0.4]
Morey 2006	38	-16.5 (9.3)	42	-14.7 (9.5)		3.27%	-0.19[-0.63,0.25]
Murphy 1982	6	-16.5 (9.3)	11	-0.8 (6.4)		0.65%	-1.99[-3.24,-0.74]
Pelham 1992	38	-8.7 (1.7)	38	-8.5 (1.6)		3.18%	-0.12[-0.57,0.33]
Quahagen 1995	28	-108.3 (14.8)	25	-104.8 (13.9)		2.53%	-0.24[-0.78,0.3]
Roongpisuthip 1999	18	-3.3 (4.2)	19	-2.9 (3.1)		1.97%	-0.11[-0.75,0.54]
Rowbotham 1996	35	-4.4 (8.7)	35	1.9 (8.7)		2.91%	-0.72[-1.2,-0.23]
Stewart 1991	25	-14.3 (5.5)	25	-12.8 (5.2)		2.43%	-0.28[-0.83,0.28]
Straub 2001	5	-5.8 (0.3)	5	-6 (0.7)		0.65%	0.27[-0.98,1.52]
Thomas 2002a	78	-0.9 (3)	78	-0.1 (2.9)		4.51%	-0.27[-0.59,0.04]
Thomas 2002b	114	-1.2 (3.5)	119	-1.6 (3.3)		5.21%	0.12[-0.14,0.37]
Tremeau 1992	39	-0.9 (1.3)	25	-1.1 (1.4)		2.78%	0.14[-0.36,0.65]
Wilcock 2008	15	-6.4 (5.1)	15	-6.7 (5.9)		1.69%	0.05[-0.66,0.77]
Yates 1988	7	-1.4 (2.5)	7	0.7 (1.4)		0.78%	-0.97[-2.1,0.16]
Total * **	**1304**		**1355**			**100%**	**-0.27[-0.37,-0.16]**

Heterogeneity: Tau^2=0.04; Chi^2=62.64, df=39(P=0.01); I^2=37.74%

Test for overall effect: Z=4.99(P<0.0001)



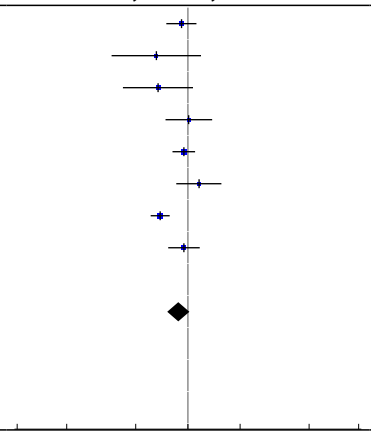
Comparison 15. Risk of bias subgroup analysis: concealed allocation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Concealed allocation adequate	8	1554	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.76, 1.02]
2 Concealed allocation unclear	36	4487	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.90, 1.01]
3 Concealed allocation adequate	20	2241	Std. Mean Difference (IV, Random, 95% CI)	-0.34 [-0.46, -0.22]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Concealed allocation unclear	138	8272	Std. Mean Difference (IV, Random, 95% CI)	-0.20 [-0.26, -0.14]

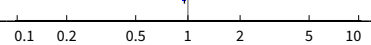
Analysis 15.1. Comparison 15 Risk of bias subgroup analysis: concealed allocation, Outcome 1 Concealed allocation adequate.

Study or subgroup	Placebo n/N	No-treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Alkaissi 2002	77/139	82/136		15.25%	0.92[0.75,1.12]
Aune 1998	11/26	9/14		4.74%	0.66[0.36,1.19]
Carter 2003	13/28	20/29		6.77%	0.67[0.42,1.07]
De Sanctis 2001	9/10	8/9		10.97%	1.01[0.74,1.38]
Faas 1993	107/162	108/155		17.46%	0.95[0.81,1.1]
Molsberger 2002	38/58	30/53		11.29%	1.16[0.86,1.56]
Scharf 2006	179/365	224/316		18.52%	0.69[0.61,0.78]
Tarrier 1998	22/26	25/28		14.99%	0.95[0.77,1.17]
Total (95% CI)	**814**	**740**		**100%**	**0.88[0.76,1.02]**
Total events: 456 (Placebo), 506 (No-treatment)					
Heterogeneity: Tau^2=0.03; Chi^2=21.38, df=7(P=0); I^2=67.26%					
Test for overall effect: Z=1.7(P=0.09)					

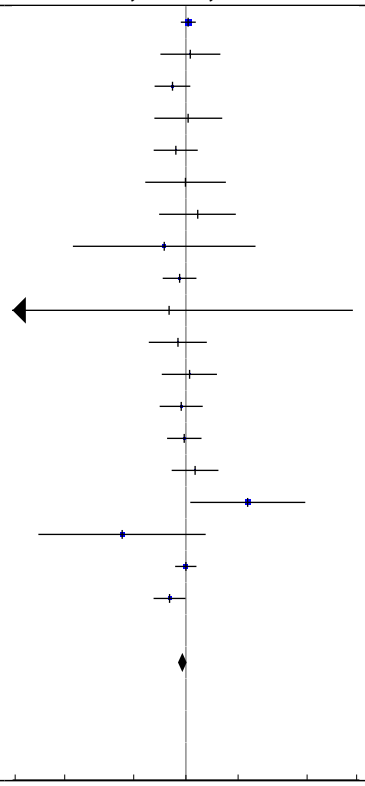


Analysis 15.2. Comparison 15 Risk of bias subgroup analysis: concealed allocation, Outcome 2 Concealed allocation unclear.

Study or subgroup	Placebo n/N	No-treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Adriaanse 1995	50/328	38/326		1.91%	1.31[0.88,1.94]
Alkaissi 1999	9/20	11/20		0.82%	0.82[0.44,1.53]
Berg 1983	9/11	9/15		1.25%	1.36[0.83,2.24]
Blackman 1964	6/12	6/12		0.52%	1[0.45,2.23]
Corver 2006	227/279	360/416		11.17%	0.94[0.88,1.01]
Double 1993	3/22	3/22		0.15%	1[0.23,4.42]
Dundee 1986	17/25	17/25		2.02%	1[0.68,1.46]
Elliott 1978	6/18	6/6		0.75%	0.37[0.19,0.71]
Fanti 2003	8/10	9/10		2.09%	0.89[0.61,1.29]
Frank 1990	14/26	14/26		1.23%	1[0.6,1.65]
Guglielmi 1982	12/12	11/12		4.5%	1.09[0.87,1.36]
Harrison 1975	24/28	25/30		4.61%	1.03[0.83,1.28]
Heinzl 1981	70/130	92/132		5.36%	0.77[0.64,0.94]
Hutton 1991	5/24	16/30		0.46%	0.39[0.17,0.91]
Hyman 1986	9/15	15/15		1.74%	0.61[0.4,0.93]
Jacobs 1971	9/15	12/39		0.82%	1.95[1.04,3.65]
Kerr 2003	28/33	32/36		5.71%	0.95[0.79,1.15]

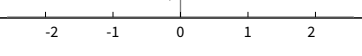


Study or subgroup	Placebo n/N	No-treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Killen 1990	226/309	219/309		9.59%	1.03[0.94,1.14]
Klerman 1974	17/25	16/25		1.86%	1.06[0.71,1.58]
Malcolm 1980	40/63	44/58		4.18%	0.84[0.66,1.06]
McMillan 1994	14/26	24/46		1.5%	1.03[0.66,1.62]
Najnigier 1997	21/30	24/30		3.05%	0.88[0.65,1.17]
Rabkin 1990	14/27	12/23		1.11%	0.99[0.58,1.7]
Roughan 1981	9/12	9/14		1.21%	1.17[0.7,1.94]
Schallreuter 2002	3/10	4/10		0.23%	0.75[0.22,2.52]
Scharff 2002	11/12	12/12		4.5%	0.92[0.74,1.15]
Stransky 1989	1/5	1/4		0.06%	0.8[0.07,9.18]
Tan 1986	8/10	8/9		1.96%	0.9[0.61,1.32]
Tarcin 2004	58/158	27/77		2.15%	1.05[0.73,1.51]
Thomas 1987	47/100	50/100		3.19%	0.94[0.71,1.25]
Tyler 1946	89/260	106/303		4.41%	0.98[0.78,1.23]
Walton 1993	19/24	21/30		2.8%	1.13[0.83,1.54]
Watzl 1986	15/34	7/36		0.56%	2.27[1.06,4.88]
Whittaker 1963	3/13	7/13		0.27%	0.43[0.14,1.3]
Williams 1988	19/20	19/20		7.42%	1[0.87,1.15]
Wilson 1980	31/40	10/10		4.84%	0.8[0.65,0.99]
Total (95% CI)	**2186**	**2301**		**100%**	**0.95[0.9,1.01]**
Total events: 1151 (Placebo), 1296 (No-treatment)					
Heterogeneity: Tau²=0.01; Chi²=49.76, df=35(P=0.05); I²=29.66%					
Test for overall effect: Z=1.56(P=0.12)					

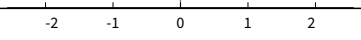


Analysis 15.3. Comparison 15 Risk of bias subgroup analysis: concealed allocation, Outcome 3 Concealed allocation adequate.

Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Brinkhaus 2006	70	-23.6 (31)	74	-6.9 (22)		6.28%	-0.62[-0.96,-0.29]
Carbajal 1999	25	7.2 (2.8)	25	6.9 (2.6)		3.48%	0.1[-0.45,0.66]
Conn 1986	13	28.2 (18.4)	14	44.4 (15.7)		1.98%	-0.92[-1.72,-0.12]
Erdogmus 2007	40	-27.4 (19.7)	40	-20.3 (19.7)		4.68%	-0.36[-0.8,0.08]
Foster 2007	112	6.5 (4.8)	105	6.8 (4.5)		7.56%	-0.06[-0.33,0.21]
Kaptchuk 2008	88	-4.3 (1.4)	87	-3.8 (1)		6.92%	-0.41[-0.71,-0.11]
Kotani 2001	23	15 (4.5)	24	18 (6)		3.24%	-0.55[-1.14,0.03]
Lander 1993	172	28.5 (29.3)	168	32.3 (33.4)		8.65%	-0.12[-0.33,0.09]
Licciardone 2003	19	2.5 (1.7)	15	3.5 (2.7)		2.53%	-0.49[-1.17,0.2]
Lincoln 2003	42	14.4 (10)	38	16.7 (10)		4.7%	-0.23[-0.67,0.21]
Linde 2005	76	-2.2 (2.7)	64	-0.8 (2.2)		6.21%	-0.56[-0.9,-0.22]
Melchart 2005	57	10.8 (8.3)	63	16.3 (7.4)		5.71%	-0.7[-1.07,-0.33]
Moffet 1996	22	24 (18.6)	27	34.6 (23.2)		3.34%	-0.49[-1.06,0.08]
O'Brien 1996	53	6.7 (5.6)	54	7.5 (5.1)		5.55%	-0.15[-0.53,0.23]
Rawling 2001	89	5.3 (4.7)	96	5.6 (4.9)		7.12%	-0.06[-0.35,0.23]
Robinson 2001	13	3.9 (3.5)	10	4.3 (3.7)		1.88%	-0.11[-0.93,0.72]
Shen 2000	33	40.7 (12.4)	34	43.7 (11.3)		4.22%	-0.25[-0.73,0.23]
Steinsbekk 2004	102	44.5 (58.9)	74	53 (45.2)		6.91%	-0.16[-0.46,0.14]

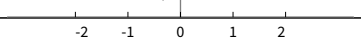


Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Werntoft 2001	20	5.9 (2.4)	20	6.5 (2.2)		2.95%	-0.26[-0.88,0.37]
Witt 2005	73	35.8 (16.2)	67	49.6 (16.3)		6.08%	-0.84[-1.19,-0.5]
Total ***	**1142**		**1099**			**100%**	**-0.34[-0.46,-0.22]**
Heterogeneity: Tau²=0.03; Chi²=36.31, df=19(P=0.01); I²=47.67%							
Test for overall effect: Z=5.4(P<0.0001)							

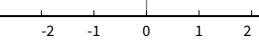


Analysis 15.4. Comparison 15 Risk of bias subgroup analysis: concealed allocation, Outcome 4 Concealed allocation unclear.

Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Abikoff 2004	35	-91.4 (18.9)	34	-89.5 (22.8)		1%	-0.09[-0.56,0.38]
Alfano 2001	24	6.2 (2.8)	14	6.6 (2.7)		0.65%	-0.14[-0.8,0.52]
Allen 1998	11	-2.9 (7.9)	11	-6.1 (10.9)		0.45%	0.32[-0.52,1.17]
Allen 2006	45	12 (9.6)	44	19 (9.6)		1.11%	-0.72[-1.15,-0.29]
Andersen 1990	18	35 (27.2)	16	25 (23.6)		0.62%	0.38[-0.3,1.06]
Anderson 1999	30	-2.7 (0.8)	27	-2.7 (0.8)		0.89%	0.08[-0.44,0.6]
Antivalle 1990	11	-1.6 (5.6)	10	-3.9 (7.3)		0.43%	0.34[-0.52,1.21]
Antonio 1999	6	79.7 (12.2)	6	72.6 (11.2)		0.26%	0.56[-0.6,1.72]
Ascher 1979	8	50.6 (44.1)	9	62.4 (25.3)		0.36%	-0.32[-1.28,0.64]
Asmar 1996	34	-0.2 (7.7)	34	0.7 (6.5)		0.99%	-0.12[-0.6,0.35]
Benedetti 1995	13	-2 (1.2)	11	-0.8 (1)		0.43%	-1.07[-1.94,-0.2]
Benedetti 1997	106	0.3 (0.1)	115	0.3 (0.1)		1.64%	-0.17[-0.43,0.1]
Biro 1997	29	3.6 (2.5)	29	3.3 (2.1)		0.9%	0.13[-0.39,0.64]
Blades 2001	40	-16 (6)	40	-16 (6)		1.09%	0[-0.44,0.44]
Blanchard 1990a	13	8.3 (13.6)	11	22.5 (25.1)		0.46%	-0.7[-1.53,0.13]
Blanchard 1990b	18	11.9 (23.9)	24	20.7 (34.8)		0.72%	-0.28[-0.9,0.33]
Block 1980	16	22.4 (6.6)	8	24.7 (9.2)		0.44%	-0.3[-1.15,0.56]
Bosley 1989	13	86 (10)	14	89 (10)		0.53%	-0.29[-1.05,0.47]
Bova 1999	34	3.8 (2.2)	36	4.1 (2.3)		1.01%	-0.14[-0.61,0.33]
Bramston 1985	12	-78 (14.2)	12	-72 (13.8)		0.48%	-0.41[-1.22,0.4]
Cabrini 2006	16	61.7 (24)	16	66.6 (28)		0.6%	-0.18[-0.88,0.51]
Canino 1994	4	99 (2.7)	9	95.6 (7.6)		0.25%	0.48[-0.72,1.67]
Chenard 1991	12	29 (19)	16	30 (19)		0.54%	-0.05[-0.8,0.7]
Classen 1983	15	11.3 (8.3)	15	14.4 (6.1)		0.57%	-0.41[-1.14,0.31]
Colker 1999	7	82.7 (18)	4	77.7 (10.5)		0.23%	0.29[-0.95,1.53]
Costello 2006	48	33 (25)	42	31 (25)		1.15%	0.08[-0.33,0.49]
Coyne 1995	21	0.7 (0.7)	21	0.6 (0.7)		0.73%	0.13[-0.47,0.74]
Crosby 1994	26	13.6 (1.3)	33	13.5 (1.3)		0.91%	0.08[-0.44,0.59]
Cupal 2001	10	2.7 (1)	10	2.7 (1.3)		0.42%	0[-0.88,0.88]
Davidson 1980	10	1.8 (0.9)	10	2.9 (1.3)		0.38%	-0.94[-1.88,-0.01]
Defrin 2005	9	7.3 (0.8)	8	7.6 (0.7)		0.36%	-0.39[-1.35,0.58]
Dibble 2007	49	3.1 (2.9)	51	3.5 (3.1)		1.21%	-0.12[-0.51,0.27]
Ditto 2003	200	0.5 (0.4)	189	0.5 (0.4)		1.87%	-0.02[-0.22,0.17]
Ditto 2006	140	0.4 (0.4)	155	0.5 (0.4)		1.77%	-0.06[-0.28,0.17]
Espie 1989	14	63.5 (30.6)	13	96.5 (63.5)		0.51%	-0.65[-1.43,0.13]
Etringer 1982	13	-11.4 (4)	12	-10.1 (3.7)		0.5%	-0.33[-1.12,0.46]



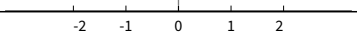
Study or subgroup	Placebo		No-treatment		Std. Mean Difference	Weight	Std. Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
Etter 2002	269	20.6 (10)	389	25.4 (12.6)		2.01%	-0.41[-0.57,-0.26]
Fisher 2006	12	3.8 (1.9)	15	4.1 (2.5)		0.53%	-0.13[-0.89,0.63]
Forster 1994	15	3.2 (2.8)	15	4.6 (2.2)		0.56%	-0.54[-1.27,0.19]
Foster 2004	6	-3.6 (0.6)	12	-2.6 (1.1)		0.31%	-0.98[-2.02,0.06]
Frankel 1978	7	93 (5)	8	95 (3)		0.32%	-0.47[-1.5,0.57]
Frega 1994	21	20 (16)	21	23 (16)		0.73%	-0.18[-0.79,0.42]
Fuchs 1977	10	14.3 (7)	10	21.4 (7)		0.38%	-0.97[-1.91,-0.03]
Godfrey 1973	44	34.9 (16.7)	44	46.9 (16.2)		1.1%	-0.72[-1.15,-0.29]
Goodenough 1997	39	1.1 (1.6)	39	1.6 (1.9)		1.07%	-0.28[-0.73,0.16]
Gracely 1983	17	-2.9 (5.4)	12	0.2 (5.5)		0.53%	-0.54[-1.3,0.21]
GRECHO 1989	150	94.4 (40.7)	150	95.4 (33)		1.77%	-0.03[-0.25,0.2]
Hall 1974	23	-0.5 (7.8)	22	0.9 (7.8)		0.77%	-0.17[-0.76,0.41]
Hanson 1976	11	-0.9 (3.8)	10	-0.3 (2.2)		0.43%	-0.19[-1.05,0.67]
Hargreaves 1989	25	4.5 (2.5)	25	4.9 (2.4)		0.82%	-0.16[-0.72,0.39]
Hashish 1986	25	16 (11.7)	50	30 (18.9)		0.94%	-0.82[-1.32,-0.32]
Hashish 1988	25	42 (25)	25	60 (23)		0.79%	-0.74[-1.31,-0.16]
Hawkins 1995	10	37.4 (8.5)	10	52.1 (9.3)		0.32%	-1.58[-2.61,-0.55]
Helms 1987	11	103 (91)	11	79 (99)		0.45%	0.24[-0.6,1.08]
Hong 1993	16	-1.1 (0.2)	21	-1 (0.1)		0.65%	-0.53[-1.19,0.13]
Hossmann 1981	12	94.2 (4.8)	12	95.1 (4.8)		0.48%	-0.18[-0.98,0.62]
Hovell 2003	98	-155.4 (69.9)	96	-151 (73.8)		1.58%	-0.06[-0.34,0.22]
Hruby 2006	49	1.2 (2.1)	51	0.9 (1.5)		1.21%	0.21[-0.19,0.6]
Hyland 2006	10	6 (0.9)	10	6.2 (0.9)		0.42%	-0.21[-1.09,0.67]
Irvin 1996	11	3.3 (0.7)	11	3.7 (1.4)		0.45%	-0.35[-1.19,0.5]
Jacobson 1978	7	2.5 (0.9)	6	3.5 (0.5)		0.24%	-1.17[-2.39,0.04]
Karst 2007	19	45.2 (10.8)	10	56.5 (9.1)		0.47%	-1.07[-1.89,-0.25]
Karunakaran 1997	58	6.2 (1.2)	57	5.9 (0.6)		1.29%	0.31[-0.05,0.68]
Kendall 1979	11	7.5 (2.3)	11	8.2 (3)		0.45%	-0.23[-1.07,0.61]
Killeen 2004	24	1 (2.5)	35	1.9 (3.5)		0.89%	-0.28[-0.81,0.24]
Kilmann 1987	4	-33 (47)	4	-35 (47)		0.19%	0.04[-1.35,1.42]
Kober 2002	20	66.7 (10)	21	64.4 (13.3)		0.72%	0.19[-0.42,0.8]
Kokol 2005	16	9.5 (10.5)	10	7.3 (6.6)		0.49%	0.23[-0.56,1.02]
Lee 2005	27	-21.4 (25.9)	27	-5.9 (9.2)		0.82%	-0.79[-1.34,-0.23]
Leibing 2002	40	3.2 (1.8)	39	4.3 (1.9)		1.05%	-0.59[-1.04,-0.14]
Levine 1984	12	-0.3 (0.7)	24	0.4 (2.5)		0.6%	-0.31[-1.01,0.38]
Lick 1975	9	60.6 (32.7)	9	92.2 (22.1)		0.33%	-1.08[-2.09,-0.07]
Lick 1977	10	66 (25)	10	63 (32)		0.42%	0.1[-0.78,0.98]
Limoges 2004	30	2.3 (1)	30	2.2 (1)		0.92%	0.04[-0.47,0.55]
Lin 2002	25	30.2 (14.4)	25	38.1 (16)		0.81%	-0.51[-1.07,0.05]
Lindholm 1996	227	6.8 (0.5)	226	6.8 (0.5)		1.92%	0.15[-0.04,0.33]
Liossi 2003	20	4.3 (0.6)	20	4.6 (0.6)		0.69%	-0.49[-1.12,0.14]
Longo 1988	10	3.6 (0.6)	9	3.6 (0.4)		0.4%	0[-0.9,0.9]
Lorr 1961	42	58.3 (9.9)	38	57.5 (9.9)		1.08%	0.08[-0.36,0.52]
Macaluso 1995	30	-3.3 (3.8)	30	-1.8 (3.3)		0.91%	-0.41[-0.93,0.1]
Markland 1993	7	37.3 (11.8)	7	36.9 (11.9)		0.31%	0.03[-1.01,1.08]
Matros 2006	23	76 (36.3)	21	72 (28.3)		0.76%	0.12[-0.47,0.71]
May 1988	24	-1.2 (0.5)	24	-1.2 (0.5)		0.8%	-0.02[-0.59,0.54]
McLachlan 1991	8	6.3 (12.3)	12	5.7 (17.4)		0.41%	0.04[-0.86,0.93]
Medici 2002	23	-0.2 (0.3)	18	-0.1 (0.3)		0.71%	-0.31[-0.93,0.32]
Moreland 2006	50	-2 (1.3)	99	-2.1 (1.7)		1.38%	0.06[-0.28,0.4]
Morey 2006	38	-16.5 (9.3)	42	-14.7 (9.5)		1.08%	-0.19[-0.63,0.25]



Favours experimental

Favours control

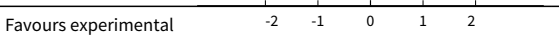
Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Morton 1993	13	22.1 (16.4)	13	24.5 (16.4)		0.52%	-0.14[-0.91,0.63]
Murphy 1982	6	-16.5 (9.3)	11	-0.8 (6.4)		0.23%	-1.99[-3.24,-0.74]
Nandi 1976	10	53.2 (11.2)	8	57.5 (13.8)		0.38%	-0.33[-1.27,0.61]
Nawrocki 1997	40	9.5 (6)	42	17 (4.8)		0.97%	-1.37[-1.85,-0.89]
Nicassio 1974	7	117.3 (133.7)	9	99.3 (35.3)		0.34%	0.19[-0.8,1.18]
Nocella 1982	10	0.8 (0.9)	10	0.8 (0.7)		0.42%	-0.02[-0.9,0.85]
Parker 1995	49	4 (1.9)	45	3.8 (2.2)		1.18%	0.1[-0.31,0.5]
Parker 2003	13	16.2 (7.5)	14	14.2 (7.5)		0.53%	0.26[-0.5,1.02]
Pelham 1992	38	-8.7 (1.7)	38	-8.5 (1.6)		1.06%	-0.12[-0.57,0.33]
Quahagen 1995	28	-108.3 (14.8)	25	-104.8 (13.9)		0.85%	-0.24[-0.78,0.3]
Reading 1982	18	1.6 (1.3)	20	2.3 (2)		0.67%	-0.4[-1.05,0.24]
Ristikankare 1999	61	40.3 (21.5)	61	36 (21.5)		1.33%	0.2[-0.16,0.55]
Roongpisuthip 1999	18	-3.3 (4.2)	19	-2.9 (3.1)		0.67%	-0.11[-0.75,0.54]
Roscoe 2002	27	5.9 (5.2)	27	6.6 (3.6)		0.86%	-0.15[-0.69,0.38]
Roscoe 2005	31	2.4 (1.3)	33	2.8 (1.3)		0.95%	-0.3[-0.8,0.19]
Rosen 1976	9	6.9 (2)	5	8.3 (1.9)		0.27%	-0.67[-1.8,0.46]
Rossi 1982	6	107 (17)	6	108 (20)		0.27%	-0.05[-1.18,1.08]
Rowbotham 1996	35	-4.4 (8.7)	35	1.9 (8.7)		0.97%	-0.72[-1.2,-0.23]
Rybarczyk 1990	25	7.1 (2.2)	24	7.5 (2.8)		0.81%	-0.16[-0.73,0.4]
Röschke 2000	24	23 (16.2)	24	26 (16)		0.8%	-0.18[-0.75,0.38]
Rösler 2003	13	5.9 (3.4)	14	6 (3)		0.53%	-0.02[-0.78,0.73]
Sanders 1990	6	2 (0.4)	6	2.1 (0.3)		0.27%	-0.13[-1.26,1]
Seer 1980	14	92.5 (9.8)	13	104.5 (11)		0.47%	-1.12[-1.94,-0.3]
Senediak 1985	11	47.5 (8.4)	10	47.9 (7.5)		0.44%	-0.04[-0.9,0.81]
Sinaiko 1991	60	66.5 (9.7)	27	64.1 (13.9)		1.04%	0.21[-0.24,0.67]
Sipich 1974	10	8 (14)	10	32.5 (14)		0.31%	-1.68[-2.73,-0.63]
Spanos 1995	13	21.4 (9.7)	12	19.1 (10.3)		0.5%	0.22[-0.56,1.01]
Sprott 1993	10	7.9 (3)	10	7.4 (3)		0.42%	0.16[-0.72,1.04]
Stabholz 1991	10	1.4 (0.5)	10	1.8 (0.6)		0.4%	-0.69[-1.6,0.22]
Stewart 1991	25	-14.3 (5.5)	25	-12.8 (5.2)		0.82%	-0.28[-0.83,0.28]
Straub 2001	5	-5.8 (0.3)	5	-6 (0.7)		0.23%	0.27[-0.98,1.52]
Sumaya 2001	10	15.4 (2.7)	10	14.9 (1.8)		0.42%	0.21[-0.67,1.09]
Tan 1982	12	1.3 (0.6)	12	1.7 (0.8)		0.47%	-0.55[-1.36,0.27]
Tashjian 2006	19	3.4 (2.2)	24	3.3 (1.8)		0.74%	0.05[-0.55,0.65]
Theroux 1993	17	3.2 (0.7)	15	2.9 (0.6)		0.59%	0.48[-0.22,1.19]
Thomas 1999	14	13.4 (10.3)	26	16.5 (9.7)		0.66%	-0.31[-0.96,0.35]
Thomas 2002a	78	-0.9 (3)	78	-0.1 (2.9)		1.46%	-0.27[-0.59,0.04]
Thomas 2002b	114	-1.2 (3.5)	119	-1.6 (3.3)		1.66%	0.12[-0.14,0.37]
Tremeau 1992	39	-0.9 (1.3)	25	-1.1 (1.4)		0.93%	0.14[-0.36,0.65]
Tritrakarn 2000	41	49 (16)	41	61 (17)		1.06%	-0.72[-1.17,-0.27]
Tsay 2003	32	9.2 (4.4)	32	9.6 (4)		0.96%	-0.08[-0.57,0.41]
Tsay 2004	35	4.7 (1.5)	36	5.7 (1.8)		0.99%	-0.6[-1.07,-0.12]
Tuomilehto 1980	11	9 (1.4)	11	8.7 (1.6)		0.45%	0.24[-0.6,1.08]
Turner 1979	10	44.2 (41.3)	10	59.8 (22.9)		0.41%	-0.45[-1.34,0.44]
Vlaeyen 1996	39	0.4 (1.8)	40	0.4 (1.8)		1.08%	0[-0.44,0.44]
Wang 1997	25	10.7 (7.3)	26	13.4 (5.8)		0.82%	-0.4[-0.96,0.15]
Weingaertner 1971	15	1.1 (1.3)	15	1.2 (1.6)		0.58%	-0.1[-0.81,0.62]
Wilcock 2008	15	-6.4 (5.1)	15	-6.7 (5.9)		0.58%	0.05[-0.66,0.77]
Wojciechowski 1984	9	264 (122)	12	238 (190)		0.43%	0.15[-0.71,1.02]
Woods 2005	19	1.2 (1.3)	19	1.5 (1.1)		0.68%	-0.2[-0.83,0.44]



Favours experimental

Favours control

Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Yates 1988	7	-1.4 (2.5)	7	0.7 (1.4)		0.27%	-0.97[-2.1,0.16]
Total ***	**4046**		**4226**			**100%**	**-0.2[-0.26,-0.14]**
Heterogeneity: Tau²=0.04; Chi²=224.48, df=137(P<0.0001); I²=38.97%							
Test for overall effect: Z=6.24(P<0.0001)							



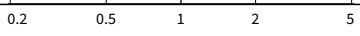
Comparison 16. Risk of bias subgroup analysis: trial size

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Trial size >49	27	5586	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.88, 1.01]
2 Trial size 49 or less	17	455	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.80, 1.04]
3 Trial size >49	65	8050	Std. Mean Difference (IV, Random, 95% CI)	-0.22 [-0.29, -0.14]
4 Trial size 49 or less	93	2463	Std. Mean Difference (IV, Fixed, 95% CI)	-0.24 [-0.32, -0.16]

Analysis 16.1. Comparison 16 Risk of bias subgroup analysis: trial size, Outcome 1 Trial size >49.

Study or subgroup	Placebo n/N	No-treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Adriaanse 1995	50/328	38/326		2.27%	1.31[0.88,1.94]
Alkaissi 2002	77/139	82/136		5.07%	0.92[0.75,1.12]
Carter 2003	13/28	20/29		1.73%	0.67[0.42,1.07]
Corver 2006	227/279	360/416		8.37%	0.94[0.88,1.01]
Dundee 1986	17/25	17/25		2.38%	1[0.68,1.46]
Faas 1993	107/162	108/155		6.29%	0.95[0.81,1.1]
Frank 1990	14/26	14/26		1.53%	1[0.6,1.65]
Harrison 1975	24/28	25/30		4.68%	1.03[0.83,1.28]
Heinzl 1981	70/130	92/132		5.23%	0.77[0.64,0.94]
Hutton 1991	5/24	16/30		0.6%	0.39[0.17,0.91]
Jacobs 1971	9/15	12/39		1.05%	1.95[1.04,3.65]
Kerr 2003	28/33	32/36		5.47%	0.95[0.79,1.15]
Killen 1990	226/309	219/309		7.67%	1.03[0.94,1.14]
Klerman 1974	17/25	16/25		2.22%	1.06[0.71,1.58]
Malcolm 1980	40/63	44/58		4.35%	0.84[0.66,1.06]
McMillan 1994	14/26	24/46		1.83%	1.03[0.66,1.62]
Molsberger 2002	38/58	30/53		3.29%	1.16[0.86,1.56]
Najnigier 1997	21/30	24/30		3.38%	0.88[0.65,1.17]
Rabkin 1990	14/27	12/23		1.39%	0.99[0.58,1.7]
Scharf 2006	179/365	224/316		6.95%	0.69[0.61,0.78]
Tarcin 2004	58/158	27/77		2.52%	1.05[0.73,1.51]
Tarrier 1998	22/26	25/28		4.94%	0.95[0.77,1.17]

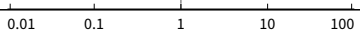
Study or subgroup	Placebo n/N	No-treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Thomas 1987	47/100	50/100		3.51%	0.94[0.71,1.25]
Tyler 1946	89/260	106/303		4.52%	0.98[0.78,1.23]
Walton 1993	19/24	21/30		3.15%	1.13[0.83,1.54]
Watzl 1986	15/34	7/36		0.73%	2.27[1.06,4.88]
Wilson 1980	31/40	10/10		4.86%	0.8[0.65,0.99]
Total (95% CI)	**2762**	**2824**		**100%**	**0.94[0.88,1.01]**
Total events: 1471 (Placebo), 1655 (No-treatment)					
Heterogeneity: Tau^2=0.01; Chi^2=57.09, df=26(P=0); I^2=54.45%					
Test for overall effect: Z=1.75(P=0.08)					



Favours placebo — Favours no-treatment

Analysis 16.2. Comparison 16 Risk of bias subgroup analysis: trial size, Outcome 2 Trial size 49 or less.

Study or subgroup	Placebo n/N	No-treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Alkaissi 1999	9/20	11/20		3.62%	0.82[0.44,1.53]
Aune 1998	11/26	9/14		3.93%	0.66[0.36,1.19]
Berg 1983	9/11	9/15		5.17%	1.36[0.83,2.24]
Blackman 1964	6/12	6/12		2.38%	1[0.45,2.23]
De Sanctis 2001	9/10	8/9		9.52%	1.01[0.74,1.38]
Double 1993	3/22	3/22		0.75%	1[0.23,4.42]
Elliott 1978	6/18	6/6		3.34%	0.37[0.19,0.71]
Fanti 2003	8/10	9/10		7.7%	0.89[0.61,1.29]
Guglielmi 1982	12/12	11/12		12.73%	1.09[0.87,1.36]
Hyman 1986	9/15	15/15		6.71%	0.61[0.4,0.93]
Roughan 1981	9/12	9/14		5.01%	1.17[0.7,1.94]
Schallreuter 2002	3/10	4/10		1.11%	0.75[0.22,2.52]
Scharff 2002	11/12	12/12		12.73%	0.92[0.74,1.15]
Stransky 1989	1/5	1/4		0.29%	0.8[0.07,9.18]
Tan 1986	8/10	8/9		7.35%	0.9[0.61,1.32]
Whittaker 1963	3/13	7/13		1.3%	0.43[0.14,1.3]
Williams 1988	19/20	19/20		16.36%	1[0.87,1.15]
Total (95% CI)	**238**	**217**		**100%**	**0.91[0.8,1.04]**
Total events: 136 (Placebo), 147 (No-treatment)					
Heterogeneity: Tau^2=0.02; Chi^2=25.64, df=16(P=0.06); I^2=37.59%					
Test for overall effect: Z=1.44(P=0.15)					



Favours experimental — Favours control

Analysis 16.3. Comparison 16 Risk of bias subgroup analysis: trial size, Outcome 3 Trial size >49.

Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Abikoff 2004	35	-91.4 (18.9)	34	-89.5 (22.8)		1.34%	-0.09[-0.56,0.38]
Allen 2006	45	12 (9.6)	44	19 (9.6)		1.47%	-0.72[-1.15,-0.29]
Anderson 1999	30	-2.7 (0.8)	27	-2.7 (0.8)		1.21%	0.08[-0.44,0.6]

Favours placebo — Favours no-treatment

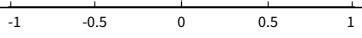
Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Asmar 1996	34	-0.2 (7.7)	34	0.7 (6.5)		1.33%	-0.12[-0.6,0.35]
Benedetti 1997	106	0.3 (0.1)	115	0.3 (0.1)		2.05%	-0.17[-0.43,0.1]
Biro 1997	29	3.6 (2.5)	29	3.3 (2.1)		1.22%	0.13[-0.39,0.64]
Blades 2001	40	-16 (6)	40	-16 (6)		1.44%	0[-0.44,0.44]
Bova 1999	34	3.8 (2.2)	36	4.1 (2.3)		1.35%	-0.14[-0.61,0.33]
Brinkhaus 2006	70	-23.6 (31)	74	-6.9 (22)		1.79%	-0.62[-0.96,-0.29]
Carbajal 1999	25	7.2 (2.8)	25	6.9 (2.6)		1.13%	0.1[-0.45,0.66]
Costello 2006	48	33 (25)	42	31 (25)		1.52%	0.08[-0.33,0.49]
Crosby 1994	26	13.6 (1.3)	33	13.5 (1.3)		1.23%	0.08[-0.44,0.59]
Dibble 2007	49	3.1 (2.9)	51	3.5 (3.1)		1.59%	-0.12[-0.51,0.27]
Ditto 2003	200	0.5 (0.4)	189	0.5 (0.4)		2.29%	-0.02[-0.22,0.17]
Ditto 2006	140	0.4 (0.4)	155	0.5 (0.4)		2.19%	-0.06[-0.28,0.17]
Erdogmus 2007	40	-27.4 (19.7)	40	-20.3 (19.7)		1.43%	-0.36[-0.8,0.08]
Etter 2002	269	20.6 (10)	389	25.4 (12.6)		2.43%	-0.41[-0.57,-0.26]
Foster 2007	112	6.5 (4.8)	105	6.8 (4.5)		2.05%	-0.06[-0.33,0.21]
Godfrey 1973	44	34.9 (16.7)	44	46.9 (16.2)		1.46%	-0.72[-1.15,-0.29]
Goodenough 1997	39	1.1 (1.6)	39	1.6 (1.9)		1.42%	-0.28[-0.73,0.16]
GRECHO 1989	150	94.4 (40.7)	150	95.4 (33)		2.19%	-0.03[-0.25,0.2]
Hargreaves 1989	25	4.5 (2.5)	25	4.9 (2.4)		1.12%	-0.16[-0.72,0.39]
Hashish 1986	25	16 (11.7)	50	30 (18.9)		1.27%	-0.82[-1.32,-0.32]
Hashish 1988	25	42 (25)	25	60 (23)		1.08%	-0.74[-1.31,-0.16]
Hovell 2003	98	-155.4 (69.9)	96	-151 (73.8)		1.99%	-0.06[-0.34,0.22]
Hruby 2006	49	1.2 (2.1)	51	0.9 (1.5)		1.59%	0.21[-0.19,0.6]
Kaptchuk 2008	88	-4.3 (1.4)	87	-3.8 (1)		1.92%	-0.41[-0.71,-0.11]
Karunakaran 1997	58	6.2 (1.2)	57	5.9 (0.6)		1.67%	0.31[-0.05,0.68]
Killeen 2004	24	1 (2.5)	35	1.9 (3.5)		1.21%	-0.28[-0.81,0.24]
Lander 1993	172	28.5 (29.3)	168	32.3 (33.4)		2.24%	-0.12[-0.33,0.09]
Lee 2005	27	-21.4 (25.9)	27	-5.9 (9.2)		1.12%	-0.79[-1.34,-0.23]
Leibing 2002	40	3.2 (1.8)	39	4.3 (1.9)		1.4%	-0.59[-1.04,-0.14]
Limoges 2004	30	2.3 (1)	30	2.2 (1)		1.25%	0.04[-0.47,0.55]
Lin 2002	25	30.2 (14.4)	25	38.1 (16)		1.1%	-0.51[-1.07,0.05]
Lincoln 2003	42	14.4 (10)	38	16.7 (10)		1.44%	-0.23[-0.67,0.21]
Linde 2005	76	-2.2 (2.7)	64	-0.8 (2.2)		1.78%	-0.56[-0.9,-0.22]
Lindholm 1996	227	6.8 (0.5)	226	6.8 (0.5)		2.34%	0.15[-0.04,0.33]
Lorr 1961	42	58.3 (9.9)	38	57.5 (9.9)		1.44%	0.08[-0.36,0.52]
Macaluso 1995	30	-3.3 (3.8)	30	-1.8 (3.3)		1.23%	-0.41[-0.93,0.1]
Melchart 2005	57	10.8 (8.3)	63	16.3 (7.4)		1.67%	-0.7[-1.07,-0.33]
Moreland 2006	50	-2 (1.3)	99	-2.1 (1.7)		1.77%	0.06[-0.28,0.4]
Morey 2006	38	-16.5 (9.3)	42	-14.7 (9.5)		1.44%	-0.19[-0.63,0.25]
Nawrocki 1997	40	9.5 (6)	42	17 (4.8)		1.31%	-1.37[-1.85,-0.89]
O'Brien 1996	53	6.7 (5.6)	54	7.5 (5.1)		1.63%	-0.15[-0.53,0.23]
Parker 1995	49	4 (1.9)	45	3.8 (2.2)		1.55%	0.1[-0.31,0.5]
Pelham 1992	38	-8.7 (1.7)	38	-8.5 (1.6)		1.41%	-0.12[-0.57,0.33]
Quahagen 1995	28	-108.3 (14.8)	25	-104.8 (13.9)		1.16%	-0.24[-0.78,0.3]
Rawling 2001	89	5.3 (4.7)	96	5.6 (4.9)		1.96%	-0.06[-0.35,0.23]
Ristikankare 1999	61	40.3 (21.5)	61	36 (21.5)		1.72%	0.2[-0.16,0.55]
Roscoe 2002	27	5.9 (5.2)	27	6.6 (3.6)		1.18%	-0.15[-0.69,0.38]
Roscoe 2005	31	2.4 (1.3)	33	2.8 (1.3)		1.28%	-0.3[-0.8,0.19]
Rowbotham 1996	35	-4.4 (8.7)	35	1.9 (8.7)		1.31%	-0.72[-1.2,-0.23]
Shen 2000	33	40.7 (12.4)	34	43.7 (11.3)		1.32%	-0.25[-0.73,0.23]

Favours placebo -1 -0.5 0 0.5 1 Favours no-treatment

Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Sinaiko 1991	60	66.5 (9.7)	27	64.1 (13.9)		1.39%	0.21[-0.24,0.67]
Steinsbekk 2004	102	44.5 (58.9)	74	53 (45.2)		1.92%	-0.16[-0.46,0.14]
Stewart 1991	25	-14.3 (5.5)	25	-12.8 (5.2)		1.12%	-0.28[-0.83,0.28]
Thomas 2002a	78	-0.9 (3)	78	-0.1 (2.9)		1.86%	-0.27[-0.59,0.04]
Thomas 2002b	114	-1.2 (3.5)	119	-1.6 (3.3)		2.08%	0.12[-0.14,0.37]
Tremeau 1992	39	-0.9 (1.3)	25	-1.1 (1.4)		1.26%	0.14[-0.36,0.65]
Tritrakarn 2000	41	49 (16)	41	61 (17)		1.41%	-0.72[-1.17,-0.27]
Tsay 2003	32	9.2 (4.4)	32	9.6 (4)		1.29%	-0.08[-0.57,0.41]
Tsay 2004	35	4.7 (1.5)	36	5.7 (1.8)		1.33%	-0.6[-1.07,-0.12]
Vlaeyen 1996	39	0.4 (1.8)	40	0.4 (1.8)		1.43%	0[-0.44,0.44]
Wang 1997	25	10.7 (7.3)	26	13.4 (5.8)		1.12%	-0.4[-0.96,0.15]
Witt 2005	73	35.8 (16.2)	67	49.6 (16.3)		1.75%	-0.84[-1.19,-0.5]
Total ***	**3960**		**4090**			**100%**	**-0.22[-0.29,-0.14]**

Heterogeneity: Tau²=0.06; Chi²=172.7, df=64(P<0.0001); I²=62.94%

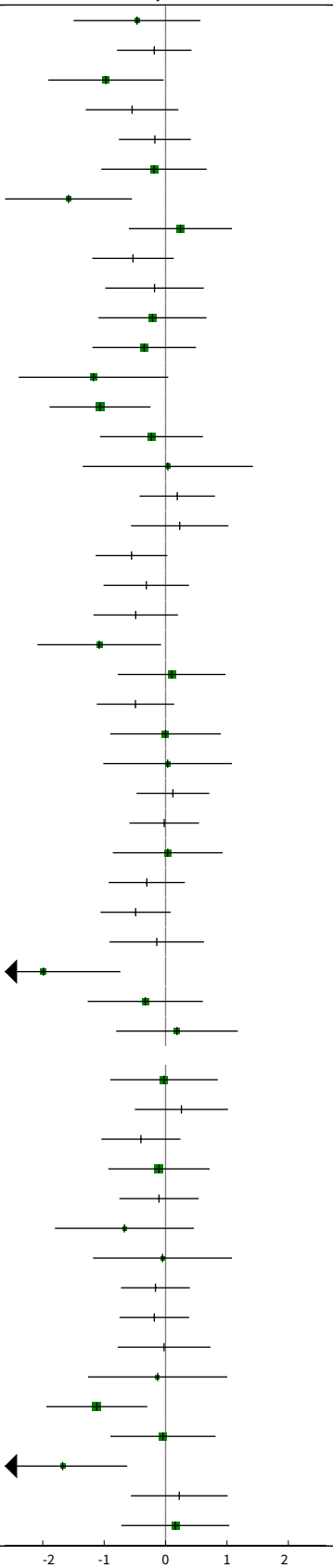
Test for overall effect: Z=5.53(P<0.0001)



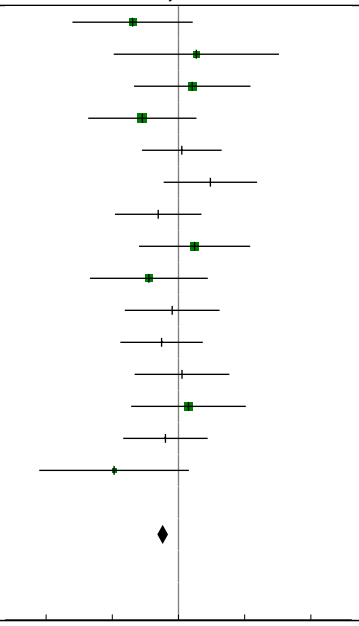
Analysis 16.4. Comparison 16 Risk of bias subgroup analysis: trial size, Outcome 4 Trial size 49 or less.

Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Alfano 2001	24	6.2 (2.8)	14	6.6 (2.7)		1.5%	-0.14[-0.8,0.52]
Allen 1998	11	-2.9 (7.9)	11	-6.1 (10.9)		0.92%	0.32[-0.52,1.17]
Andersen 1990	18	35 (27.2)	16	25 (23.6)		1.41%	0.38[-0.3,1.06]
Antivalle 1990	11	-1.6 (5.6)	10	-3.9 (7.3)		0.88%	0.34[-0.52,1.21]
Antonio 1999	6	79.7 (12.2)	6	72.6 (11.2)		0.48%	0.56[-0.6,1.72]
Ascher 1979	8	50.6 (44.1)	9	62.4 (25.3)		0.71%	-0.32[-1.28,0.64]
Benedetti 1995	13	-2 (1.2)	11	-0.8 (1)		0.87%	-1.07[-1.94,-0.2]
Blanchard 1990a	13	8.3 (13.6)	11	22.5 (25.1)		0.95%	-0.7[-1.53,0.13]
Blanchard 1990b	18	11.9 (23.9)	24	20.7 (34.8)		1.73%	-0.28[-0.9,0.33]
Block 1980	16	22.4 (6.6)	8	24.7 (9.2)		0.9%	-0.3[-1.15,0.56]
Bosley 1989	13	86 (10)	14	89 (10)		1.13%	-0.29[-1.05,0.47]
Bramston 1985	12	-78 (14.2)	12	-72 (13.8)		0.99%	-0.41[-1.22,0.4]
Cabrini 2006	16	61.7 (24)	16	66.6 (28)		1.35%	-0.18[-0.88,0.51]
Canino 1994	4	99 (2.7)	9	95.6 (7.6)		0.46%	0.48[-0.72,1.67]
Chenard 1991	12	29 (19)	16	30 (19)		1.17%	-0.05[-0.8,0.7]
Classen 1983	15	11.3 (8.3)	15	14.4 (6.1)		1.24%	-0.41[-1.14,0.31]
Colker 1999	7	82.7 (18)	4	77.7 (10.5)		0.43%	0.29[-0.95,1.53]
Conn 1986	13	28.2 (18.4)	14	44.4 (15.7)		1.02%	-0.92[-1.72,-0.12]
Coyne 1995	21	0.7 (0.7)	21	0.6 (0.7)		1.78%	0.13[-0.47,0.74]
Cupal 2001	10	2.7 (1)	10	2.7 (1.3)		0.85%	0[-0.88,0.88]
Davidson 1980	10	1.8 (0.9)	10	2.9 (1.3)		0.75%	-0.94[-1.88,-0.01]
Defrin 2005	9	7.3 (0.8)	8	7.6 (0.7)		0.7%	-0.39[-1.35,0.58]
Espie 1989	14	63.5 (30.6)	13	96.5 (63.5)		1.08%	-0.65[-1.43,0.13]
Etringer 1982	13	-11.4 (4)	12	-10.1 (3.7)		1.04%	-0.33[-1.12,0.46]
Fisher 2006	12	3.8 (1.9)	15	4.1 (2.5)		1.13%	-0.13[-0.89,0.63]
Forster 1994	15	3.2 (2.8)	15	4.6 (2.2)		1.22%	-0.54[-1.27,0.19]
Foster 2004	6	-3.6 (0.6)	12	-2.6 (1.1)		0.6%	-0.98[-2.02,0.06]

Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Frankel 1978	7	93 (5)	8	95 (3)		0.61%	-0.47[-1.5,0.57]
Frega 1994	21	20 (16)	21	23 (16)		1.78%	-0.18[-0.79,0.42]
Fuchs 1977	10	14.3 (7)	10	21.4 (7)		0.74%	-0.97[-1.91,-0.03]
Gracely 1983	17	-2.9 (5.4)	12	0.2 (5.5)		1.15%	-0.54[-1.3,0.21]
Hall 1974	23	-0.5 (7.8)	22	0.9 (7.8)		1.9%	-0.17[-0.76,0.41]
Hanson 1976	11	-0.9 (3.8)	10	-0.3 (2.2)		0.89%	-0.19[-1.05,0.67]
Hawkins 1995	10	37.4 (8.5)	10	52.1 (9.3)		0.61%	-1.58[-2.61,-0.55]
Helms 1987	11	103 (91)	11	79 (99)		0.93%	0.24[-0.6,1.08]
Hong 1993	16	-1.1 (0.2)	21	-1 (0.1)		1.49%	-0.53[-1.19,0.13]
Hossmann 1981	12	94.2 (4.8)	12	95.1 (4.8)		1.02%	-0.18[-0.98,0.62]
Hyland 2006	10	6 (0.9)	10	6.2 (0.9)		0.84%	-0.21[-1.09,0.67]
Irvin 1996	11	3.3 (0.7)	11	3.7 (1.4)		0.92%	-0.35[-1.19,0.5]
Jacobson 1978	7	2.5 (0.9)	6	3.5 (0.5)		0.44%	-1.17[-2.39,0.04]
Karst 2007	19	45.2 (10.8)	10	56.5 (9.1)		0.97%	-1.07[-1.89,-0.25]
Kendall 1979	11	7.5 (2.3)	11	8.2 (3)		0.93%	-0.23[-1.07,0.61]
Kilmann 1987	4	-33 (47)	4	-35 (47)		0.34%	0.04[-1.35,1.42]
Kober 2002	20	66.7 (10)	21	64.4 (13.3)		1.73%	0.19[-0.42,0.8]
Kokol 2005	16	9.5 (10.5)	10	7.3 (6.6)		1.04%	0.23[-0.56,1.02]
Kotani 2001	23	15 (4.5)	24	18 (6)		1.92%	-0.55[-1.14,0.03]
Levine 1984	12	-0.3 (0.7)	24	0.4 (2.5)		1.34%	-0.31[-1.01,0.38]
Licciardone 2003	19	2.5 (1.7)	15	3.5 (2.7)		1.38%	-0.49[-1.17,0.2]
Lick 1975	9	60.6 (32.7)	9	92.2 (22.1)		0.64%	-1.08[-2.09,-0.07]
Lick 1977	10	66 (25)	10	63 (32)		0.85%	0.1[-0.78,0.98]
Liossi 2003	20	4.3 (0.6)	20	4.6 (0.6)		1.65%	-0.49[-1.12,0.14]
Longo 1988	10	3.6 (0.6)	9	3.6 (0.4)		0.81%	0[-0.9,0.9]
Markland 1993	7	37.3 (11.8)	7	36.9 (11.9)		0.6%	0.03[-1.01,1.08]
Matros 2006	23	76 (36.3)	21	72 (28.3)		1.86%	0.12[-0.47,0.71]
May 1988	24	-1.2 (0.5)	24	-1.2 (0.5)		2.04%	-0.02[-0.59,0.54]
McLachlan 1991	8	6.3 (12.3)	12	5.7 (17.4)		0.82%	0.04[-0.86,0.93]
Medici 2002	23	-0.2 (0.3)	18	-0.1 (0.3)		1.7%	-0.31[-0.93,0.32]
Moffet 1996	22	24 (18.6)	27	34.6 (23.2)		2%	-0.49[-1.06,0.08]
Morton 1993	13	22.1 (16.4)	13	24.5 (16.4)		1.1%	-0.14[-0.91,0.63]
Murphy 1982	6	-16.5 (9.3)	11	-0.8 (6.4)		0.42%	-1.99[-3.24,-0.74]
Nandi 1976	10	53.2 (11.2)	8	57.5 (13.8)		0.74%	-0.33[-1.27,0.61]
Nicassio 1974	7	117.3 (133.7)	9	99.3 (35.3)		0.67%	0.19[-0.8,1.18]
Nocella 1982	10	0.8 (0.9)	10	0.8 (0.7)		0.85%	-0.02[-0.9,0.85]
Parker 2003	13	16.2 (7.5)	14	14.2 (7.5)		1.14%	0.26[-0.5,1.02]
Reading 1982	18	1.6 (1.3)	20	2.3 (2)		1.58%	-0.4[-1.05,0.24]
Robinson 2001	13	3.9 (3.5)	10	4.3 (3.7)		0.96%	-0.11[-0.93,0.72]
Roongpisuthip 1999	18	-3.3 (4.2)	19	-2.9 (3.1)		1.57%	-0.11[-0.75,0.54]
Rosen 1976	9	6.9 (2)	5	8.3 (1.9)		0.51%	-0.67[-1.8,0.46]
Rossi 1982	6	107 (17)	6	108 (20)		0.51%	-0.05[-1.18,1.08]
Rybarczyk 1990	25	7.1 (2.2)	24	7.5 (2.8)		2.07%	-0.16[-0.73,0.4]
Röschke 2000	24	23 (16.2)	24	26 (16)		2.03%	-0.18[-0.75,0.38]
Rösler 2003	13	5.9 (3.4)	14	6 (3)		1.15%	-0.02[-0.78,0.73]
Sanders 1990	6	2 (0.4)	6	2.1 (0.3)		0.51%	-0.13[-1.26,1]
Seer 1980	14	92.5 (9.8)	13	104.5 (11)		0.97%	-1.12[-1.94,-0.3]
Senediak 1985	11	47.5 (8.4)	10	47.9 (7.5)		0.89%	-0.04[-0.9,0.81]
Sipich 1974	10	8 (14)	10	32.5 (14)		0.59%	-1.68[-2.73,-0.63]
Spanos 1995	13	21.4 (9.7)	12	19.1 (10.3)		1.05%	0.22[-0.56,1.01]
Sprott 1993	10	7.9 (3)	10	7.4 (3)		0.85%	0.16[-0.72,1.04]



Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Fixed, 95% CI	Weight	Std. Mean Difference Fixed, 95% CI
Stabholz 1991	10	1.4 (0.5)	10	1.8 (0.6)		0.79%	-0.69[-1.6,0.22]
Straub 2001	5	-5.8 (0.3)	5	-6 (0.7)		0.42%	0.27[-0.98,1.52]
Sumaya 2001	10	15.4 (2.7)	10	14.9 (1.8)		0.84%	0.21[-0.67,1.09]
Tan 1982	12	1.3 (0.6)	12	1.7 (0.8)		0.98%	-0.55[-1.36,0.27]
Tashjian 2006	19	3.4 (2.2)	24	3.3 (1.8)		1.8%	0.05[-0.55,0.65]
Theroux 1993	17	3.2 (0.7)	15	2.9 (0.6)		1.31%	0.48[-0.22,1.19]
Thomas 1999	14	13.4 (10.3)	26	16.5 (9.7)		1.53%	-0.31[-0.96,0.35]
Tuomilehto 1980	11	9 (1.4)	11	8.7 (1.6)		0.93%	0.24[-0.6,1.08]
Turner 1979	10	44.2 (41.3)	10	59.8 (22.9)		0.82%	-0.45[-1.34,0.44]
Weingaertner 1971	15	1.1 (1.3)	15	1.2 (1.6)		1.27%	-0.1[-0.81,0.62]
Werntoft 2001	20	5.9 (2.4)	20	6.5 (2.2)		1.69%	-0.26[-0.88,0.37]
Wilcock 2008	15	-6.4 (5.1)	15	-6.7 (5.9)		1.27%	0.05[-0.66,0.77]
Wojciechowski 1984	9	264 (122)	12	238 (190)		0.87%	0.15[-0.71,1.02]
Woods 2005	19	1.2 (1.3)	19	1.5 (1.1)		1.61%	-0.2[-0.83,0.44]
Yates 1988	7	-1.4 (2.5)	7	0.7 (1.4)		0.51%	-0.97[-2.1,0.16]
Total ***	**1228**		**1235**			**100%**	**-0.24[-0.32,-0.16]**
Heterogeneity: Tau^2=0; Chi^2=95.63, df=92(P=0.38); I^2=3.79%							
Test for overall effect: Z=5.8(P<0.0001)							

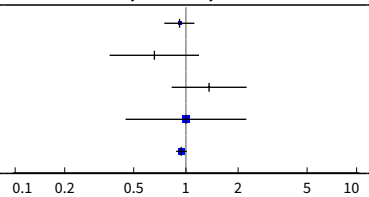


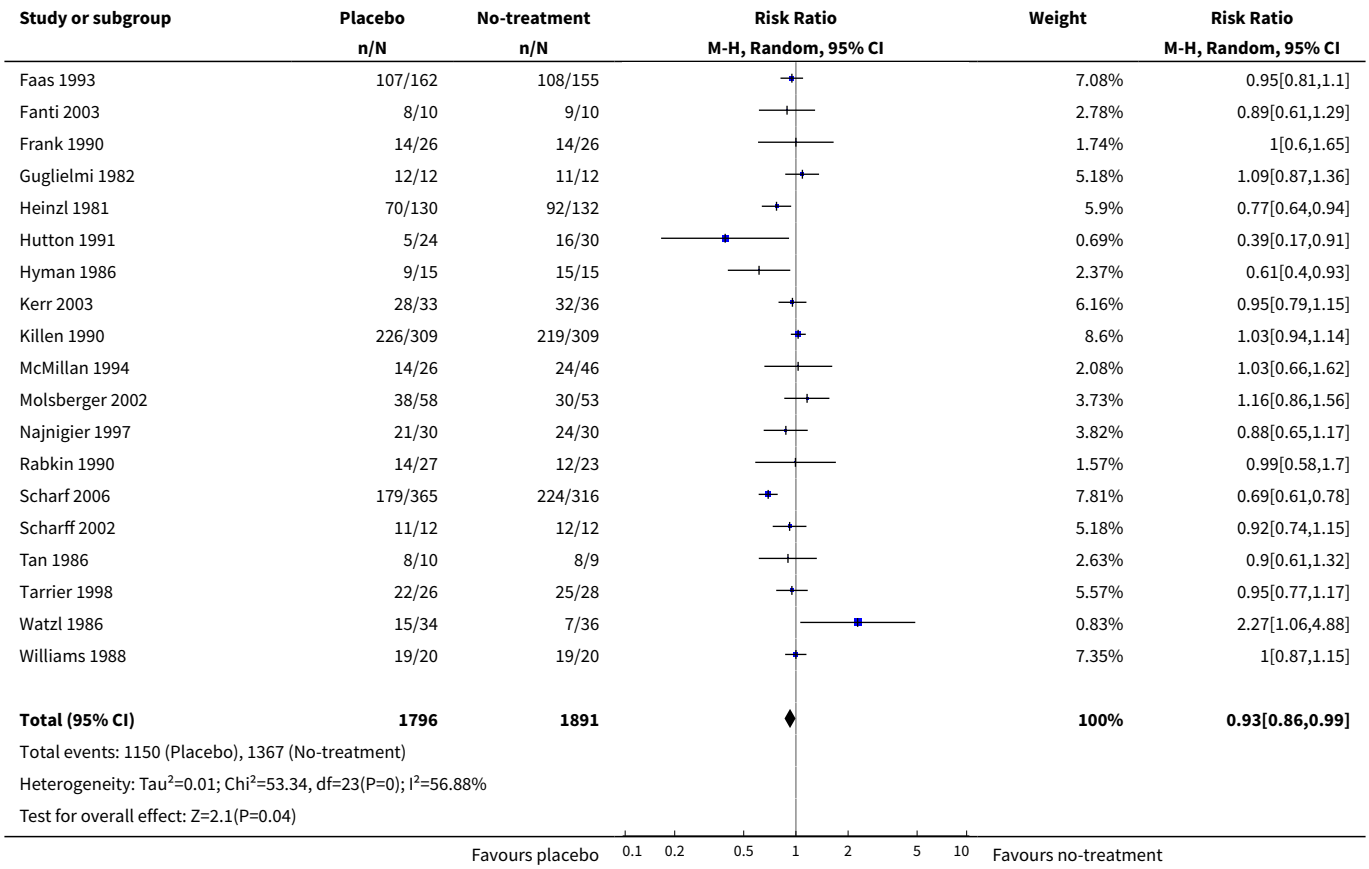
Comparison 17. Risk of bias subgroup analysis: dropouts

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Dropout rates no more than 15%	24	3687	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.86, 0.99]
2 Dropout rates >15%, or not stated	20	2354	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.86, 1.06]
3 Dropout rates no more than 15%	64	4973	Std. Mean Difference (IV, Random, 95% CI)	-0.25 [-0.34, -0.16]
4 Dropout rates > 15%, or not stated	94	5540	Std. Mean Difference (IV, Random, 95% CI)	-0.20 [-0.27, -0.13]

Analysis 17.1. Comparison 17 Risk of bias subgroup analysis: dropouts, Outcome 1 Dropout rates no more than 15%.

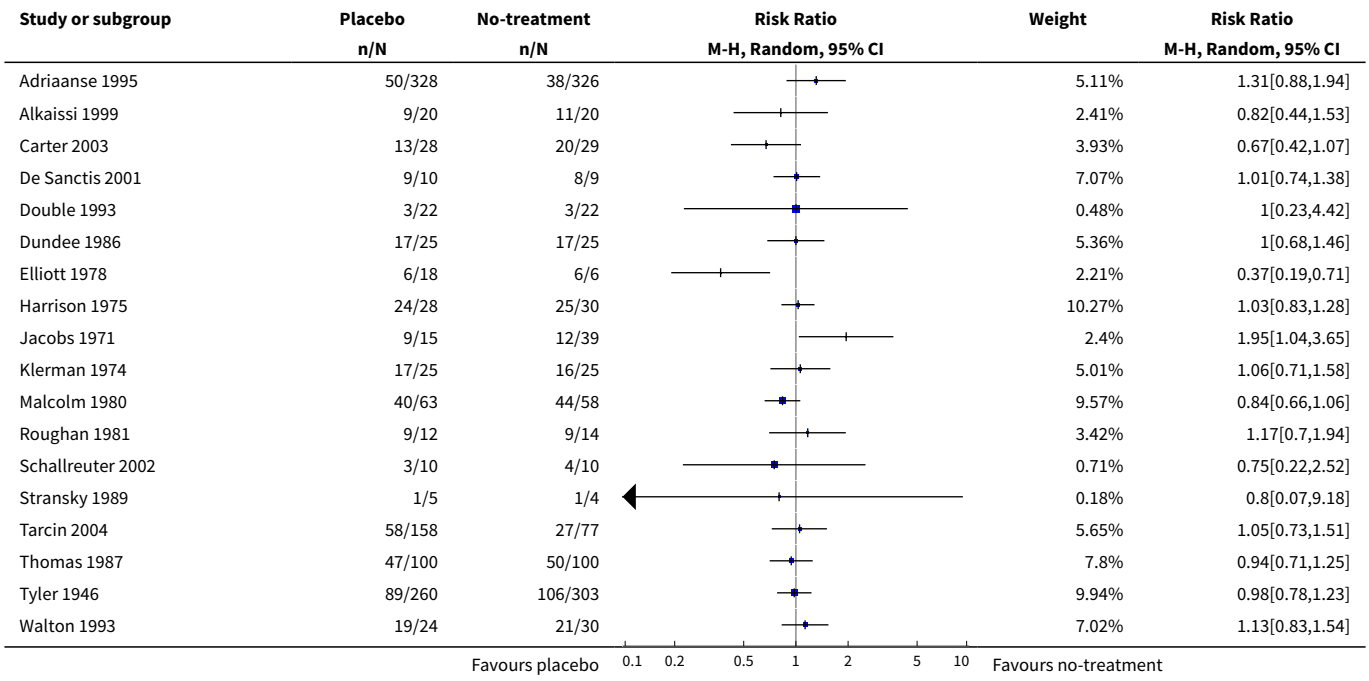
Study or subgroup	Placebo n/N	No-treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Alkaissi 2002	77/139	82/136		5.71%	0.92[0.75,1.12]
Aune 1998	11/26	9/14		1.31%	0.66[0.36,1.19]
Berg 1983	9/11	9/15		1.77%	1.36[0.83,2.24]
Blackman 1964	6/12	6/12		0.77%	1[0.45,2.23]
Corver 2006	227/279	360/416		9.38%	0.94[0.88,1.01]





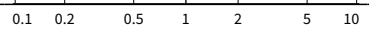
Study or subgroup	Placebo n/N	No-treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Faas 1993	107/162	108/155		7.08%	0.95[0.81,1.1]
Fanti 2003	8/10	9/10		2.78%	0.89[0.61,1.29]
Frank 1990	14/26	14/26		1.74%	1[0.6,1.65]
Guglielmi 1982	12/12	11/12		5.18%	1.09[0.87,1.36]
Heinzl 1981	70/130	92/132		5.9%	0.77[0.64,0.94]
Hutton 1991	5/24	16/30		0.69%	0.39[0.17,0.91]
Hyman 1986	9/15	15/15		2.37%	0.61[0.4,0.93]
Kerr 2003	28/33	32/36		6.16%	0.95[0.79,1.15]
Killen 1990	226/309	219/309		8.6%	1.03[0.94,1.14]
McMillan 1994	14/26	24/46		2.08%	1.03[0.66,1.62]
Molsberger 2002	38/58	30/53		3.73%	1.16[0.86,1.56]
Najnigier 1997	21/30	24/30		3.82%	0.88[0.65,1.17]
Rabkin 1990	14/27	12/23		1.57%	0.99[0.58,1.7]
Scharf 2006	179/365	224/316		7.81%	0.69[0.61,0.78]
Scharff 2002	11/12	12/12		5.18%	0.92[0.74,1.15]
Tan 1986	8/10	8/9		2.63%	0.9[0.61,1.32]
Tarrier 1998	22/26	25/28		5.57%	0.95[0.77,1.17]
Watzl 1986	15/34	7/36		0.83%	2.27[1.06,4.88]
Williams 1988	19/20	19/20		7.35%	1[0.87,1.15]
Total (95% CI)	**1796**	**1891**		**100%**	**0.93[0.86,0.99]**
Total events: 1150 (Placebo), 1367 (No-treatment)					
Heterogeneity: Tau²=0.01; Chi²=53.34, df=23(P=0); I²=56.88%					
Test for overall effect: Z=2.1(P=0.04)					

Analysis 17.2. Comparison 17 Risk of bias subgroup analysis: dropouts, Outcome 2 Dropout rates >15%, or not stated.



Study or subgroup	Placebo n/N	No-treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Adriaanse 1995	50/328	38/326		5.11%	1.31[0.88,1.94]
Alkaissi 1999	9/20	11/20		2.41%	0.82[0.44,1.53]
Carter 2003	13/28	20/29		3.93%	0.67[0.42,1.07]
De Sanctis 2001	9/10	8/9		7.07%	1.01[0.74,1.38]
Double 1993	3/22	3/22		0.48%	1[0.23,4.42]
Dundee 1986	17/25	17/25		5.36%	1[0.68,1.46]
Elliott 1978	6/18	6/6		2.21%	0.37[0.19,0.71]
Harrison 1975	24/28	25/30		10.27%	1.03[0.83,1.28]
Jacobs 1971	9/15	12/39		2.4%	1.95[1.04,3.65]
Klerman 1974	17/25	16/25		5.01%	1.06[0.71,1.58]
Malcolm 1980	40/63	44/58		9.57%	0.84[0.66,1.06]
Roughan 1981	9/12	9/14		3.42%	1.17[0.7,1.94]
Schallreuter 2002	3/10	4/10		0.71%	0.75[0.22,2.52]
Stransky 1989	1/5	1/4		0.18%	0.8[0.07,9.18]
Tarcin 2004	58/158	27/77		5.65%	1.05[0.73,1.51]
Thomas 1987	47/100	50/100		7.8%	0.94[0.71,1.25]
Tyler 1946	89/260	106/303		9.94%	0.98[0.78,1.23]
Walton 1993	19/24	21/30		7.02%	1.13[0.83,1.54]

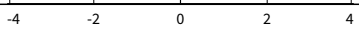
Study or subgroup	Placebo n/N	No-treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Whittaker 1963	3/13	7/13		0.83%	0.43[0.14,1.3]
Wilson 1980	31/40	10/10		10.63%	0.8[0.65,0.99]
Total (95% CI)	**1204**	**1150**		**100%**	**0.96[0.86,1.06]**
Total events: 457 (Placebo), 435 (No-treatment)					
Heterogeneity: Tau^2=0.01; Chi^2=27.16, df=19(P=0.1); I^2=30.04%					
Test for overall effect: Z=0.87(P=0.39)					



Favours placebo — Favours no-treatment

Analysis 17.3. Comparison 17 Risk of bias subgroup analysis: dropouts, Outcome 3 Dropout rates no more than 15%.

Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Allen 1998	11	-2.9 (7.9)	11	-6.1 (10.9)		0.89%	0.32[-0.52,1.17]
Allen 2006	45	12 (9.6)	44	19 (9.6)		2.09%	-0.72[-1.15,-0.29]
Anderson 1999	30	-2.7 (0.8)	27	-2.7 (0.8)		1.71%	0.08[-0.44,0.6]
Antivalle 1990	11	-1.6 (5.6)	10	-3.9 (7.3)		0.85%	0.34[-0.52,1.21]
Antonio 1999	6	79.7 (12.2)	6	72.6 (11.2)		0.52%	0.56[-0.6,1.72]
Asmar 1996	34	-0.2 (7.7)	34	0.7 (6.5)		1.89%	-0.12[-0.6,0.35]
Biro 1997	29	3.6 (2.5)	29	3.3 (2.1)		1.73%	0.13[-0.39,0.64]
Blanchard 1990a	13	8.3 (13.6)	11	22.5 (25.1)		0.9%	-0.7[-1.53,0.13]
Bova 1999	34	3.8 (2.2)	36	4.1 (2.3)		1.91%	-0.14[-0.61,0.33]
Bramston 1985	12	-78 (14.2)	12	-72 (13.8)		0.94%	-0.41[-1.22,0.4]
Brinkhaus 2006	70	-23.6 (31)	74	-6.9 (22)		2.58%	-0.62[-0.96,-0.29]
Colker 1999	7	82.7 (18)	4	77.7 (10.5)		0.47%	0.29[-0.95,1.53]
Costello 2006	48	33 (25)	42	31 (25)		2.17%	0.08[-0.33,0.49]
Coyne 1995	21	0.7 (0.7)	21	0.6 (0.7)		1.42%	0.13[-0.47,0.74]
Crosby 1994	26	13.6 (1.3)	33	13.5 (1.3)		1.73%	0.08[-0.44,0.59]
Dibble 2007	49	3.1 (2.9)	51	3.5 (3.1)		2.27%	-0.12[-0.51,0.27]
Erdogmus 2007	40	-27.4 (19.7)	40	-20.3 (19.7)		2.04%	-0.36[-0.8,0.08]
Etringer 1982	13	-11.4 (4)	12	-10.1 (3.7)		0.98%	-0.33[-1.12,0.46]
Etter 2002	269	20.6 (10)	389	25.4 (12.6)		3.58%	-0.41[-0.57,-0.26]
Foster 2004	6	-3.6 (0.6)	12	-2.6 (1.1)		0.62%	-0.98[-2.02,0.06]
Foster 2007	112	6.5 (4.8)	105	6.8 (4.5)		2.97%	-0.06[-0.33,0.21]
Hashish 1988	25	42 (25)	25	60 (23)		1.52%	-0.74[-1.31,-0.16]
Hawkins 1995	10	37.4 (8.5)	10	52.1 (9.3)		0.64%	-1.58[-2.61,-0.55]
Helms 1987	11	103 (91)	11	79 (99)		0.89%	0.24[-0.6,1.08]
Hovell 2003	98	-155.4 (69.9)	96	-151 (73.8)		2.88%	-0.06[-0.34,0.22]
Hyland 2006	10	6 (0.9)	10	6.2 (0.9)		0.83%	-0.21[-1.09,0.67]
Jacobson 1978	7	2.5 (0.9)	6	3.5 (0.5)		0.48%	-1.17[-2.39,0.04]
Kaptchuk 2008	88	-4.3 (1.4)	87	-3.8 (1)		2.78%	-0.41[-0.71,-0.11]
Kilmann 1987	4	-33 (47)	4	-35 (47)		0.38%	0.04[-1.35,1.42]
Kober 2002	20	66.7 (10)	21	64.4 (13.3)		1.4%	0.19[-0.42,0.8]
Kokol 2005	16	9.5 (10.5)	10	7.3 (6.6)		0.97%	0.23[-0.56,1.02]
Kotani 2001	23	15 (4.5)	24	18 (6)		1.49%	-0.55[-1.14,0.03]
Lander 1993	172	28.5 (29.3)	168	32.3 (33.4)		3.28%	-0.12[-0.33,0.09]
Lee 2005	27	-21.4 (25.9)	27	-5.9 (9.2)		1.58%	-0.79[-1.34,-0.23]

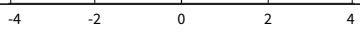


Favours placebo — Favours no-treatment

Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Leibing 2002	40	3.2 (1.8)	39	4.3 (1.9)		1.99%	-0.59[-1.04,-0.14]
Lick 1975	9	60.6 (32.7)	9	92.2 (22.1)		0.66%	-1.08[-2.09,-0.07]
Limoges 2004	30	2.3 (1)	30	2.2 (1)		1.76%	0.04[-0.47,0.55]
Lin 2002	25	30.2 (14.4)	25	38.1 (16)		1.55%	-0.51[-1.07,0.05]
Lincoln 2003	42	14.4 (10)	38	16.7 (10)		2.04%	-0.23[-0.67,0.21]
Linde 2005	76	-2.2 (2.7)	64	-0.8 (2.2)		2.55%	-0.56[-0.9,-0.22]
Lindholm 1996	227	6.8 (0.5)	226	6.8 (0.5)		3.44%	0.15[-0.04,0.33]
Liossi 2003	20	4.3 (0.6)	20	4.6 (0.6)		1.35%	-0.49[-1.12,0.14]
Longo 1988	10	3.6 (0.6)	9	3.6 (0.4)		0.8%	0[-0.9,0.9]
Markland 1993	7	37.3 (11.8)	7	36.9 (11.9)		0.62%	0.03[-1.01,1.08]
Medici 2002	23	-0.2 (0.3)	18	-0.1 (0.3)		1.38%	-0.31[-0.93,0.32]
Melchart 2005	57	10.8 (8.3)	63	16.3 (7.4)		2.39%	-0.7[-1.07,-0.33]
Morey 2006	38	-16.5 (9.3)	42	-14.7 (9.5)		2.05%	-0.19[-0.63,0.25]
Nandi 1976	10	53.2 (11.2)	8	57.5 (13.8)		0.75%	-0.33[-1.27,0.61]
Nicassio 1974	7	117.3 (133.7)	9	99.3 (35.3)		0.68%	0.19[-0.8,1.18]
O'Brien 1996	53	6.7 (5.6)	54	7.5 (5.1)		2.34%	-0.15[-0.53,0.23]
Parker 1995	49	4 (1.9)	45	3.8 (2.2)		2.21%	0.1[-0.31,0.5]
Reading 1982	18	1.6 (1.3)	20	2.3 (2)		1.31%	-0.4[-1.05,0.24]
Roscoe 2005	31	2.4 (1.3)	33	2.8 (1.3)		1.82%	-0.3[-0.8,0.19]
Rossi 1982	6	107 (17)	6	108 (20)		0.54%	-0.05[-1.18,1.08]
Rowbotham 1996	35	-4.4 (8.7)	35	1.9 (8.7)		1.85%	-0.72[-1.2,-0.23]
Sanders 1990	6	2 (0.4)	6	2.1 (0.3)		0.54%	-0.13[-1.26,1]
Seer 1980	14	92.5 (9.8)	13	104.5 (11)		0.92%	-1.12[-1.94,-0.3]
Shen 2000	33	40.7 (12.4)	34	43.7 (11.3)		1.87%	-0.25[-0.73,0.23]
Sumaya 2001	10	15.4 (2.7)	10	14.9 (1.8)		0.83%	0.21[-0.67,1.09]
Tsay 2003	32	9.2 (4.4)	32	9.6 (4)		1.83%	-0.08[-0.57,0.41]
Tuomilehto 1980	11	9 (1.4)	11	8.7 (1.6)		0.89%	0.24[-0.6,1.08]
Vlaeyen 1996	39	0.4 (1.8)	40	0.4 (1.8)		2.04%	0[-0.44,0.44]
Wilcock 2008	15	-6.4 (5.1)	15	-6.7 (5.9)		1.13%	0.05[-0.66,0.77]
Witt 2005	73	35.8 (16.2)	67	49.6 (16.3)		2.51%	-0.84[-1.19,-0.5]
Total ***	**2443**		**2530**			**100%**	**-0.25[-0.34,-0.16]**

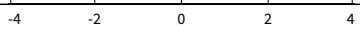
Heterogeneity: Tau^2=0.05; Chi^2=123.34, df=63(P<0.0001); I^2=48.92%

Test for overall effect: Z=5.56(P<0.0001)

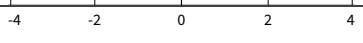


Analysis 17.4. Comparison 17 Risk of bias subgroup analysis: dropouts, Outcome 4 Dropout rates > 15%, or not stated.

Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Abikoff 2004	35	-91.4 (18.9)	34	-89.5 (22.8)		1.44%	-0.09[-0.56,0.38]
Alfano 2001	24	6.2 (2.8)	14	6.6 (2.7)		0.91%	-0.14[-0.8,0.52]
Andersen 1990	18	35 (27.2)	16	25 (23.6)		0.87%	0.38[-0.3,1.06]
Ascher 1979	8	50.6 (44.1)	9	62.4 (25.3)		0.5%	-0.32[-1.28,0.64]
Benedetti 1995	13	-2 (1.2)	11	-0.8 (1)		0.59%	-1.07[-1.94,-0.2]
Benedetti 1997	106	0.3 (0.1)	115	0.3 (0.1)		2.48%	-0.17[-0.43,0.1]
Blades 2001	40	-16 (6)	40	-16 (6)		1.58%	0[-0.44,0.44]



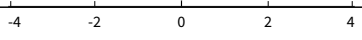
Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Blanchard 1990b	18	11.9 (23.9)	24	20.7 (34.8)		1.01%	-0.28[-0.9,0.33]
Block 1980	16	22.4 (6.6)	8	24.7 (9.2)		0.61%	-0.3[-1.15,0.56]
Bosley 1989	13	86 (10)	14	89 (10)		0.73%	-0.29[-1.05,0.47]
Cabrini 2006	16	61.7 (24)	16	66.6 (28)		0.84%	-0.18[-0.88,0.51]
Canino 1994	4	99 (2.7)	9	95.6 (7.6)		0.33%	0.48[-0.72,1.67]
Carbajal 1999	25	7.2 (2.8)	25	6.9 (2.6)		1.17%	0.1[-0.45,0.66]
Chenard 1991	12	29 (19)	16	30 (19)		0.75%	-0.05[-0.8,0.7]
Classen 1983	15	11.3 (8.3)	15	14.4 (6.1)		0.79%	-0.41[-1.14,0.31]
Conn 1986	13	28.2 (18.4)	14	44.4 (15.7)		0.67%	-0.92[-1.72,-0.12]
Cupal 2001	10	2.7 (1)	10	2.7 (1.3)		0.58%	0[-0.88,0.88]
Davidson 1980	10	1.8 (0.9)	10	2.9 (1.3)		0.52%	-0.94[-1.88,-0.01]
Defrin 2005	9	7.3 (0.8)	8	7.6 (0.7)		0.49%	-0.39[-1.35,0.58]
Ditto 2003	200	0.5 (0.4)	189	0.5 (0.4)		2.9%	-0.02[-0.22,0.17]
Ditto 2006	140	0.4 (0.4)	155	0.5 (0.4)		2.71%	-0.06[-0.28,0.17]
Espie 1989	14	63.5 (30.6)	13	96.5 (63.5)		0.71%	-0.65[-1.43,0.13]
Fisher 2006	12	3.8 (1.9)	15	4.1 (2.5)		0.73%	-0.13[-0.89,0.63]
Forster 1994	15	3.2 (2.8)	15	4.6 (2.2)		0.78%	-0.54[-1.27,0.19]
Frankel 1978	7	93 (5)	8	95 (3)		0.44%	-0.47[-1.5,0.57]
Frega 1994	21	20 (16)	21	23 (16)		1.03%	-0.18[-0.79,0.42]
Fuchs 1977	10	14.3 (7)	10	21.4 (7)		0.52%	-0.97[-1.91,-0.03]
Godfrey 1973	44	34.9 (16.7)	44	46.9 (16.2)		1.6%	-0.72[-1.15,-0.29]
Goodenough 1997	39	1.1 (1.6)	39	1.6 (1.9)		1.54%	-0.28[-0.73,0.16]
Gracely 1983	17	-2.9 (5.4)	12	0.2 (5.5)		0.74%	-0.54[-1.3,0.21]
GRECHO 1989	150	94.4 (40.7)	150	95.4 (33)		2.72%	-0.03[-0.25,0.2]
Hall 1974	23	-0.5 (7.8)	22	0.9 (7.8)		1.09%	-0.17[-0.76,0.41]
Hanson 1976	11	-0.9 (3.8)	10	-0.3 (2.2)		0.6%	-0.19[-1.05,0.67]
Hargreaves 1989	25	4.5 (2.5)	25	4.9 (2.4)		1.17%	-0.16[-0.72,0.39]
Hashish 1986	25	16 (11.7)	50	30 (18.9)		1.35%	-0.82[-1.32,-0.32]
Hong 1993	16	-1.1 (0.2)	21	-1 (0.1)		0.91%	-0.53[-1.19,0.13]
Hossmann 1981	12	94.2 (4.8)	12	95.1 (4.8)		0.67%	-0.18[-0.98,0.62]
Hruby 2006	49	1.2 (2.1)	51	0.9 (1.5)		1.78%	0.21[-0.19,0.6]
Irvin 1996	11	3.3 (0.7)	11	3.7 (1.4)		0.62%	-0.35[-1.19,0.5]
Karst 2007	19	45.2 (10.8)	10	56.5 (9.1)		0.65%	-1.07[-1.89,-0.25]
Karunakaran 1997	58	6.2 (1.2)	57	5.9 (0.6)		1.9%	0.31[-0.05,0.68]
Kendall 1979	11	7.5 (2.3)	11	8.2 (3)		0.62%	-0.23[-1.07,0.61]
Killeen 2004	24	1 (2.5)	35	1.9 (3.5)		1.27%	-0.28[-0.81,0.24]
Levine 1984	12	-0.3 (0.7)	24	0.4 (2.5)		0.84%	-0.31[-1.01,0.38]
Licciardone 2003	19	2.5 (1.7)	15	3.5 (2.7)		0.86%	-0.49[-1.17,0.2]
Lick 1977	10	66 (25)	10	63 (32)		0.58%	0.1[-0.78,0.98]
Lorr 1961	42	58.3 (9.9)	38	57.5 (9.9)		1.57%	0.08[-0.36,0.52]
Macaluso 1995	30	-3.3 (3.8)	30	-1.8 (3.3)		1.3%	-0.41[-0.93,0.1]
Matros 2006	23	76 (36.3)	21	72 (28.3)		1.07%	0.12[-0.47,0.71]
May 1988	24	-1.2 (0.5)	24	-1.2 (0.5)		1.14%	-0.02[-0.59,0.54]
McLachlan 1991	8	6.3 (12.3)	12	5.7 (17.4)		0.56%	0.04[-0.86,0.93]
Moffet 1996	22	24 (18.6)	27	34.6 (23.2)		1.12%	-0.49[-1.06,0.08]
Moreland 2006	50	-2 (1.3)	99	-2.1 (1.7)		2.04%	0.06[-0.28,0.4]
Morton 1993	13	22.1 (16.4)	13	24.5 (16.4)		0.72%	-0.14[-0.91,0.63]
Murphy 1982	6	-16.5 (9.3)	11	-0.8 (6.4)		0.31%	-1.99[-3.24,-0.74]
Nawrocki 1997	40	9.5 (6)	42	17 (4.8)		1.4%	-1.37[-1.85,-0.89]
Nocella 1982	10	0.8 (0.9)	10	0.8 (0.7)		0.58%	-0.02[-0.9,0.85]
Parker 2003	13	16.2 (7.5)	14	14.2 (7.5)		0.73%	0.26[-0.5,1.02]
Pelham 1992	38	-8.7 (1.7)	38	-8.5 (1.6)		1.53%	-0.12[-0.57,0.33]



Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
Quahagen 1995	28	-108.3 (14.8)	25	-104.8 (13.9)		1.21%	-0.24[-0.78,0.3]
Rawling 2001	89	5.3 (4.7)	96	5.6 (4.9)		2.34%	-0.06[-0.35,0.23]
Ristikankare 1999	61	40.3 (21.5)	61	36 (21.5)		1.96%	0.2[-0.16,0.55]
Robinson 2001	13	3.9 (3.5)	10	4.3 (3.7)		0.64%	-0.11[-0.93,0.72]
Roongpisuthip 1999	18	-3.3 (4.2)	19	-2.9 (3.1)		0.94%	-0.11[-0.75,0.54]
Roscoe 2002	27	5.9 (5.2)	27	6.6 (3.6)		1.23%	-0.15[-0.69,0.38]
Rosen 1976	9	6.9 (2)	5	8.3 (1.9)		0.37%	-0.67[-1.8,0.46]
Rybarczyk 1990	25	7.1 (2.2)	24	7.5 (2.8)		1.15%	-0.16[-0.73,0.4]
Röschke 2000	24	23 (16.2)	24	26 (16)		1.14%	-0.18[-0.75,0.38]
Rösler 2003	13	5.9 (3.4)	14	6 (3)		0.74%	-0.02[-0.78,0.73]
Senediak 1985	11	47.5 (8.4)	10	47.9 (7.5)		0.6%	-0.04[-0.9,0.81]
Sinaiko 1991	60	66.5 (9.7)	27	64.1 (13.9)		1.51%	0.21[-0.24,0.67]
Sipich 1974	10	8 (14)	10	32.5 (14)		0.42%	-1.68[-2.73,-0.63]
Spanos 1995	13	21.4 (9.7)	12	19.1 (10.3)		0.69%	0.22[-0.56,1.01]
Sprott 1993	10	7.9 (3)	10	7.4 (3)		0.58%	0.16[-0.72,1.04]
Stabholz 1991	10	1.4 (0.5)	10	1.8 (0.6)		0.54%	-0.69[-1.6,0.22]
Steinsbekk 2004	102	44.5 (58.9)	74	53 (45.2)		2.27%	-0.16[-0.46,0.14]
Stewart 1991	25	-14.3 (5.5)	25	-12.8 (5.2)		1.16%	-0.28[-0.83,0.28]
Straub 2001	5	-5.8 (0.3)	5	-6 (0.7)		0.31%	0.27[-0.98,1.52]
Tan 1982	12	1.3 (0.6)	12	1.7 (0.8)		0.65%	-0.55[-1.36,0.27]
Tashjian 2006	19	3.4 (2.2)	24	3.3 (1.8)		1.04%	0.05[-0.55,0.65]
Theroux 1993	17	3.2 (0.7)	15	2.9 (0.6)		0.82%	0.48[-0.22,1.19]
Thomas 1999	14	13.4 (10.3)	26	16.5 (9.7)		0.93%	-0.31[-0.96,0.35]
Thomas 2002a	78	-0.9 (3)	78	-0.1 (2.9)		2.18%	-0.27[-0.59,0.04]
Thomas 2002b	114	-1.2 (3.5)	119	-1.6 (3.3)		2.53%	0.12[-0.14,0.37]
Tremeau 1992	39	-0.9 (1.3)	25	-1.1 (1.4)		1.33%	0.14[-0.36,0.65]
Tritrakarn 2000	41	49 (16)	41	61 (17)		1.54%	-0.72[-1.17,-0.27]
Tsay 2004	35	4.7 (1.5)	36	5.7 (1.8)		1.43%	-0.6[-1.07,-0.12]
Turner 1979	10	44.2 (41.3)	10	59.8 (22.9)		0.56%	-0.45[-1.34,0.44]
Wang 1997	25	10.7 (7.3)	26	13.4 (5.8)		1.17%	-0.4[-0.96,0.15]
Weingaertner 1971	15	1.1 (1.3)	15	1.2 (1.6)		0.81%	-0.1[-0.81,0.62]
Werntoft 2001	20	5.9 (2.4)	20	6.5 (2.2)		1%	-0.26[-0.88,0.37]
Wojciechowski 1984	9	264 (122)	12	238 (190)		0.59%	0.15[-0.71,1.02]
Woods 2005	19	1.2 (1.3)	19	1.5 (1.1)		0.96%	-0.2[-0.83,0.44]
Yates 1988	7	-1.4 (2.5)	7	0.7 (1.4)		0.37%	-0.97[-2.1,0.16]
Total ***	**2745**		**2795**			**100%**	**-0.2[-0.27,-0.13]**

Heterogeneity: Tau^2=0.04; Chi^2=141.6, df=93(P=0); I^2=34.32%

Test for overall effect: Z=5.43(P<0.0001)



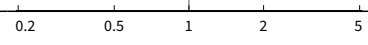
Comparison 18. Risk of bias subgroup analysis: clearly concealed allocation + trial size >49 + dropout max 15%

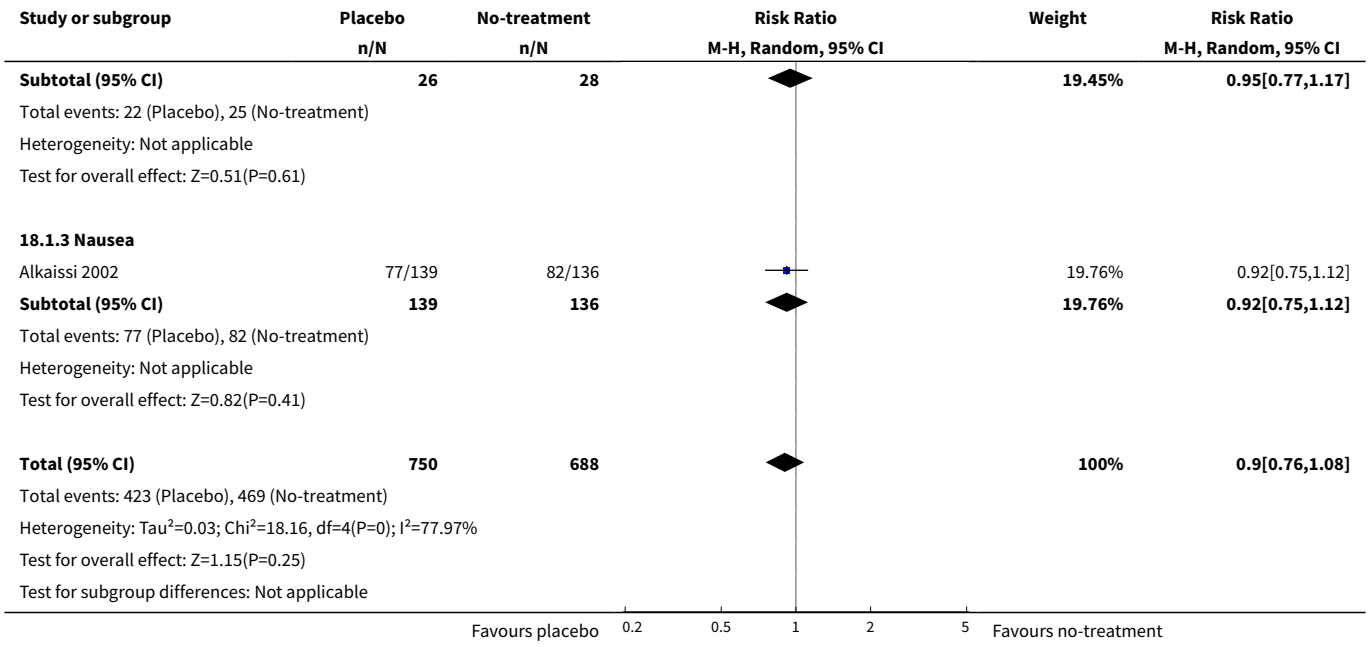
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Binary outcomes	5	1438	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.76, 1.08]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Pain (incidence)	3	1109	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.67, 1.19]
1.2 Schizophrenia (lack of 50% improvement)	1	54	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.77, 1.17]
1.3 Nausea	1	275	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.75, 1.12]
2 Continuous outcomes	11	1610	Std. Mean Difference (IV, Random, 95% CI)	-0.38 [-0.55, -0.22]
2.1 Pain (various scales, see table of included studies for details)	7	1181	Std. Mean Difference (IV, Random, 95% CI)	-0.45 [-0.69, -0.21]
2.2 Nausea (Rhodes inventory of nausea and vomiting, escape medication)	2	174	Std. Mean Difference (IV, Random, 95% CI)	-0.19 [-0.49, 0.11]
2.3 Irritable bowel syndrome (Global improvement scale)	1	175	Std. Mean Difference (IV, Random, 95% CI)	-0.41 [-0.71, -0.11]
2.4 Depression (Beck depression inventory)	1	80	Std. Mean Difference (IV, Random, 95% CI)	-0.23 [-0.67, 0.21]
3 Pain heterogeneity	7	1181	Std. Mean Difference (IV, Random, 95% CI)	-0.45 [-0.69, -0.21]
3.1 GAT	4	544	Std. Mean Difference (IV, Random, 95% CI)	-0.68 [-0.85, -0.50]
3.2 Not GAT	3	637	Std. Mean Difference (IV, Random, 95% CI)	-0.13 [-0.28, 0.03]

Analysis 18.1. Comparison 18 Risk of bias subgroup analysis: clearly concealed allocation + trial size >49 + dropout max 15%, Outcome 1 Binary outcomes.

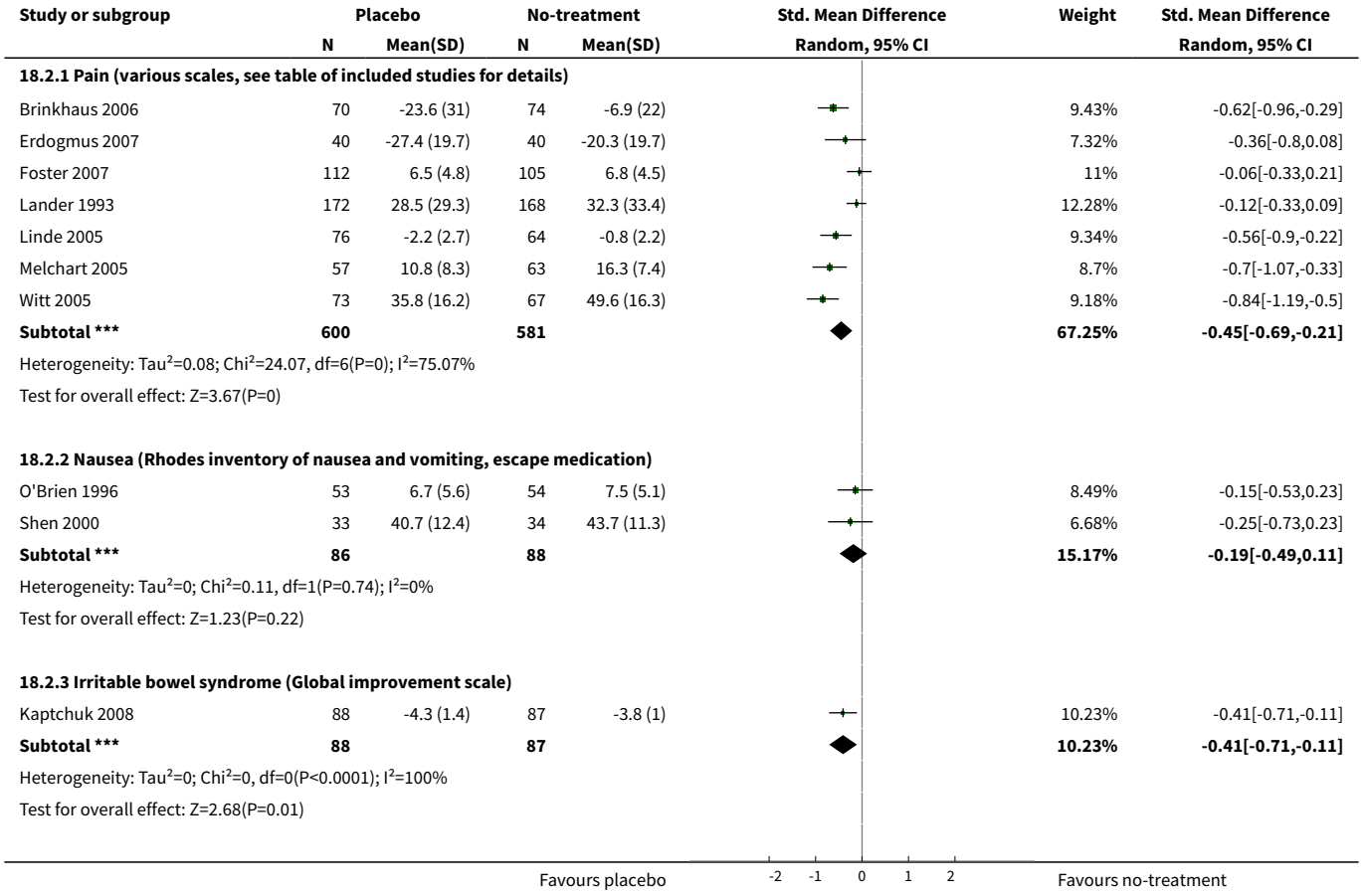
Study or subgroup	Placebo n/N	No-treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
18.1.1 Pain (incidence)					
Faas 1993	107/162	108/155		22.3%	0.95[0.81,1.1]
Molsberger 2002	38/58	30/53		15.01%	1.16[0.86,1.56]
Scharf 2006	179/365	224/316		23.49%	0.69[0.61,0.78]
Subtotal (95% CI)	**585**	**524**		**60.79%**	**0.89[0.67,1.19]**
Total events: 324 (Placebo), 362 (No-treatment)					
Heterogeneity: Tau^2=0.05; Chi^2=15.62, df=2(P=0); I^2=87.19%					
Test for overall effect: Z=0.79(P=0.43)					
18.1.2 Schizophrenia (lack of 50% improvement)					
Tarrier 1998	22/26	25/28		19.45%	0.95[0.77,1.17]



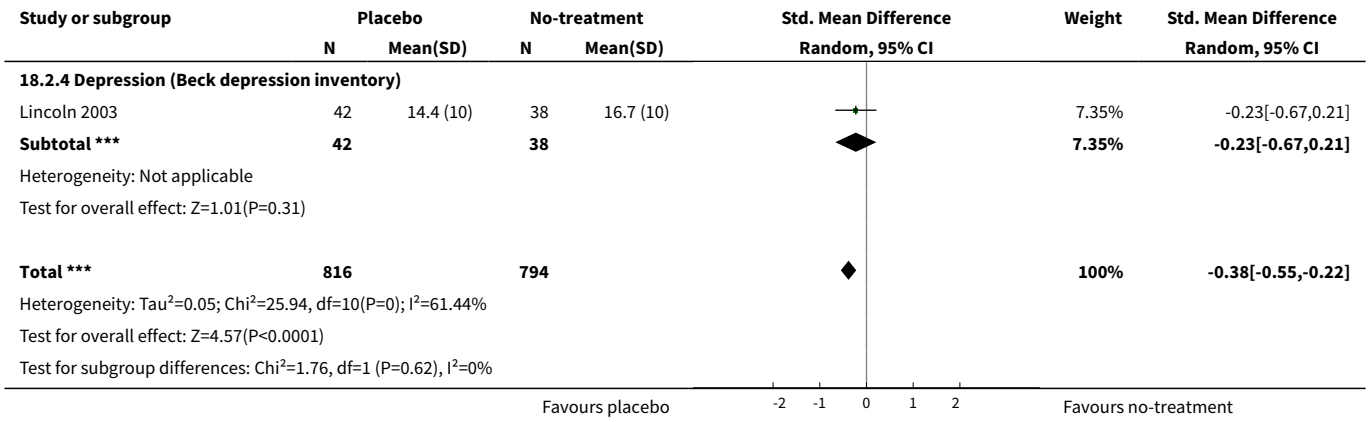


Study or subgroup	Placebo n/N	No-treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Subtotal (95% CI)	**26**	**28**		**19.45%**	**0.95[0.77,1.17]**
Total events: 22 (Placebo), 25 (No-treatment)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.51(P=0.61)					
18.1.3 Nausea					
Alkaissi 2002	77/139	82/136		19.76%	0.92[0.75,1.12]
Subtotal (95% CI)	**139**	**136**		**19.76%**	**0.92[0.75,1.12]**
Total events: 77 (Placebo), 82 (No-treatment)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.82(P=0.41)					
Total (95% CI)	**750**	**688**		**100%**	**0.9[0.76,1.08]**
Total events: 423 (Placebo), 469 (No-treatment)					
Heterogeneity: Tau²=0.03; Chi²=18.16, df=4(P=0); I²=77.97%					
Test for overall effect: Z=1.15(P=0.25)					
Test for subgroup differences: Not applicable					

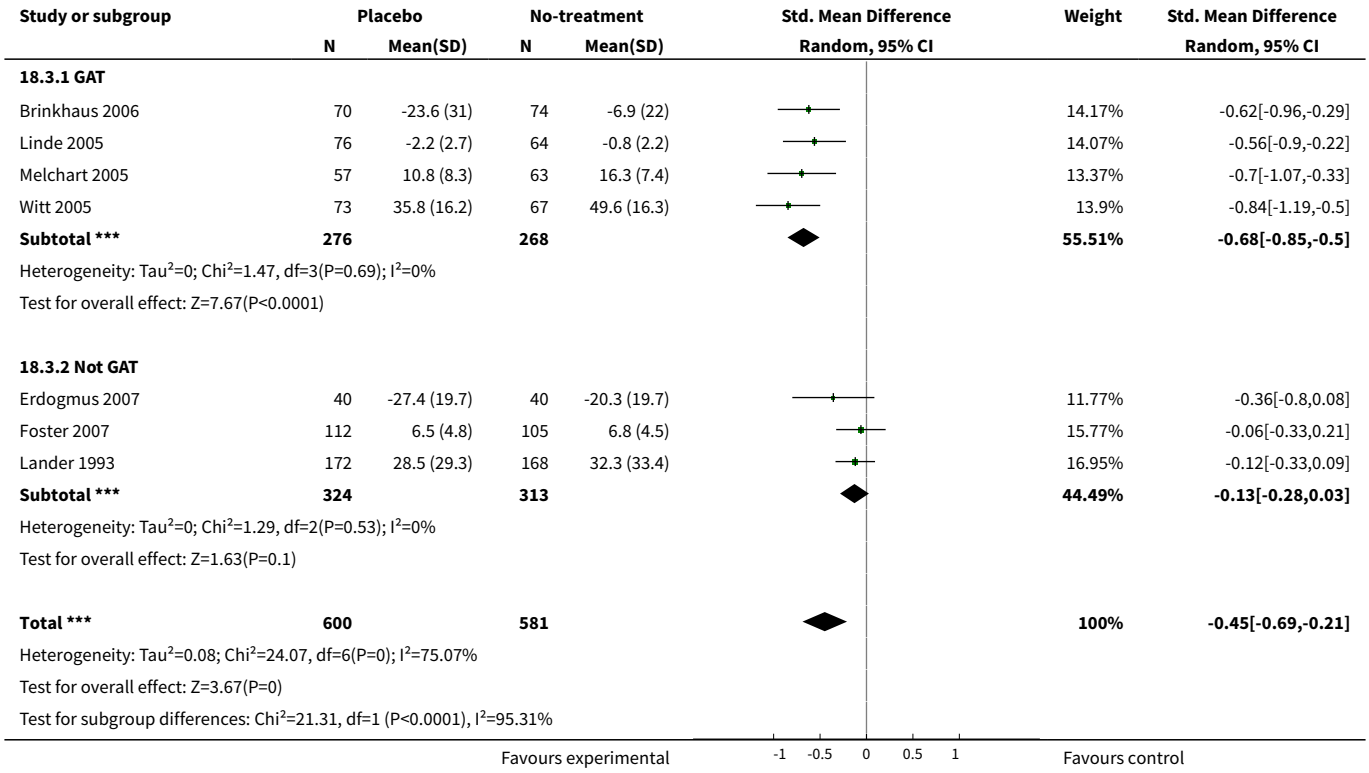
Analysis 18.2. Comparison 18 Risk of bias subgroup analysis: clearly concealed allocation + trial size >49 + dropout max 15%, Outcome 2 Continuous outcomes.



Study or subgroup	Placebo N	Placebo Mean(SD)	No-treatment N	No-treatment Mean(SD)	Std. Mean Difference Random, 95% CI	Weight	Std. Mean Difference Random, 95% CI
18.2.1 Pain (various scales, see table of included studies for details)							
Brinkhaus 2006	70	-23.6 (31)	74	-6.9 (22)		9.43%	-0.62[-0.96,-0.29]
Erdogmus 2007	40	-27.4 (19.7)	40	-20.3 (19.7)		7.32%	-0.36[-0.8,0.08]
Foster 2007	112	6.5 (4.8)	105	6.8 (4.5)		11%	-0.06[-0.33,0.21]
Lander 1993	172	28.5 (29.3)	168	32.3 (33.4)		12.28%	-0.12[-0.33,0.09]
Linde 2005	76	-2.2 (2.7)	64	-0.8 (2.2)		9.34%	-0.56[-0.9,-0.22]
Melchart 2005	57	10.8 (8.3)	63	16.3 (7.4)		8.7%	-0.7[-1.07,-0.33]
Witt 2005	73	35.8 (16.2)	67	49.6 (16.3)		9.18%	-0.84[-1.19,-0.5]
Subtotal ***	**600**		**581**			**67.25%**	**-0.45[-0.69,-0.21]**
Heterogeneity: Tau²=0.08; Chi²=24.07, df=6(P=0); I²=75.07%							
Test for overall effect: Z=3.67(P=0)							
18.2.2 Nausea (Rhodes inventory of nausea and vomiting, escape medication)							
O'Brien 1996	53	6.7 (5.6)	54	7.5 (5.1)		8.49%	-0.15[-0.53,0.23]
Shen 2000	33	40.7 (12.4)	34	43.7 (11.3)		6.68%	-0.25[-0.73,0.23]
Subtotal ***	**86**		**88**			**15.17%**	**-0.19[-0.49,0.11]**
Heterogeneity: Tau²=0; Chi²=0.11, df=1(P=0.74); I²=0%							
Test for overall effect: Z=1.23(P=0.22)							
18.2.3 Irritable bowel syndrome (Global improvement scale)							
Kaptchuk 2008	88	-4.3 (1.4)	87	-3.8 (1)		10.23%	-0.41[-0.71,-0.11]
Subtotal ***	**88**		**87**			**10.23%**	**-0.41[-0.71,-0.11]**
Heterogeneity: Tau²=0; Chi²=0, df=0(P<0.0001); I²=100%							
Test for overall effect: Z=2.68(P=0.01)							



Analysis 18.3. Comparison 18 Risk of bias subgroup analysis: clearly concealed allocation + trial size >49 + dropout max 15%, Outcome 3 Pain heterogeneity.



ADDITIONAL TABLES

Table 1. Effect of placebo interventions across all clinical conditions (binary outcomes)

	All trials			Trials with low risk of bias			Quality of the evidence
Outcomes	**Relative Risk (95% CI)**	**No. of participants (studies)**	**Comments**	**Relative Risk (95% CI)**	**No. of participants (studies)**	**Comments**	
All clinical conditions	0.93 (0.88 to 0.99)	6041 (44)	Symmetrical funnel plot Moderate heterogeneity	0.90 (0.76 to 1.08)	1,438 (5)	Substantial heterogeneity. One German acupuncture trial found RR 0.69 (0.61 to 0.78) and the other four trials RR 0.96 (0.87 to 1.06)	Moderate
Trials with patient-reported outcomes	0.93 (0.86 to 1.00)	4046 (31)	Symmetrical funnel plot Moderate heterogeneity	0.89 (0.72 to 1.11)	845 (4)	Substantial heterogeneity (see above).	Moderate
Trials with observer-reported outcomes	0.93 (0.85 to 1.02)	1995 (13)	Symmetrical funnel plot Moderate heterogeneity	0.95 (0.77 to 1.17)	54 (1)	One small trial	Moderate

Table 2. Effect of placebo interventions on specific clinical conditions (binary outcomes)

	All trials			Trials with low risk of bias			Quality of the evidence
Condition [1]	**Relative risk (95% CI)**	**No. of participants (studies)**	**Comments**	**Relative risk (95% CI)**	**No. of participants (studies)**	**Comments**	
Pain	0.92 (0.76 to 1.11)	1207 (6)	Substantial heterogeneity	0.89 (0.67 to 1.19)	1109 (3)	No heterogeneity	Moderate
• GAT [2] excluded	0.98 (0.88 to 1.10)	525 (5)	No heterogeneity	1.00 (0.84 to 1.20)	428 (2)	No heterogeneity	
• GAT [2] only	0.69 (0.61 to 0.78)	681 (1)	NA	0.69 (0.61 to 0.78)	681 (1)	NA	
Nausea	0.94 (0.82 to 1.07)	732 (6)	No heterogeneity	0.92 (0.75 to 1.12)	275 (1)	NA	Moderate
Smoking	0.89 (0.73 to 1.10)	887 (6)	Substantial heterogeneity	NA	NA	NA	Low

Table 2. Effect of placebo interventions on specific clinical conditions (binary outcomes) *(Continued)*

Depression	1.03 (0.78 to 1.34)	152 (3)	No heterogeneity	NA	NA	NA	Low

[1]. Clinical conditions studied in three trials or more.
[2]. German acupuncture trials.
NA: not applicable.

Table 3. Effect of placebo interventions across all clinical conditions (continuous outcomes)

	All trials			Trials with low risk of bias			Quality of the evidence
Outcomes	**Standardised mean difference (95% CI)**	**No. of participants (studies)**	**Comments**	**Standardised mean difference (95% CI)**	**No. of participants (studies)**	**Comments**	
All clinical conditions	-0.23 (-0.28 to -0.17)	10,525 (158)	Asymmetrical funnel plot Moderate heterogeneity	-0.38 (-0.55 to -0.22)	1610 (11)	Substantial heterogeneity. Four German acupuncture trials had a pooled SMD -0.68 (-0.85 to -0.50), whereas 7 other trials had a pooled SMD of -0.19 (-0.31 to -0.07)	Moderate
Trials with patient-reported outcomes	-0.26 (-0.32 to -0.19)	8000 (109)	Asymmetrical funnel plot Moderate heterogeneity	-0.39 (-0.57 to -0.22)	1543 (10)	Substantial heterogeneity (see above).	Moderate
Trials with observer-reported outcomes	-0.13 (-0.24 to -0.02)	2513 (49)	Asymmetrical funnel plot Moderate heterogeneity	-0.25 (-0.73 to 0.23)	67 (1)	One small trial	Moderate

Table 4. Effect of placebo interventions on specific clinical conditions (continuous outcomes)

	All trials			Trials with low risk of bias			Quality of the evidence
Condition [1]	**Standardised mean difference (95% CI)**	**No. of participants (studies)**	**Comments**	**Standardised mean difference (95% CI)**	**No. of participants (studies)**	**Comments**	

Table 4. Effect of placebo interventions on specific clinical conditions (continuous outcomes) *(Continued)*

Pain	-0.28 (-0.36 to -0.19)	4154 (60)	Moderate heterogeneity	-0.45 (-0.69 to -0.21)	1198 (7)	Substantial heterogeneity	Moderate
• GAT [2] excluded	-0.22 (-0.30 to -0.14)	3534 (56)	Low heterogeneity	-0.13 (-0.28 to 0.03)	637 (3)	No heterogeneity	
• GAT [2] only	-0.68 (-0.85 to -0.50)	544 (4)	No heterogeneity	-0.68 (-0.85 to -0.50)	544 (4)	No heterogeneity	
Nausea	-0.25 (-0.46 to -0.04)	452 (7)	Low heterogeneity	-0.19 (-0.49 to 0.11)	174 (2)	No heterogeneity	Moderate
Depression	-0.25 (-0.55 to 0.05)	324 (8)	Moderate heterogeneity	-0.23 (-0.63 to 0.21)	123 (1)		Moderate
Hypertension	-0.17 (-0.46 to 0.12)	308 (10)	Low heterogeneity	NA	0 (0)		Low
Anxiety	-0.16 (-0.48 to 0.16)	286 (7)	Moderate heterogeneity	NA	0 (0)		Low
Asthma	-0.35 (-0.70 to -0.01)	203 (4)	Moderate heterogeneity	NA	0 (0)		Low
Obesity	-0.20 (-0.57 to 0.17)	188 (8)	Moderate heterogeneity	NA	0 (0)		Low
Insomnia	-0.19 (-0.50 to 0.12)	164 (6)	No heterogeneity	NA	0 (0)		Low
Dementia	-0.18 (-0.55 to 0.20)	111 (3)	No heterogeneity	NA	0 (0)		Low
Phobia	-0.63 (-1.17 to -0.08)	57 (3)	No heterogeneity	NA	0 (0)		Low

[1]. Clinical conditions studied in three trials or more.
[2]. German acupuncture trials.
NA: not applicable.

Table 5. Meta-regression analyses

	All trials (n = 158)			All trials excluding German acupuncture trials (n = 154)		
Model	**Co-variates [1]**	**Coefficient (SE) [2]**	**P value**	**Co-variates**	**Coefficient (SE)**	**P value**
Multiple meta-regression of all co-variates simultaneously	Pt-involved outcome Study aim was placebo	-0.17 (0.084) -0.15 (0.072)	0.047 0.043	Study aim was placebo	-0.18 (0.072)	0.012
Multiple meta-regression by stepwise elimination	Pt-involved outcome Physical placebos Placebo undisclosed Study aim was placebo	-0.18 (0.077) -0.13 (0.056) -0.17 (0.070) -0.14 (0.070)	0.023 0.020 0.014 0.046	Pt-involved outcome Study aim was placebo Precision	-0.19 (0.072) -0.18 (0.067) 0.025 (0.010)	0.011 0.008 0.016

[1]. We studied 11 predefined co-variates. A model based on stepwise elimination of the co-variate with the highest P-value resulted in four co-variates with $P < 0.05$. The model had a $tau^2 = 0.0207$, compared to the overall random effects meta-analysis of $tau^2 = 0.0450$. Thus, the model explains 54% of the initial variation. The model was sensitive to the exclusion of the four German acupuncture trials. The inclusion of these trials especially influenced the statistical significance of the importance of disclosing to patients that the trial involved a possible placebo treatment.
[2]. SE: Standard error

APPENDICES

Appendix 1. Electronic search strategies

Search strategy for Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library,* Issue 4, 2007)

(PLACEBO* or MOCK* or SHAM* or FAKE* or VEHICLE* or DUMM* or ATTENTION* CONTROL* or PSEUDO* TREAT* or UNSPECIFIC* or NON SPECIFIC*) and

(NO TREAT* or NON TREAT* or NOTREAT* or NONTREAT* or UNTREAT* or MINIMALTREAT* or MINIM* TREAT* or USUAL TREAT* or NO INTERV* or NON INTERV* or NOINTERV* or NONINTERV* or NO CONTACT* or NON CONTACT or NOCONTACT* or NONCONTACT or USUAL CONTACT* or USUAL CARE* or NO PILL* or NOPILL* or NONPILL* or NO TABLET* or NOTABLET* or NONTABLET* or NO MEDIC* or NON MEDIC* or NOMEDIC* or NONMEDIC* or UNMEDIC* or MINIM* MEDIC* or MINIMALMEDIC* or NO SURGER* or NON SURGER* or NOSURGER* or NONSURGER* or NO OPERAT* or NON OPERAT or NOOPERAT* or NONOPERAT* or WAITING LIST* or WAITINGLIST* or NO THERAP* or NON THERAP* or NOTHERAP* or NONTHERAP* or MINIM* THERAP* or MINIMALTHERAP* or USUAL* THERAP* or USUALTHERAP* or NATURAL COURSE or NATURAL DEVELOPMENT or NATURAL HISTORY or SPONTANEOUS COURSE or SPONTANEOUS DEVELOPMENT or SPONTANEOUS HISTORY or (TWO GROUPS) near CONTROL* or (THREE GROUPS) near CONTROL* or (FOUR GROUPS) near CONTROL* or (FIVE GROUPS) near CONTROL* or (SIX GROUPS) near CONTROL* or (SEVEN GROUPS) near CONTROL* or (TWO TREATMENT GROUPS) near CONTROL* or (THREE TREATMENT GROUPS) near CONTROL* or (FOUR TREATMENT GROUPS) near CONTROL* or (FIVE TREATMENT GROUPS) near CONTROL* or (SIX TREATMENT GROUPS) near CONTROL* or (SEVEN TREATMENT GROUPS) near CONTROL*) and

(RANDOM* or DOUBLE* BLIND* or SINGLE* BLIND*)

Search strategy for MEDLINE 1966 to March 2008

(PLACEBO* or MOCK* or SHAM* or FAKE* or VEHICLE* or DUMM* or ATTENTION* CONTROL* or PSEUDO* TREAT* or UN?SPECIFIC* or NON?SPECIFIC*) and

(NO??TREAT* or NO TREAT* or NON TREAT* or UN?TREAT* or UN TREAT* or MINIM* TREAT* or USUAL?TREAT* or USUAL TREAT* or NO INTERV* or NON INTERV* or NO??INTERV* or NO CONTACT* or NON CONTACT* or NO??CONTACT?* or USUAL CONTACT* or USUAL CARE* or NO PILL* or NON PILL* or NO??PILL* or NO TABLET* or NON TABLET* or NO??TABLET* or NO MEDIC* or NON MEDIC* or NO??MEDIC* or UN MEDIC* or UN?MEDIC* or MINIM* MEDIC* or NO??SURGER* or NO OPERAT* or NON OPERAT* or NO??OPERAT* or NO SURGER* or NON SURGER* or NO??SURGER* or (NO THERAP* or NO??THERAP* or NON THERAP* or MINIM* THERAP* or USUAL* THERAP*) in AB or (NO THERAP* or NO??THERAP* or NON THERAP* or MINIM* THERAP* or USUAL* THERAP*) in TI or WAITING LIST* or WAITING?LIST* or ((NATURAL or SPONTANEOUS) NEAR1 (COURSE or DEVELOPMENT or HISTORY)) or ((TWO or "2" or THREE or "3" or FOUR or "4" or FIVE or "5" or SIX or "6" or SEVEN or "7") NEAR1 (GROUPS or TREATMENT GROUPS)) NEAR (CONTROL or CONTROLS)) and

(DOUBLE-BLIND-METHOD or SINGLE-BLIND-METHOD or RANDOM-ALLOCATION or RANDOMIZED-CONTROLLED-TRIALS/ ALL SUBHEADINGS or CLINICAL-TRIALS/ ALL SUBHEADINGS or (CLINICAL-TRIAL or RANDOMIZED-CONTROLLED-TRIAL or CONTROLLED-CLINICAL-TRIAL) in PT or RANDOM* or (CLINICAL near TRIAL*) or DOUBLE* BLIND* or SINGLE* BLIND*) and HUMAN in TG

Search strategy for EMBASE 1980 to March 2008
(PLACEBO* or MOCK* or SHAM* or FAKE* or VEHICLE* or DUMM* or ATTENTION* CONTROL* or PSEUDO* TREAT* or UN?SPECIFIC* or NON?SPECIFIC*) and

(NO??TREAT* or NO TREAT* or NON TREAT* or UN?TREAT* or UN TREAT* or MINIM* TREAT* or USUAL?TREAT* or USUAL TREAT* or WITHOUT TREAT* or WITHOUT?TREAT* or NO INTERV* or NON INTERV* or NO??INTERV* or NO CONTACT* or NON CONTACT* or NO??CONTACT* or USUAL CONTACT* or USUAL CARE* or (NO THERAP* or NO??THERAP* or NON THERAP* or MINIM* THERAP* or USUAL* THERAP*) in AB or (NO THERAP* or NO??THERAP* or NON THERAP* or MINIM* THERAP* or USUAL* THERAP*) in TI or NO PILL* or NON PILL* or NO??PILL* or NO TABLET* or NON TABLET* or NO??TABLET* or WAITING LIST* or WAITING?LIST* or ((NATURAL or SPONTANEOUS) NEAR1 (COURSE or DEVELOPMENT or HISTORY)) or NO MEDIC* or NON MEDIC* or NO??MEDIC* or UN MEDIC* or UN?MEDIC* or MINIM* MEDIC* or NO OPERAT* or NON OPERAT* or NO??OPERAT* or NO SURGER* or NON SURGER* or NO??SURGER* or ((TWO or "2" or THREE or "3" or FOUR or "4" or FIVE or "5" or SIX or "6" or SEVEN or "7") NEAR1 (GROUPS or TREATMENT GROUPS)) NEAR (CONTROL or CONTROLS)) and

(CLINICAL-TRIAL or RANDOMIZED-CONTROLLED-TRIAL or RANDOMIZATION or DOUBLE-BLIND-PROCEDURE or SINGLE-BLIND-PROCEDURE or CONTROLLED-STUDY or MAJOR-CLINICAL-STUDY or CLINICAL-ARTICLE or RANDOM* or (CLINICAL near TRIAL*) or DOUBLE* BLIND* or SINGLE* BLIND*) and HUMAN- in DE.

Search Strategy for PsycINFO 1887 to March 2008
Neither the indexation of clinical trials nor the reporting in abstracts in PsycINFO was helpful with respect to a reliable identification of randomised trials. With the purpose of minimising the number of missed randomised trials, any search terms aimed at identifying clinical trials were omitted. In a later manual filtering process abstracts were read in full.

(PLACEBO* or MOCK* or SHAM* or FAKE* or VEHICLE* or DUMM* or PSEUDO* TREAT* or ATTENTION* CONTROL* or UNSPECIFIC* or NON?SPECIFIC*) and

(NO??TREAT* or NO TREAT* or NON TREAT* or UN?TREAT* or UN TREAT* or MINIM* TREAT* or WITHOUT TREAT* or NO??INTERV* or NO INTERV* or NON INTERV* or UN?INTERV* or UN INTERV* or MINIM* INTERV* or WITHOUT INTERV* or NO??MEDIC* or NO MEDIC* or NON MEDIC* or UN?MEDIC* or UN MEDIC* or MINIM* MEDIC* or WITHOUT MEDIC* or NO??PILL* or NO PILL* or NON PILL* or NO??OPERAT* or NO OPERAT* or NON OPERAT* or UN?OPERAT* or UN OPERAT* or MINIM* OPERAT* or WITHOUT OPERAT* or NO??SURGER* or NO SURGER* or NON SURGER* or MINIM* SURGER* or WITHOUT SURGER* or WAITING?LIST* or WAITING LIST or VISITATION* or ((NATURAL or SPONTANEOUS) NEAR1 (COURSE* or DEVELOPMENT* or HISTORY*)) or ((TWO or "2" OR THREE OR "3" OR "4" OR FOUR OR FIVE OR "5" OR SIX "6" OR SEVEN OR "7") NEAR1 (GROUPS OR TREATMENT GROUOPS)) NEAR (CONTROL OR CONTROLS))
and not ANIMAL in (PO or DE).

Search strategy for Biological Abstracts 1986 to March 2008
(PLACEBO* or MOCK* or SHAM* or FAKE* or VEHICLE* or DUMM* or ATTENTION* CONTROL* or PSEUDO* CONTROL* or UN?SPECIFIC* or NON?SPECIFIC*) and

(NO??TREAT* or NO TREAT* or NON TREAT* or UN?TREAT* or UN TREAT* or MINIM* TREAT* or USUAL?TREAT* or USUAL TREAT* or WITHOUT TREAT* or WITHOUT?TREAT* or NO INTERV* or NON INTERV* or NO??INTERV* or NO CONTACT* or NON CONTACT* or NO??CONTACT?* or NO CONTACT* or NON CONTACT* or NO??CONTACT* or USUAL CONTACT* or USUAL CARE* or NO PILL* or NON PILL* or NO??PILL* or NO TABLET* or NON TABLET* or NO??TABLET* or (NO THERAP* OR NO??THERAP* OR NON THERAP* OR MINIM* THERAP* OR USUAL* THERAP*) in TI or (NO THERAP* OR NO??THERAP* OR NON THERAP* OR MINIM* THERAP* OR USUAL* THERAP*) in AB or NO MEDIC* or NON MEDIC* or NO??MEDIC* or UN MEDIC* or UN?MEDIC* or MINIM* MEDIC* or NO OPERAT* OR NON OPERAT* OR NO??OPERAT* OR NO SURGER* OR NON SURGER* OR NO??SURGER* or WAITING LIST* OR WAITING?LIST* OR ((NATURAL OR SPONTANEOUS) NEAR1 (COURSE OR DEVELOPMENT OR HISTORY)) or ((TWO or "2" OR THREE OR "3" OR FOUR OR "4" OR FIVE OR "5" OR SIX OR "6" OR SEVEN OR "7") NEAR1 (GROUPS OR TREATMENT GROUPS)) NEAR (CONTROL OR CONTROLS)) and

(RANDOM* or (CLINICAL near TRIAL*) or DOUBLE* BLIND* or SINGLE* BLIND*) and (HUMAN- in OR or HUMAN in DE or HUMANS in ST).

WHAT'S NEW

Date	Event	Description
11 November 2009	New search has been performed	The update (published on issue 1 2010) includes 234 trials (52 trials added) and over 16,000 patients. The updated review includes more precise subgroup analysis, especially among trials with low risk of bias, and involves meta-regression analyses to explain heterogeneity.
11 November 2009	New citation required and conclusions have changed	We have applied new methods and use Summary of Findings tables to assist in conveying the main findings. In contrast to the previous versions of the review (Hróbjartsson 2004a) we now find both a notable pooled effect of placebo in trials with low risk of bias, especially on pain, and a large variation in effects among trials with low risk of bias. Also new is the identification of five factors explaining roughly half of the variation. However, when all trials are pooled, disregarding the risk of bias, results are fairly similar to the previous versions.

HISTORY

Protocol first published: Issue 3, 1999
Review first published: Issue 1, 2003

Date	Event	Description
12 June 2008	Amended	Converted to new review format.
18 April 2004	New search has been performed	We identified 52 new trials and increased the number of included patients from 8525 to 11,737 (38%). Confidence intervals became narrower, more clinical conditions had been investigated by three trials or more.
18 April 2004	New citation required and conclusions have changed	We updated the review on issue 3 2004 of *The Cochrane Library*. The degree of heterogeneity between trials with continuous outcomes was more pronounced in this update, but the main findings were(identical to the previous version of the review (Hróbjartsson 2003a).

CONTRIBUTIONS OF AUTHORS

Asbjørn Hróbjartsson (AH) and Peter C. Gøtzsche (PCG) conceived the idea of the review. AH had the main responsibility for developing the search strategy, retrieving the trials, accessing additional data, and writing the first draft of the review. AH and PCG read all included trial reports. AH analysed the data.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Faculty of Health Sciences, University of Copenhagen, Denmark.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

In the protocol we planned the following procedure for extraction of data: 'The primary outcome is that which is considered clinically most relevant to patients'. In the review we extracted data according to the following procedure: 'We primarily chose the outcome indicated as the main outcome in a trial report (e.g. through a power calculation). If a main outcome was not clearly indicated we chose the outcome measure we considered most relevant to patients'. The primary idea in the protocol was to minimise the risk of bias due to selective reporting of positive results in trials. We modified the procedure in an attempt to balance this risk against the risk of review author bias.

In the protocol for the first version of our review we specified a limited number of subgroup analyses (see Methods subgroup analyses 1-8). Before we conducted this update we expanded the number of planned subgroup analyses (see Methods subgroup analyses 9-12), and planned a number of meta-regression analyses (see Methods). One subgroup-analyses was conducted post-hoc (see Methods subgroup analysis 13). Furthermore, in the protocol we planned to analyse trials that reported corresponding patient-reported and observer-reported outcomes. However, it became clear that the distinction between corresponding and not corresponding patient-reported and observer-reported outcomes was very subjective, and we decided to abort this comparison.

NOTES

This review was originally published with the title 'Placebo treatment versus no treatment' (Hróbjartsson 2003a). For the 2003-4 update (Hróbjartsson 2004a), the title was changed to 'Placebo interventions for all clinical conditions'.

INDEX TERMS

Medical Subject Headings (MeSH)

*Placebo Effect; Nausea [prevention & control]; Pain [prevention & control]; Randomized Controlled Trials as Topic; Refusal to Treat; Treatment Outcome

MeSH check words

Humans