Supplement

Additional Background

The benefits of empathic communication appear to be robust across both affluent and deprived patient groups,[1] and among patients with multimorbidities.[2]

Additional methods (eMethods)

Search strategy

The systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. [40] We searched the following databases from inception to 10 August 2017: MEDLINE from inception to 10 August 2017, using a search strategy adapted from earlier reviews [16,38] using the terms "placebo and placebo effects", "expectations", "empathy", "patient-practitioner communication", "suggestion", "communication", "practitioner", together with standard participants, intervention, comparison and outcome (PICO) components. To identify randomized trials we applied the Cochrane Highly Sensitive Search Strategy for identifying randomized trials. We adapted the MEDLINE search for other databases (CENTRAL, MEDLINE, EMBASE, PsychINFO, CINAHL, ProQuest (see eTable 1). We also searched the grey literature, [41,42] trial registries, [43,44] and hand searched bibliographies of included studies and contacted experts. We applied no language restrictions.

Types of interventions

We included two studies negative *control* interventions (where practitioners who delivered enhanced empathy or expectations were compared with practitioners who were less positive or less empathic than usual). [3, 4]This was to reflect the variation in clinical practice, where some practitioners are in fact negative. [5]

Study selection

Also for reasons of clinical relevance, we excluded experimental studies in which the intervention was introduced in an artificial environment, such as experimental pain.

Data Extraction and Risk of Bias Assessment

Two authors independently assessed risk of bias for the following domains: selection bias (randomization and allocation concealment), performance bias (blinding of participants and investigators), detection bias (blinding of outcome adjudicators), attrition bias (differential loss to follow-up), and reporting bias (selective outcome reporting). These were judged to be of low, unclear, or high risk for each trial. We ranked studies in which both the patients and practitioners were blinded as having a low risk of performance bias, and studies in which either patients or practitioners (but not both) were blinded as having an unclear risk of performance bias. We also considered other potential sources of bias that might have influenced the results, including fidelity to the intervention, funding, and selective recruitment.

We performed sensitivity analyses to determine whether a high risk of bias influenced results. We assessed the likelihood of reporting/publication bias qualitatively based on the

characteristics of the included studies (e.g., where only small studies that indicate positive findings were included in the review), and using funnel plots.

Data synthesis

Effects were calculated based on the mean, standard deviation (SD) and number of people assessed for both the intervention and comparison groups at the end of follow-up to calculate mean difference and 95% confidence interval (CI). Where the mean difference was reported without individual group data, we used this to report the study results. Since included studies measured the same outcome using different tools, we calculated the standardized mean difference (SMD) and 95% confidence intervals using the generic inverse variance method in Review Manager 5 to pool the results.

Three studies reported interquartile ranges; [4, 6, 7] in two of these, [4, 7] the data was normally distributed, and we imputed the standard deviation. [8] We reported the study that lacked normally distributed data narratively. [6]

Ensuring relevance to decisions in health care

This review has benefited from extensive comments from patient representatives, who were clear that this review was important. The key role of our patient and public involvement panel was to provide input related to the design and conduct of our research. In an extensive commentary on the draft protocol, that representative raised the following points.

1. Expectations and empathy are related yet conceptually distinct. The representative cited the following personal experience: "The consultant [doctor]...was much more cautious, pointing out that there was no real evidence available for this operation in cases like mine, and saying 'I can't promise that it will be better, only that it will be different.' I felt that the doctor who gave a far less optimistic (that is, not inducing positive expectations)... took a far more empathetic approach and helped me to make a properly informed decision about my treatment...In the end I chose not to have the surgery."
2. The representative emphasized the importance of quality-of-life outcomes over and above biological outcomes.

We modified our protocol considering these comments by emphasizing the differences and potential interactions between empathy and expectations. Patient and public involvement input benefitted our project by:

- ensuring the outcomes we chose are relevant to patients;
- ensuring we report the results in ways that patients understand and are acceptable;
- planning actibve dissemination of the results to relevant groups;
- supporting translation of the results.

The protocol and review received feedback from two Cochrane Consumer and Communications Review Group referees in addition to health professionals as part of the Cochrane Consumers and Communication Group's standard editorial process.

Dealing with heterogeneity

The complex nature of empathy and how it is expressed meant we anticipated a degree of heterogeneity. Differences in setting, population, and definition of treatment effect can introduce heterogeneity in a meta-analysis of any intervention, [9] but some differences are more pronounced when meta-analyzing data from trials of behavioral interventions. Unlike most drug interventions, empathy and expectation-inducing interventions are not modular, their delivery being more 'bespoke', and patient-centered, and depend on the context. [10-12] Behavioral and psychological mechanisms, while sometimes described simply, often involve dozens of components that interact in different ways, many of which may potentially contribute to the physician being perceived as more empathetic and the patient being more encouraged by positive suggestion. For example, the physician's countenance, facial expression and outward form may influence how well the empathy intervention is received by the patient. Because potential components of physician behavior such as

countenance or appearance are difficult to standardize and control, highly standardized and homogenous empathy interventions are few and far between, and these interventions resist complete standardization.

The inherent heterogeneous nature of these types and other behavioral intervention of trials discourages researchers from synthesizing data of highly heterogeneous clinical pathways and processes. However, the observation that empathy and expectations intervention are delivered through widely different pathways should be considered a standard part of clinical practice. At a higher level, all the interventions had the same aim and appealed to the same basic characterization of empathy or expectation, which suggests that they may share enough in common to legitimize pooling. Their inherent heterogeneity should not preclude the possibility of these interventions achieving the same type of behavioral and psychological treatment effect through different means and behavioral and psychological processes. We therefore did not rule out pooling results even where statistical heterogeneity was high, preferring instead to identify and contextualize the likely causes of the heterogeneity. Another justification for pooling results is that it provides an overview of the size of effects these types of interventions can be expected to produce, and for guiding future research.

Classifying studies as psychological or physical

Patient and public involvement

This review has benefited from extensive comments from patient representatives (eMethods).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Additional results (eResults)

Results of study with data ineligible for pooling

The effect was positive but not statistically significant in the study without data eligible for pooling. [12] In this study, 100 patients were randomized to receive a positive or neutral message immediately before intravenous and reported their pain on a 0-10 verbal numerical rating scale (VNRS) and a 5-point Likert scale. The median VRNS score was 1 (interquartile range 2) for both groups, with a positive but not statistically significant difference between the groups (P=0.53). The median score was 2 in the intervention group (interquartile range 1) and 3 for the control group (interquartile range 1), and a non-significant difference between the groups (P=0.13).

Harms (empathy, subgroup analysis with high risk of bias trial removed)

For harms, when the only empathy study with a high risk of bias was removed from the analysis,[18] the control intervention appeared to produce a harm (initial result: OR 0.65 [95% CI0.31 to 1.39]; result from the single remaining study: OR 0.41 [95% CI0.17 to 0.94]).

Contamination by practitioner training method

We suspected that a potential source of bias could be contamination in the trials where the same group of practitioners delivered both empathic/standard or positive messages/standard

interventions, as compared with trials where separate groups of clinicians were trained to deliver the intervention or the control (but not both). We tested this hypothesis by comparing the two types of trials for both empathy and expectations interventions in an exploratory (not pre-planned) subgroup analysis.

- In the empathy interventions, the three trials were the practitioners were either trained in empathy or not (and not both): Chassany 2006, Fujimori 2014, Little 2015, had a larger effect size (SMD -0.20, 95% CI -0.30 to -0.10, I^2 = 0%) than trials where the same practitioners either delivered enhanced empathy or not (SMD 0.07, 95% CI-0.13 to 0.27, I^2 = 0%). This difference was statistically significant (P = 0.02), and the heterogeneity between the two types of trials was high (I^2 = 82.6%).
- Among expectations interventions with physical outcomes, two trials (Kemeny 2007; Resnick 1996) used different practitioners to either deliver positive messages or not. There was no statistically significant difference between these two types of trials (SMD 0.06, 95% CI -0.37 to 0.24, I^2 = 0% versus SMD -0.20, 95% CI -0.35 to -0.05, I^2 = 45%, test for difference between two groups: P = 0.43, I^2 = 0%.

Quality of life

Quality of life was assessed in different ways. Wise et al. (2009) [13] used the 32 question Asthma Quality of Life Questionnaire [14] assessed 4 weeks after the intervention, Kaptchuk et al. (2008) [15] used the 34-question IBS Quality of Life [16]score at 6 and 3 weeks after the intervention, respectively, and Rief 2017 used the Health-related quality of life was assessed by the 36-question Short Form Health Survey [17] 6 months after the intervention. Suarez-Almazor [18] used the Short Form Health Survey (SF-12), assessed 3 months after the after the intervention. Empathy and expectations interventions seemed to slightly improve quality of life (SMD 0·20 [95% CI 0·09 to 0·3]), see appendix p46. The heterogeneity was high (I^2 = 74%), and the overall risk of bias for these studies was low.

Effect of timing of outcome assessment

For expectations interventions, we explored how long the effect of these interventions might last in two ways. First, we identified one study that assessed outcomes over multiple time points: Kaptchuk 2008 measured outcomes at three and six weeks. For the main analysis we chose the longest follow up (6 weeks), and there was little difference between the results at the different time points. Second, we conducted an exploratory subgroup analysis comparing studies with shorter (less than a week) versus longer (one week or greater) follow up. There was no statistically significant difference between shorter and longer follow up for either empathy or expectations interventions. Three empathy interventions had longer follow up of 6 weeks, [21] 2 weeks, [18]and 1 week, [37] there was no difference in the results of these studies compared with studies with shorter follow up (P=0.98, I^2=0%) (eFigure 4).

Following the same method we used for empathy interventions, we conducted an exploratory analysis to test whether timing of the outcome assessment affected outcomes. We identified a study that assessed outcomes over multiple time points: Suarez-Almazor 2010 measured outcomes at 4 weeks, 6 weeks, and 3 months. For the main analysis we chose the longest follow up (3 months), and there was little difference between the results at the different time points. Eight expectations intervention trials within six publication had outcomes with longer follow up (6 months, [28] 3 months, [31] 4 weeks, [23,36] and 2 weeks. [54,56] Outcomes measured sooner after treatment delivery had larger effects (-0.44 [-0.67 to -0.20]) compared with outcomes measured later (-0.23 [-0.42 to -0.04]). However, there was no statistically significant difference between the two groups of studies (P=0.17, I^2=47.2%) (eFigure 6).

Exploratory analyses

We explored how empathy was taught, and found that the content of the training was rarely specified. For example, one trial within our review [11] involved a 4-hour training session delivered by expert trainers and subsequent reminders, but did not describe the content of these interventions. In another trial, empathy training lasted two days, but again the content was not described in any detail. [13]

We also explored whether there was a difference between subjective and objective outcomes. This most relevant within expectations with physical outcomes, and we found effect sizes to be greater in studies with objective outcomes (-0.26 [-0.47, -0.05] versus -0.08 [-0.23, 0.07], P-value for difference = 0.17). See eFigure 10.

Differences between protocol and review

1. We searched six databases from their inception to August 10, 2017. In the protocol we stated that we would also search: Web of Knowledge; EED; Sociological Abstracts; PubMed; Database of Abstracts of Reviews of Effects (DARE); and LILACS. A sensitivity analysis conducted with a research librarian and the Cochrane editors suggested that these would not add studies, and we did not search them.
2. Trials in which placebo responsiveness was measured; we will study the subgroup of patients within these trials who were deemed to be placebo responsive, should this data be available. No studies measured this so we did not do a separate analysis.
3. There were not enough cluster randomized trials (just one) to perform a subgroup analysis with cluster trials.
4. In the protocol we stated that we would analyse the difference between subjective and objective outcomes. We did not do this because this mapped onto our psychological / physiological distinction very closely. We did, however explore this in an exploratory analysis (see eFigure 10).
5. In the protocol we stated that we would consider interventions that aimed to modify both empathy and expectations, however no studies did this explicitly.
6. We did an exploratory subgroup analysis comparing trials with shorter and longer follow-up.

eTable 1. Search strategies

MEDLINE (OvidSP)

1. patient care/
2. patient centered care/
3. ambulatory care/
4. preoperative care/
5. (preoperative education or (await* adj3 surg*)).ti,ab,kw.
6. exp perioperative care/ or anesthesia/
7. exp nursing care/
8. palliative care/
9. hospice care/
10. "referral and consultation"/
11. (consultation* or consult?).ti,ab,kw.
12. office visits/
13. (office visit* or (attend* adj5 clinic?)).ti,ab,kw.
14. interview psychological/
15. exp professional patient relations/
16. ((professional or physician or doctor or gp or surgeon or nurse or clinician or practitioner or provider or therapist) adj1 (patient or client)).ti,ab,kw.
17. exp professional role/

18. ((treatment or therapeutic) adj alliance).ti,ab,kw.
19. exp patients/
20. (patient? or subject? or client* or inpatient* or outpatient* or participant* or hospitali#ed or institutionali#ed or survivor*).ti,ab,kw.
21. exp health personnel/
22. ((health* adj2 (personnel or practitioner* or provider*)) or doctor* or physician* or general practitioner* or gp or gps or nurse* or clinician* or dentist* or pharmacist* or an?esthetist* or midwi* or hospitalist* or surgeon* or oncologist* or obstetrician* or gyn?ecologist* or geriatrician* or gerontologist* or pediatrician* or radiologist* or therapist* or physiotherapist* or dietitian* or psychologist* or counsel?or*).ti,ab,kw.
23. (19 or 20) and (21 or 22)
24. interviews as topic/
25. (visit* or interview*).ti,ab,kw.
26. communication/ or interpersonal relations/
27. (communicat* or verbal* or interaction* or information or encounter* or interpersonal).ti,ab,kw.
28. 23 and (24 or 25 or 26 or 27)
29. or/1-18,28
30. attitude of health personnel/
31. (attitud* adj5 (health* personnel or health* practitioner* or health* provider* or doctor* or physician* or general practitioner* or gp or gps or nurse* or clinician* or dentist* or pharmacist* or an?esthetist* or midwi* or hospitalist* or surgeon* or oncologist* or obstetrician* or gyn?ecologist* or geriatrician* or gerontologist* or pediatrician* or radiologist* or therapist* or physiotherapist* or dietitian* or psychologist* or counsel?or*)).ti,ab,kw.
32. 30 or 31
33. (positiv* or negativ* or understanding or caring or engage* or disengage* or attentive* or inattentive* or interested or uninterested or disinterested or supportive* or warm or cold).ti,ab,kw.
34. 32 and 33
35. empathy/
36. (empath* or unempath* or sympath* or unsympath* or compassion* or dispassion* or uncaring or welcoming or enthusias* or kindness or warmth or warmly or friendl* or unfriendl* or coldness or coldly).ti,ab,kw.
37. exp facial expression/
38. (smiling or smile?).ti,ab,kw.
39. (emotional support or affective or reassur* or reduc* anxiety or comforting).ti,ab,kw.
40. ((positiv* or negativ*) adj (consultatation or information or attitude* or messag*)).ti,ab,kw.
41. suggestion/
42. persuasive communication/
43. (suggestion or suggestive or persuasion or persuasive or warn* or frame? or framing).ti,ab,kw.
44. hope/
45. trust/
46. (expectation* or expectanc* or hope? or hopeful* or optimism or optimist* or anticipat* or belief* or trust).ti,ab,kw.
47. negativism/
48. (doubt* or disbelief* or mistrust* or distrust* or pessimis* or skeptic* or negativism).ti,ab,kw.
49. (coach* or priming or conditioned or conditioning).ti,ab,kw.
50. placebo effect/
51. nocebo effect/
52. "set (psychology)"/
53. "unconscious (psychology)"/
54. or/34-53
55. 29 and 54
56. randomized controlled trial.pt.
57. controlled clinical trial.pt.
58. randomized.ab.
59. placebo.ab.

60. clinical trials as topic.sh.
61. randomly.ab.
62. trial.ti.
63. or/56-62
64. 55 and 63
65. (editorial or review).pt.
66. 64 not 65

EMBASE

1. patient centered care.sh.
2. ambulatory care/
3. preoperative care/
4. preoperative education/
5. (preoperative education or (await* adj3 surg*)).ti,ab,kw.
6. perioperative period/
7. anesthesia/
8. exp nursing care/
9. exp palliative therapy/
10. hospice care/
11. consultation/
12. (consultation* or consult?).ti,ab,kw.
13. (office visit* or (attend* adj5 clinic?)).ti,ab,kw.
14. doctor patient relation/
15. nurse patient relationship/
16. ((professional or physician or doctor or gp or surgeon or nurse or clinician or practitioner or provider or therapist) adj1 (patient or client)).ti,ab,kw.
17. ((treatment or therapeutic) adj alliance).ti,ab,kw.
18. exp patient/
19. (patient? or subject? or client* or inpatient* or outpatient* or participant* or hospitali#ed or institutionali#ed or survivor*).ti,ab,kw.
20. exp health care personnel/
21. ((health* adj2 (personnel or practitioner* or provider*)) or doctor* or physician* or general practitioner* or gp or gps or nurse* or clinician* or dentist* or pharmacist* or an?esthetist* or midwi* or hospitalist* or surgeon* or oncologist* or obstetrician* or gyn?ecologist* or geriatrician* or gerontologist* or pediatrician* or radiologist* or therapist* or physiotherapist* or dietitian* or psychologist* or counsel?or*).ti,ab,kw.
22. (18 or 19) and (20 or 21)
23. human relation/
24. interview/
25. (visit* or interview*).ti,ab,kw.
26. interpersonal communication/
27. (communicat* or verbal* or interaction* or information or encounter* or interpersonal).ti,ab,kw.
28. 22 and (23 or 24 or 25 or 26 or 27)
29. or/1-17,28
30. exp health personnel attitude/
31. (attitud* adj5 (health* personnel or health* practitioner* or health* provider* or doctor* or physician* or general practitioner* or gp or gps or nurse* or clinician* or dentist* or pharmacist* or an?esthetist* or midwi* or hospitalist* or surgeon* or oncologist* or obstetrician* or gyn?ecologist* or geriatrician* or gerontologist* or pediatrician* or radiologist* or therapist* or physiotherapist* or dietitian* or psychologist* or counsel?or*)).ti,ab,kw.
32. 30 or 31
33. (positiv* or negativ* or understanding or caring or engage* or disengage* or attentive* or inattentive* or interested or uninterested or disinterested or supportive* or warm or cold).ti,ab,kw.
34. 32 and 33
35. empathy/

36. (empath* or unempath* or sympath* or unsympath* or compassion* or dispassion* or uncaring or welcoming or enthusias* or kindness or warmth or warmly or friendl* or unfriendl* or coldness or coldly).ti,ab,kw.
37. nonverbal communication/
38. facial expression/
39. (smiling or smile? or facial expression* or nonverbal*).ti,ab,kw.
40. (emotional* support* or affective or reassur* or reduc* anxiety or comforting).ti,ab,kw.
41. ((positiv* or negativ*) adj (consult* or information or attitude* or messag*)).ti,ab,kw.
42. suggestion/
43. persuasive communication/
44. (suggestion or suggestive or persuasion or persuasive or warn* or frame? or framing).ti,ab,kw.
45. hope/
46. trust/
47. expectation/
48. (expectation* or expectanc* or hope? or hopeful* or optimism or optimist* or anticipat* or belief* or trust).ti,ab,kw.
49. (doubt* or disbelief* or mistrust* or distrust* or pessimis* or skeptic* or negativism).ti,ab,kw.
50. (coach* or priming or conditioned or conditioning).ti,ab,kw.
51. placebo effect/
52. nocebo effect/
53. or/34-52
54. 29 and 53
55. randomized controlled trial/
56. controlled clinical trial/
57. single blind procedure/ or double blind procedure/
58. crossover procedure/
59. random*.tw.
60. placebo*.tw.
61. ((singl* or doubl*) adj (blind* or mask*)).tw.
62. (crossover or cross over or factorial* or latin square).tw.
63. (assign* or allocat* or volunteer*).tw.
64. or/55-63
65. 54 and 64
66. (editorial or review).pt.
67. 65 not 66

PsychINFO

1. health care services/
2. "medical treatment (general)"/
3. (preoperative education or (await* adj3 surg*)).ti,ab,id.
4. exp nursing/
5. palliative care/
6. professional consultation/
7. (consultation* or consult?).ti,ab,id.
8. (office visit* or (attend* adj5 clinic?)).ti,ab,id.
9. therapeutic processes/
10. ((professional or physician or doctor or gp or surgeon or nurse or clinician or practitioner or provider or therapist) adj1 (patient or client)).ti,ab,id.
11. ((treatment or therapeutic) adj alliance).ti,ab,hw,id.
12. exp patients/
13. (patient? or subject? or client* or inpatient* or outpatient* or participant* or hospitali#ed or institutionali#ed or survivor*).ti,ab,id.
14. exp health personnel/
15. ((health* adj2 (personnel or practitioner* or provider*)) or doctor* or physician* or general

practitioner* or gp or gps or nurse* or clinician* or dentist* or pharmacist* or an?esthetist* or midwi* or hospitalist* or surgeon* or oncologist* or obstetrician* or gyn?ecologist* or geriatrician* or gerontologist* or pediatrician* or radiologist* or therapist* or physiotherapist* or dietitian* or psychologist* or counsel?or*).ti,ab,id.
16. (12 or 13) and (14 or 15)
17. interviews/
18. (visit* or interview*).ti,ab,id.
19. interpersonal.hw.
20. (communicat* or verbal* or interaction* or information or encounter* or interpersonal).ti,ab,id.
21. 16 and (17 or 18 or 19 or 20)
22. or/1-11,21
23. health personnel attitudes/ or therapist attitudes/
24. (attitud* adj5 (health* personnel or health* practitioner* or health* provider* or doctor* or physician* or general practitioner* or gp or gps or nurse* or clinician* or dentist* or pharmacist* or an?esthetist* or midwi* or hospitalist* or surgeon* or oncologist* or obstetrician* or gyn?ecologist* or geriatrician* or gerontologist* or pediatrician* or radiologist* or therapist* or physiotherapist* or dietitian* or psychologist* or counsel?or*)).ti,ab,id.
25. 23 or 24
26. (positiv* or negativ* or understanding or caring or engage* or disengage* or attentive* or inattentive* or interested or uninterested or disinterested or supportive* or warm or cold).ti,ab,id.
27. 25 and 26
28. empathy/
29. (empath* or unempath* or sympath* or unsympath* or compassion* or dispassion* or uncaring or welcoming or enthusias* or kindness or agreeab* or warmth or warmly or friendl* or unfriendl* or coldness or coldly).ti,ab,hw,id.
30. exp nonverbal communication/
31. (smiling or smile? or facial expression* or nonverbal*).ti,ab,id.
32. (emotional* support* or affective or reassur* or reduc* anxiety or comforting).ti,ab,hw,id.
33. ((positiv* or negativ*) adj (consult* or information or communication or attitude* or messag*)).ti,ab,id.
34. (suggestion or suggestive or suggestibility or persuasion or persuasive or warn* or frame? or framing).ti,ab,hw,id.
35. (expectation* or expectanc* or hope? or hopeful* or optimism or optimist* or anticipat* or belief* or trust).ti,ab,hw,id.
36. (doubt* or disbelief* or mistrust* or distrust* or pessimis* or skeptic* or negativism).ti,ab,hw,id.
37. (coach* or priming or conditioned or conditioning).ti,ab,hw,id.
38. placebo/
39. ((placebo or nocebo) adj effect*).ti,ab,id.
40. or/27-39
41. 22 and 40
42. random*.ti,ab,hw,id.
43. trial*.ti,ab,hw,id.
44. controlled stud*.ti,ab,hw,id.
45. placebo*.ti,ab,hw,id.
46. ((singl* or doubl* or trebl* or tripl*) and (blind* or mask*)).ti,ab,hw,id.
47. (cross over or crossover or factorial* or latin square).ti,ab,hw,id.
48. (assign* or allocat* or volunteer*).ti,ab,hw,id.
49. treatment effectiveness evaluation/
50. mental health program evaluation/
51. exp experimental design/
52. "2000".md.
53. or/42-52
54. 41 and 53
55. (editorial or review*).dt.
56. 54 not 55

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all(attitude* or empath* or unempath* or sympath* or unsympath* or compassion* or dispassion* or uncaring or welcoming or enthusias* or kindness or warmth or warmly or friendl* or unfriendl* or coldness or coldly or "communication skill*" or smiling or smile* or "facial expression*" or nonverbal* or "emotional* support*" or affective or reassur* or "reduc* anxiety" or comforting or ((positiv* or negativ*) n/1 (consult* or information or attitude* or messag*)) or suggestion or suggestive or suggestibility or persuasion or persuasive* or warn* or frame* or framing or expectation* or expectanc* or hope* or optimism or optimist* or anticipat* or belief* or trust or doubt* or disbelief* or mistrust* or distrust* or pessimis* or skeptic* or negativism or coach* or priming or conditioned or conditioning or ((placebo or nocebo) n/1 effect*)) and all(((health* n/2 (personnel or practitioner* or provider*)) or doctor* or physician* or "general practitioner*" or gp or gps or nurse* or clinician* or dentist* or pharmacist* or anesthetist* or midwi* or hospitalist* or surgeon* or oncologist* or obstetrician* or gynecologist* or geriatrician* or gerontologist* or pediatrician* or radiologist* or therapist* or physiotherapist* or dietitian* or psychologist* or counselor*) and (patient* or client* or inpatient* or outpatient* or hospitali*ed or institutionali*ed or survivor*)) and all(communicat* or interpersonal or interview* or consult* or visit* or (attend* n/5 clinic*) or "preoperative education" or (await* n/3 surg*) or "patient cent*red care" or ((professional or physician or doctor or gp or surgeon or nurse or clinician or practitioner or provider or therapist) n/1 (patient or client))) and all(random* or trial* or placebo* or assign* or allocat* or volunteer* or ((singl* or doubl* or tripl* or trebl*) and (blind* or mask*)) or crossover or "cross over" or factorial* or "latin square")

CINAHL

#	Query	Limiters/Expanders	Results
S45	s44	Limiters - Exclude MEDLINE records Search modes - Boolean/Phrase	1,591
S44	s33 and s43	Search modes - Boolean/Phrase	5,881
S43	S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42	Search modes - Boolean/Phrase	253,838
S42	TI (singl* or doubl* or tripl* or trebl*) and TI (blind* or mask*)	Search modes - Boolean/Phrase	5,701
S41	AB (singl* or doubl* or tripl* or trebl*) and AB (blind* or mask*)	Search modes - Boolean/Phrase	16,387
S40	AB (random* or trial or placebo*) or TI (random* or trial or placebo*)	Search modes - Boolean/Phrase	175,791
S39	MH Quantitative Studies	Search modes - Boolean/Phrase	11,472
S38	MH Placebos	Search modes - Boolean/Phrase	7,568
S37	MH Random Assignment	Search modes - Boolean/Phrase	33,203
S36	MH Clinical Trials+	Search modes - Boolean/Phrase	133,950
S35	PT Clinical Trial	Search modes - Boolean/Phrase	52,730
S34	"randomi?ed controlled trial" or PT randomized controlled trial	Search modes - Boolean/Phrase	38,317
S33	s18 and s32	Search modes - Boolean/Phrase	66,612

S32	s23 or s24 or s25 or s26 or s27 or s28 or s29 or s30 or s31	Search modes - Boolean/Phrase	236,268
S31	(placebo or nocebo) n1 effect*	Search modes - Boolean/Phrase	2,227
S30	coach* or priming or conditioned or conditioning	Search modes - Boolean/Phrase	10,427
S29	doubt* or disbelief* or mistrust* or distrust* or pessimis* or skeptic* or negativism	Search modes - Boolean/Phrase	5,745
S28	expectation* or expectanc* or hope* or optimism or optimist* or anticipat* or belief* or trust	Search modes - Boolean/Phrase	92,045
S27	suggestion or suggestive or suggestibility or persuasion or persuasive* or warn* or frame* or framing	Search modes - Boolean/Phrase	85,998
S26	"emotional* support*" or affective or reassur* or "reduc* anxiety" or comforting or ((positiv* or negativ*) n1 (consult* or information or attitude* or messag*))	Search modes - Boolean/Phrase	20,519
S25	smiling or smile* or "facial expression*" or nonverbal*	Search modes - Boolean/Phrase	5,397
S24	empath* or unempath* or sympath* or unsympath* or compassion* or dispassion* or uncaring or welcoming or enthusias* or kindness or warmth or warmly or friendl* or unfriendl* or coldness or coldly or "communication skill*"	Search modes - Boolean/Phrase	29,261
S23	s21 and s22	Search modes - Boolean/Phrase	12,180
S22	positiv* or negativ* or understanding or caring or engage* or disengage* or attentive* or inattentive* or interested or uninterested or disinterested or supportive* or warm or cold	Search modes - Boolean/Phrase	293,493
S21	s19 or s20	Search modes - Boolean/Phrase	53,401
S20	attitud* n4 ("health* personnel" or "health* practitioner*" or "health* provider*" or doctor* or physician* or "general practitioner*" or gp or gps or nurse* or clinician* or dentist* or pharmacist* or anesthetist* or midwi* or hospitalist* or surgeon* or oncologist* or obstetrician* or gynecologist* or geriatrician* or gerontologist* or pediatrician* or radiologist* or therapist* or physiotherapist* or dietitian* or psychologist* or counselor*)	Search modes - Boolean/Phrase	51,707
S19	MH attitude of health personnel+	Search modes - Boolean/Phrase	51,625
S18	s10 or s17	Search modes - Boolean/Phrase	495,799
S17	s15 and s16	Search modes - Boolean/Phrase	106,021
S16	visit* or interview* or communicat* or verbal* or interaction* or information or encounter* or interpersonal	Search modes - Boolean/Phrase	555,339
S15	(s11 or s12) and (s13 or s14)	Search modes - Boolean/Phrase	284,315
S14	(health* n2 (personnel or practitioner* or provider*)) or doctor* or physician* or "general practitioner*" or gp or gps or nurse* or clinician* or dentist* or pharmacist* or anesthetist* or midwi* or hospitalist* or surgeon* or oncologist* or obstetrician* or gynecologist* or geriatrician* or gerontologist* or pediatrician* or radiologist* or therapist* or physiotherapist*	Search modes - Boolean/Phrase	647,391

	or dietitian* or psychologist* or counselor*		
S13	MH health personnel+	Search modes - Boolean/Phrase	336,501
S12	patient* or subject or subjects or client* or inpatient* or outpatient* or participant* or hospitali?ed or institutionali?ed or survivor*	Search modes - Boolean/Phrase	1,060,728
S11	MH patients+	Search modes - Boolean/Phrase	168,783
S10	s1 or s2 or s3 or s4 or s5 or s6 or s7 or s8 or s9	Search modes - Boolean/Phrase	445,981
S9	(treatment or therapeutic) n1 alliance	Search modes - Boolean/Phrase	533
S8	MH professional role+	Search modes - Boolean/Phrase	66,988
S7	(professional or physician or doctor or gp or surgeon or nurse or clinician or practitioner or provider or therapist) n1 (patient or client)	Search modes - Boolean/Phrase	83,127
S6	MH professional-patient relations+	Search modes - Boolean/Phrase	56,226
S5	MH nursing care+	Search modes - Boolean/Phrase	217,559
S4	consult or consults or consultation* or "office visit*" or (attend* n4 (clinic or clinics))	Search modes - Boolean/Phrase	38,992
S3	MH anesthesia+	Search modes - Boolean/Phrase	18,257
S2	"preoperative education" or (await* n3 surg*)	Search modes - Boolean/Phrase	1,426
S1	MW (patient or ambulatory or preoperative or per*operative or palliative or hospice or nursing) n1 (care or therapy)	Search modes - Boolean/Phrase	130,085

CENTRAL Search Strategy
#1 ("patient care" or "patient cent*red care" or "health care services" or "medical treatment" or "therapeutic processes"):kw
#2 ((ambulatory or preoperative or per*operative or palliative or hospice or nursing) next (care or therapy)):ti,ab,kw
#3 ("preoperative education" or (await* near/3 surg*)):ti,ab,kw
#4 [mh "perioperative care"]
#5 "perioperative period":kw
#6 anesthesia:kw
#7 [mh "nursing care"]
#8 referral:kw
#9 (consult or consults or consultation*):ti,ab,kw
#10 ("office visit*" or (attend* near/5 clinic*)):ti,ab,kw
#11 [mh "interview psychological"]
#12 [mh "professional patient relations"]
#13 ((professional or physician or doctor or gp or surgeon or nurse or clinician or practitioner or provider or therapist) near/1 (patient or client)):ti,ab,kw
#14 [mh "professional role"]
#15 ((treatment or therapeutic) next alliance):ti,ab,kw
#16 [mh patients]

#17 (patient* or subject or subjects or client* or inpatient* or outpatient* or participant* or hospitali*ed or institutionali*ed or survivor*):ti,ab,kw
#18 [mh "health personnel"]
#19 ((health* near/2 (personnel or practitioner* or provider*)) or doctor* or physician* or "general practitioner*" or gp or gps or nurse* or clinician* or dentist* or pharmacist* or an*esthetist* or midwi* or hospitalist* or surgeon* or oncologist* or obstetrician* or gyn*ecologist* or geriatrician* or gerontologist* or pediatrician* or radiologist* or therapist* or physiotherapist* or dietitian* or psychologist* or counsel*or*):ti,ab,kw
#20 (#16 or #17) and (#18 or #19)
#21 (visit* or interview* or communicat* or verbal* or interaction* or information or encounter* or interpersonal or "human relation"):ti,ab,kw
#22 #20 and #21
#23 {or #1-#15, #22}
#24 (attitud* near/5 ("health* personnel" or "health* practitioner*" or "health* provider*" or doctor* or physician* or "general practitioner*" or gp or gps or nurse* or clinician* or dentist* or pharmacist* or an*esthetist* or midwi* or hospitalist* or surgeon* or oncologist* or obstetrician* or gyn*ecologist* or geriatrician* or gerontologist* or pediatrician* or radiologist* or therapist* or physiotherapist* or dietitian* or psychologist* or counsel*or*)):ti,ab,kw
#25 (positiv* or negativ* or understanding or caring or engage* or disengage* or attentive* or inattentive* or interested or uninterested or disinterested or supportive* or warm or cold):ti,ab,kw
#26 #24 and #25
#27 (empath* or unempath* or sympath* or unsympath* or compassion* or dispassion* or uncaring or welcoming or enthusias* or kindness or warmth or warmly or friendl* or unfriendl* or coldness or coldly or "communication skill*"):ti,ab,kw
#28 [mh "facial expression"]
#29 (smiling or smile* or "facial expression*" or nonverbal*):ti,ab,kw
#30 ("emotional* support*" or affective or reassur* or "reduc* anxiety" or comforting):ti,ab,kw
#31 ((positiv* or negativ*) next (consult* or information or attitude* or messag*)):ti,ab,kw
#32 (suggestion or suggestive or suggestibility or persuasion or persuasive* or warn* or frame* or framing):ti,ab,kw
#33 (expectation* or expectanc* or hope* or optimism or optimist* or anticipat* or belief* or trust):ti,ab,kw
#34 (doubt* or disbelief* or mistrust* or distrust* or pessimis* or skeptic* or negativism):ti,ab,kw
#35 (coach* or priming or conditioned or conditioning):ti,ab,kw
#36 ((placebo or nocebo) next effect*):kw
#37 [mh "set (psychology)"]
#38 [mh "unconscious (psychology)"]
#39 {or #26-#38}
#40 #23 and #39

eTable 2. Characteristics of included studies

Benedetti 2003a

Methods	**Design: 2-armed RCT** **Recruitment: Convenience sample of post-operative patients** **Setting: Hospital, Italy** **Inclusion criteria: Patient undergoing thoracotomy with the resection of at least three of the following muscles: latissimus dorsi, serratus anterior, trapezius, and rhomboid** **Exclusion criteria: Not reported**
Participants	Total N: 42 provided data (42 consented, no withdrawals) Randomized to Open Administration of Licodaine 21, Hidden Administration of Licodaine 21 57% male, mean age 55.2
Interventions	Intervention: Open administration of lidocaine treatment with positive suggestion performed at the bedside by a doctor, no physician training on intervention delivery provided Control: Hidden administration of lidocaine without positive suggestion
Outcomes	Psychological: Postoperative pain intensity assessed on a numerical rating scale (VAS, 0-10) 30 and 60 min after the Open or Hidden administration of lidocaine Physical: None reported Adverse events: Not reported
Notes	Funding: "This work was supported by grants from the Italian Ministry of University and Research, from the project Neuroscience of the National Research Council (01.00439.ST97 and 02.00529.ST97) and from the project Alzheimer's Disease of the Italian Ministry of Health (PFA/DML/UO6/2001 and PFA/DML/UO6/2001/AA)"

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	p3: “All the subjects were randomly assigned to either the open or the hidden treatment.” However, the method for randomization was not stated
Allocation concealment (selection bias)	Unclear risk	Unclear whether allocation was concealed
Blinding of participants and personnel (performance bias)	Unclear risk	Personnel were aware of intervention; patients unaware of intervention component
Blinding of outcome assessment (detection bias) **Physical outcome**		
Blinding of outcome assessment (detection bias) **Psychological outcome**	Unclear risk	Personnel were aware of intervention; patients unaware of intervention component
Blinding of outcome assessment (detection bias) **Harms**		
Incomplete outcome data (attrition bias)	Low risk	No attrition (all participants accounted for)
Selective reporting (reporting bias)	Low risk	No protocol available. However, all outcomes described in methods reported.
Other bias	Unclear risk	Unclear whether the effect of the intervention was due to the presence of a practitioner or the verbal message.
Selective recruitment (cluster trials only)		
Contamination		

Benedetti 2003b

Methods	Design: 2-armed RCT Recruitment: Convenience sample of post-operative patients Setting: Hospital, Italy Inclusion criteria: Patients that underwent thoracotomy with the resection of at least three of the following muscles: latissimus dorsi, serratus anterior, trapezius, and rhomboid. Exclusion criteria: Not reported
Participants	Total N: 30 47% male (14 male, 16 female), mean age 52.9
Interventions	Intervention: -Positive message delivered by a healthcare practitioner: "The open administration was performed at the bedside by a doctor, who told the patients that the medication was a potent anti-anxiety medication according to routine clinical practice. In other words, the patients were informed that their anxiety was going to subside within a few minutes." (p5) Control: -Medication given without positive message and healthcare practitioner present: "the hidden administration was given by the preprogrammed machine without any doctor or nurse in the room, so that the patients were totally unaware that a painkilling medication was being given. Thus, the main difference between open and hidden injections was the knowledge that a medication was being given" (p.5)
Outcomes	Psychological: State-anxiety assessed with a STAI–S form (questionnaire) filled in by the patients 2 hours after the intervention. Physical: Not reported Adverse events: Not reported
Notes	Funding: "This work was supported by grants from the Italian Ministry of University and Research, from the project Neuroscience of the National Research Council (01.00439.ST97 and 02.00529.ST97) and from the project Alzheimer's Disease of the Italian Ministry of Health (PFA/DML/UO6/2001 and PFA/DML/UO6/2001/AA)"

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	p3: "All the subjects were randomly assigned to either the open or the hidden treatment" However, the method for randomization was not stated
Allocation concealment (selection bias)	Unclear risk	Unclear whether allocation was concealed
Blinding of participants and personnel (performance bias)	Unclear risk	Personnel were aware of intervention; patients unaware of intervention component
Blinding of outcome assessment (detection bias) Physical outcome		
Blinding of outcome assessment (detection bias) Psychological outcome	Unclear risk	Not specified whether outcome assessment was blinded
Blinding of outcome assessment (detection bias) Harms		
Incomplete outcome data (attrition bias)	Low risk	No attrition (all participants accounted for)
Selective reporting (reporting bias)	Low risk	No protocol available. However, all outcomes described in methods reported.
Other bias	Unclear risk	Unclear whether the effect of the intervention was due to the presence of a practitioner or the verbal message.
Selective recruitment (cluster trials only)		
Contamination		

Benedetti 2003c

Methods	Design: 2-armed RCT Recruitment: Convenience sample of post-operative patients

	Setting: Hospital, Italy Inclusion criteria: Patients that underwent thoracotomy with the resection of at least three of the following muscles: latissimus dorsi, serratus anterior, trapezius, and rhomboid. Exclusion criteria: Not reported
Participants	Total N: 10
Interventions	Intervention: Open interruption of stimulation of the subthalamic nucleus Control: Hidden interruption of stimulations of the subthalamic nucleus
Outcomes	Psychological: Not reported Physical: Hand movement velocity (m/s) was measured by means of the Unified Parkinson's Disease Rating Scale: “the patients performed a visual directional-choice task in which the right index finger was positioned on a central sensor and moved toward a target when a light was turned on. In each test, 15 consecutive movement time trials were carried out, their average representing the final value for that test.” (p6) Adverse events: Not reported
Notes	Funding: "This work was supported by grants from the Italian Ministry of University and Research, from the project Neuroscience of the National Research Council (01.00439.ST97 and 02.00529.ST97) and from the project Alzheimer's Disease of the Italian Ministry of Health (PFA/DML/UO6/2001 and PFA/DML/UO6/2001/AA)"

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	p3: “All the subjects were randomly assigned to either the open or the hidden treatment.” However. the method was not stated.
Allocation concealment (selection bias)	Unclear risk	Unclear whether allocation was concealed.
Blinding of participants and personnel (performance bias)	Unclear risk	Personnel were aware of intervention; patients unaware of intervention component
Blinding of outcome assessment (detection bias) Physical outcome	Unclear risk	Not specified whether outcome assessment was blinded
Blinding of outcome assessment (detection bias) Psychological outcome		
Blinding of outcome assessment (detection bias) Harms		
Incomplete outcome data (attrition bias)	Low risk	No attrition (all participants accounted for)
Selective reporting (reporting bias)	Low risk	No protocol available. However, all outcomes described in methods reported.
Other bias	Unclear risk	Unclear whether the effect of the intervention was due to the presence of a practitioner or the verbal message.
Selective recruitment (cluster trials only)		
Contamination		

Chassany 2006

Methods	Design: 2-armed RCT Recruitment: Lower limb osteoarthritis (knee or hip OA) patients who visited the GP Setting: Primary health centre, France Inclusion criteria: Patients over 49 years of age could enter the study if they had radiographic confirmation of OA of the knee or hip for at least 6 months; had pain intensity on motion of at least 40 mm on a 100 mm visual analogue scale (VAS) the day before inclusion; and were suitable for treatment with acetaminophen Exclusion criteria: Patients were not included in the study if they had an acute painful onset of

	OA; were prescribed a non-opioid analgesic (acetaminophen, acetylsalicylic acid, low-dose nonsteroidal anti-inflammatory drug) within 24 hours of the study; required a weak or strong opioid analgesic (codeine or dextropropoxyphen, tramadol, morphine) during the 2 previous weeks; had started treatment with a NSAID within 2 weeks of the study or were likely to need a change of NSAID during the study; had started antidepressant treatment within 2 months or were likely to need a change in prescription during the study; had received a corticosteroid either orally or injected into the affected joint within the 2 previous months, or injected into another joint in the previous week; had undergone surgery of the joint under study within 3 months; or had recently received
Participants	Total N: 818 Training group 39.6% male, Control group 31.5% male
Interventions	Intervention: Treatment delivered by a GP who received empathy training, including "written statements given to patient by GP: The keys for pain relief—Did you know? 1. You are the expert on your pain! 2. Learning how to evaluate your pain so you can explain it to your doctor will lead to better care. 3. Improved communication with your doctor will help you understand the cause of your pain and its treatment. 4. Better understanding about your treatment will make sure you take it correctly and get the best from it. 5. You and your doctor are partners in the treatment of your pain." Control: Treatment as usual (consultation delivered by practitioners who were not trained to improve empathy)
Outcomes	Psychological: -Sum of patient pain relief based on the daily VAS self-evaluation during the 2 weeks of the trial on a 100mm VAS ranging from 0 (no pain) to 100 (worst possible pain) expressed as the sum of the pain intensity differences (SPID), which corresponds to the area under the curve (AUC) of pain intensity differences over time - Global perception of change (% of patients feeling slightly or much better) - Lequesne index score (patient-reported) after 2 weeks Physical: Not reported Adverse events: Adverse events measured as % of patients reporting adverse events over the 2 week treatment period
Notes	Funding: "Supported and sponsored by Sanofi-Aventis OTC, Direction Médicale, Gentilly, France"

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised but method not described
Allocation concealment (selection bias)	Unclear risk	Unclear whether allocation was concealed
Blinding of participants and personnel (performance bias)	High risk	Patients not blinded. Practitioners not blinded.
Blinding of outcome assessment (detection bias) Physical outcome		
Blinding of outcome assessment (detection bias) Psychological outcome	Unclear risk	Unclear whether outcome assessors were blinded.
Blinding of outcome assessment (detection bias) Harms	Unclear risk	Unclear whether outcome assessors were blinded.
Incomplete outcome data (attrition bias)	Low risk	15/413 patients in treatment group and 9/405 patients in control group lost to follow up. ITT included all patients with at least one assessment after baseline; Fig 1: numbers randomized into each group are clearly reported; reasons for withdrew at primary endpoint reasons for withdrew at primary endpoint seem balanced across groups; 413/428 and 405/414 were

		analysed in trained and control group
Selective reporting (reporting bias)	Low risk	Protocol reported. Primary outcome stated, all outcomes described in methods reported either in table or text.
Other bias	Low risk	None obvious
Selective recruitment (cluster trials only)		
Contamination		

de Craen 2001

Methods	Design: 2x2 factorial trial Recruitment: "Patients attending the chronic pain outpatient clinic for a routine visit. Two to five days before patients attended the outpatient clinic a letter was sent to their home address stating that their physician was going to ask them to participate in a trial. An information leaflet about the study was included with that letter. The leaflet stated that the research was aimed at investigating the analgesic effect of tramadol relative to placebo in patients with chronic pain. Furthermore, it was stated that there was a second objective of this research, and that it was important that patients were not aware of the content of this objective. If they preferred to know the second objective, the treating physician could immediately disclose this to them, or the information regarding the second objective could be mailed to them after 24 hours" Setting: Outpatient clinic, The Netherlands Inclusion criteria: "Patients at least 18 years of age, duration of pain complaints of at least 6 months, non-malignant origin of pain, currently not using tramadol, no known liver or kidney impairment, no hypersensitivity to opioids, and currently not taking monoamine oxidase inhibitors nor discontinued their consumption within the previous two weeks" Exclusion criteria: Patients were excluded "if one or more of the conditions described under 'inclusion criteria' was not met"
Participants	Total N: 111 40.25% male, mean age 52.1 (SD 14.8) Number randomized 112, Number analysed 111 Postoperative patients with chronic pain attending the chronic pain outpatient clinic for a routine visit
Interventions	Intervention: Open administration of treatment with positive suggestion Control: Open administration of treatment with neutral suggestion
Outcomes	Psychological: VNRS pain within 2 minutes of i.v. cannula placement Physical: Not reported Adverse events: Incidence of adverse events reported. However, not relative to verbal instructions (divided according to whether patients received placebo or tramadol; twice as many patients who received tramadol had an adverse event: 64% versus 36%)
Notes	Funding: Not reported Further details about the intervention: -Wording used in the intervention group: Positive attitude statements consisted of the following: "This is a medication that recently became available in the Netherlands. This drug, according to my experience, is very effective and will decrease the pain quickly after taking it." Clinicians were instructed to use their own wording. -Wording used in the control group: In the neutral attitude the following statements were used: "My own experience with this medication is limited and my impression is that it will not be beneficial in all patients. The pill becomes effective almost immediately, if it is going to have an effect." Clinicians were instructed to use their own wording. The patients were also given tramadol or placebo.

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised but method not described.
Allocation concealment (selection bias)	Unclear risk	Unclear whether allocation was concealed.
Blinding of participants and personnel (performance bias)	Low risk	All study physicians were blinded for study medication, patients and all other trial personnel were blinded for both study medication and nonpharmacological

		intervention.
Blinding of outcome assessment (detection bias) Physical outcome		
Blinding of outcome assessment (detection bias) Psychological outcome	Low risk	All study physicians were blinded for study medication, patients and all other trial personnel were blinded for both study medication and nonpharmacological intervention.
Blinding of outcome assessment (detection bias) Harms		All study physicians were blinded for study medication, patients and all other trial personnel were blinded for both study medication and nonpharmacological intervention.
Incomplete outcome data (attrition bias)	Low risk	All but 5 of 112 patients accounted for and data is reported with sufficient completeness to pool and all outcomes appear to be reported.
Selective reporting (reporting bias)	Low risk	No protocol available. However, all outcomes described in methods were reported.
Other bias	Low risk	None obvious
Selective recruitment (cluster trials only)		
Contamination		

Dutt-Gupta 2007

Methods	Design: 2-armed RCT Recruitment: "we recruited 101 unpremedicated adults awaiting elective surgery where placement of an i.v. cannula was required" (p. 872) Setting: Tertiary referral centre for surgery, Australia Inclusion criteria: "Adults awaiting elective surgery where placement of an i.v. cannula was required" Exclusion criteria: "patients were excluded if they were unable to communicate in English, intellectually impaired, age, 18 yr, had recently ingested analgesic medication, or had a known history of difficult venous access or poor peripheral veins on examination"
Participants	Total N: 101 43% male, mean age 48.9 (SD 18.75) Number eligible 103. Number refused to take part 2, Number randomized 101, Included in the analysis 101
Interventions	Intervention: Positive suggestion: "I am going to apply the tourniquet and insert the needle in a few moments. It's a sharp scratch and it may sting a little" (p. 872) Control: Neutral suggestion: "I am going to apply the tourniquet on the arm. As I do this many people find the arm becomes heavy, numb and tingly. This allows the drip to be placed more comfortably" (p. 872)
Outcomes	Psychological: Pain, measured on a 10-point patient reported (subjective) scale (VAS) Physical: Not reported Adverse events: Adverse events (measured as % of patients reporting adverse events)
Notes	Funding: Not reported The positive message was not very positive, and the control message was negative rather than neutral

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Study participants were randomly allocated to one of the two groups ('Sting' Group S and 'No Sting' Group NS). A random

		number sequence was computer generated in blocks."
Allocation concealment (selection bias)	Low risk	"Allocation concealment was assured using consecutively numbered, opaque, sealed envelopes, which were opened by the anaesthetist performing the procedure (J.D.-G.) approximately 1 min before i.v. cannulation"
Blinding of participants and personnel (performance bias)	Unclear risk	Patients described as blinded; practitioners not blinded.
Blinding of outcome assessment (detection bias) Physical outcome		
Blinding of outcome assessment (detection bias) Psychological outcome	Low risk	Outcome assessor blinded.
Blinding of outcome assessment (detection bias) Harms		Harms assessed by blinded assessors.
Incomplete outcome data (attrition bias)	Low risk	All 101 patients enrolled accounted for
Selective reporting (reporting bias)	Low risk	No protocol available. However, all outcomes described in methods reported.
Other bias	Low risk	None obvious
Selective recruitment (cluster trials only)		
Contamination		

Fujimori 2014

Methods	Design: 2-armed RCT Recruitment: "Outpatients who were attending follow-up medical appointments with oncologists at the National Cancer Centre hospitals were recruited after consultation" (p. 2) Setting: Hospital, Tokyo and Chiba, Japan Inclusion criteria: Patients who had received a diagnosis of cancer, were age 20 years, were judged capable of completing the survey physically and cognitively, and were capable of understanding spoken and written Japanese Exclusion criteria: Not stated (implied within inclusion criteria)
Participants	Total N: 601 61% male, mean age 64 (SD 10)
Interventions	Intervention: Oncologist delivered empathetic communication based on the SHARE model (S, setting up a supportive environment for the interview; H, considering how to deliver the bad news; A, discussing various additional information that patients would like to know; and RE, providing reassurance and addressing patients' emotions with empathic responses) Control: Usual care: "The control intervention (usually care) controlled for the effects of physician communication skills training"
Outcomes	Psychological: Patients' distress after consultation: "The Japanese version ofHADS21 was used to measure patients' distress. The HADS is a self-administered and standardized instrument for evaluating patients' distress. It consists of 14 items grouped into two factors: anxiety (HADS-A, seven items) and depression (HADS-D, seven items). Each item is rated on a 4-point (0 to 3) Likert scale." Physical: Not reported Adverse events: Not reported
Notes	Funding: "Supported by the Third-Term Comprehensive 10-Year Strategy for Cancer Control and Research; Japanese Ministry of Health, Labor and Welfare; and research fellowships for Young Scientists from the Japan Society for the Promotion of Science"

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised but method not described
Allocation concealment (selection bias)	Unclear risk	Unclear whether allocation was

		concealed
Blinding of participants and personnel (performance bias)	Unclear risk	Unclear whether patients were blinded. Unclear whether practitioners were blinded.
Blinding of outcome assessment (detection bias) Physical outcome		
Blinding of outcome assessment (detection bias) Psychological outcome	Unclear risk	Unclear whether outcome assessors were blinded. The objective outcome was coded by an outcome assessor reported as blinded.
Blinding of outcome assessment (detection bias) Harms		
Incomplete outcome data (attrition bias)	Unclear risk	1,181 of the 1,397 candidates who visited outpatient clinics were recruited to participate in the survey after consultation; 44 were excluded because of a physical or psychological problem, and 120 were not contacted because of refusal to participate or an inability to contact them. Of these 1,181, at baseline, 267 patients in the IG and 313 patients in the CG participated in the questionnaire survey; at follow-up, there were 292 patients in the IG and 309 patients in the CG (response rate, 84.6%)
Selective reporting (reporting bias)	Low risk	No protocol reported, however power calculation done for main outcome, and all outcomes described in methods reported in results.
Other bias	Low risk	None obvious
Selective recruitment (cluster trials only)		
Contamination		

Goodenough 1997

Methods	Design: 3-armed RCT Recruitment: Children aged 3–17 years consecutively scheduled to undergo venipuncture at the Sydney Children's Hospital in Australia, were invited to participate Setting: Hospital, Sydney, Australia Inclusion criteria: Patients scheduled to undergo venipuncture in a variety of complaints/conditions, accompanied by parent Exclusion criteria: Major mental handicap, received topical anaesthetic prior to venipuncture
Participants	Total N: 36 22 Male, age range 12-17
Interventions	Intervention: Placebo with positive suggestion Control: Placebo without positive suggestion
Outcomes	Psychological: None reported Physical: Pain intensity after venipuncture assessed on a Faces pain Scale (0=no pain; 6=most pain possible) Adverse events: Not reported
Notes	Funding: "Big Brother Movement, Brambles, Boots Co (AUS), private donations"

	Details of positive suggestion intervention: “For the Cream+ group, this cream was dispensed from a brightly wrapped container and applied to the venipuncture site as the nurse said to the child ‘We are trying out a new special cream. I am going to put some cream on your arm that might make it (the needle) hurt less’.” Details of the control intervention: “The placebo cream was a disinfectant handwash (Hexifoam; active ingredients: 5 mg/g chlorhexidine acetate, and 600 mg/g ethanol), which was an odourless thick white foam with no anaesthetic properties. For the Cream group, the cream was dispensed from a plain white wrapped container and applied to the needle site as the nurse said to the child ‘I am going to put some cream on your arm’.”

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised but method not described
Allocation concealment (selection bias)	Unclear risk	Unclear whether allocation was concealed
Blinding of participants and personnel (performance bias)	Unclear risk	Unclear whether patients were blinded. Unclear whether practitioners were blinded.
Blinding of outcome assessment (detection bias) Physical outcome		
Blinding of outcome assessment (detection bias) Psychological outcome	Low risk	Blinded observer assessed the outcome.
Blinding of outcome assessment (detection bias) Harms		
Incomplete outcome data (attrition bias)	Low risk	117 of the 121 children completed the study
Selective reporting (reporting bias)	Low risk	No protocol or power calculation however all outcomes described in methods reported in results.
Other bias	Low risk	None obvious
Selective recruitment (cluster trials only)		
Contamination		

Kaptchuk 2008

Methods	Design: 3-armed RCT Recruitment: Participants were recruited from advertisements in the media, fliers, and referrals from health professionals Setting: Hospital, Cambridge, Massachusetts, USA Inclusion criteria: Patients at least 18 years of age that meet the Rome II criteria for Irritable Bowel Syndrome (IBS) Exclusion criteria: "Unexplained findings, e.g. weight loss >10% body weight, fever, blood in stools, family history of colon cancer, or inflammatory bowel disease; previous acupuncture"
Participants	Total N: 262 24% Male, mean age 39 (SD 14), 87% white Patients suffering from irritable bowel syndrome
Interventions	Intervention: Augmented consultation (45 minutes for initial consultation, 30 minutes for remaining 5 consultations) Control: Limited patient-practitioner relationship (initial consultation duration <5 minutes)
Outcomes	Psychological: Global improvement (IBS-GIS) after 3 weeks Physical: Not reported Adverse events: Side effects measured at each outcome-measurement time
Notes	Funding: "NIH grant No 1R01 AT001414-01 from the National Center for Complementary and Alternative Medicine (NCCAM) and the National Institutes of Digestive, Diabetes and Kidney Disease (NIDDK), grant No 1R21 AT002860-01 from NCCAM and the Office of Behavioral and Social Science Research (OBSSR), and grant No 1 R21 AT002564 and 1K24 AT004095 from NCCAM. This research was also supported in part by grant RR 01032 to the Beth Israel Deaconess Medical Center (BIDMC) General Clinical Research Center from the NIH" The control intervention (no treatment) in this case meant treatment as usual. The patients had visits with practitioners and continued to take their other IBS medications and antidepressants if they were already on them. This might have boosted the 'benefits' of the untreated groups because of Hawthorne effects Further details of the empathy intervention:

	-Practitioner empathy consisting of verbal ("I can understand how difficult IBS [Irritable Bowel Syndrome] must be for you") and non-verbal components (20 seconds of thoughtful silence while feeling the pulse or pondering the treatment plan) -Positive expectation-inducing messages delivered by practitioners: "I have had much positive experience treating IBS and look forward to demonstrating that acupuncture is a valuable treatment in this trial" -Practitioner adherence to protocol: "During the trial, practitioners also received routine feedback from the videotaping of all sessions, which was used to score adherence to protocol"

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"We randomly assigned participants to the three study arms using permuted block randomisation with variable block sizes and assignments provided in sequentially numbered opaque sealed envelopes. An administrative assistant, not otherwise involved in the study, opened the assignment envelopes and recorded the assignment of each participant in a confidential log. At three weeks, we used similar methods to randomise patients in the sham acupuncture groups to continue sham acupuncture or to switch to genuine acupuncture. This randomisation was stratified by the level of abdominal pain at the three week visit (<30 v ≥30 on a 100 point visual analogue scale)"
Allocation concealment (selection bias)	Low risk	"We randomly assigned participants to the three study arms using permuted block randomisation with variable block sizes and assignments provided in sequentially numbered opaque sealed envelopes. An administrative assistant, not otherwise involved in the study, opened the assignment envelopes and recorded the assignment of each participant in a confidential log. At three weeks, we used similar methods to randomise patients in the sham acupuncture groups to continue

		sham acupuncture or to switch to genuine acupuncture. This randomisation was stratified by the level of abdominal pain at the three week visit (<30 v ≥30 on a 100 point visual analogue scale)"
Blinding of participants and personnel (performance bias)	Unclear risk	Patients blinded Practitioners not blinded
Blinding of outcome assessment (detection bias) Physical outcome		
Blinding of outcome assessment (detection bias) Psychological outcome	Low risk	All study personnel, except the practitioners, were blinded to participant assignment.
Blinding of outcome assessment (detection bias) Harms		
Incomplete outcome data (attrition bias)	Low risk	All patients that were randomized (N=262) were accounted for in the analysis
Selective reporting (reporting bias)	Low risk	Power calculation for main outcome conducted, all outcomes described in methods reported in results.
Other bias	Low risk	None obvious
Selective recruitment (cluster trials only)		
Contamination		

Kemeny 2007

Methods	Design: 2x2 factorial trial Recruitment: "subjects were recruited at the National Jewish Medical and Research Center and the University of Iowa" [no additional details provided] (p.1376) Setting: University Research Hospital, Iowa City, Iowa, USA Inclusion criteria: "Eligible subjects were men and women, aged 18 to 55 years, with mild intermittent or persistent asthma and a baseline FEV1 of 80% of predicted value or greater" (p. 1376) Exclusion criteria: "Major exclusion criteria included pregnancy or breast-feeding, serious systemic illness, recent respiratory tract infection, use of inhaled corticosteroids or other controller medications within 4 weeks, and smoking (>5 pack-year lifetime history)" (p. 1376)
Participants	Total N: 45
Interventions	Intervention: Expectation-modifying messages asserted "authoritatively" by physicians with expertise in treating asthma: "You shouldn't have any symptoms" Control: Equivocal expectations: "Physicians assigned to the efficient encounters were trained to convey an equivocal expectation about the bronchodilator efficacy ("It might work, and then again it might not") and to minimize authority (no white coat or tie; introduction as a junior member of the team) and supportiveness (e.g., encounters were about 2 minutes, and physicians displayed more efficient and brusque, although not negative, behaviours, such as inconsistent eye contact)."
Outcomes	Psychological: n/a Physical: Calculated concentration of methacholine required to induce a 20% decrease in FEV1 Adverse events: Not reported
Notes	Funding: "Supported by the Mind, Body, Brain, and Health Initiative and the National Institutes of Health (RR020645, RR00059, and ES05605)"

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised but method not described
Allocation concealment (selection bias)	Unclear risk	The testing technician was blind to conditions

Blinding of participants and personnel (performance bias)	Low risk	Patients and personnel blinded
Blinding of outcome assessment (detection bias) Physical outcome		Outcome reporter blinded.
Blinding of outcome assessment (detection bias) Psychological outcome		
Blinding of outcome assessment (detection bias) Harms		
Incomplete outcome data (attrition bias)	Low risk	5 subjects dropped out (11%)
Selective reporting (reporting bias)	High risk	Most psychological outcomes (depression, anxiety) described in methods not reported.
Other bias	Low risk	None obvious
Selective recruitment (cluster trials only)		
Contamination		

Knipschild 2005

Methods	Design: 2-armed RCT Recruitment: Patients 18 and over who came to the surgery with certain pain complaints were invited Setting: Primary Health Centre, Maastricht and surrounding areas in the Netherlands and Belgium Inclusion criteria: Adults (over 18); seen in GP practices; patients with new, certain and localized pain (including symptoms of headache, sore throat, abdominal pain, or pain related to movement); symptoms not present for more than one week; and no other episode within 3 months Exclusion criteria: Patients suspected of having underlying disease; patients who were either treated at home or on the phone; children
Participants	Total N: 128 157 patients were initially randomized, but 28 were subsequently excluded as ineligible, 1 patient was lost to follow-up. The remaining 128 patients were followed up for 100 days. Of these 128…"For 16 patients, the advice had not been tape-recorded: 8 with advice 1 and 8 with advice 2. In another 34 cases, the GP had not given the patient the correct advice in a convincing way (advice 1 unconvincing 9 times; advice 2, no less than 25 times), as evaluated by the authors. This left us with 78 patients in whom everything had gone according to the protocol, including the tape-recording" Mean age: Patients were at least 18 years old; mean age not stated
Interventions	Intervention: Positive message ("You will be better within a week or so") Control: Physician communication without doctor certainty in diagnosis and prognosis ("You probably do not have a serious underlying disease. But I do not know what precisely is the matter with you. If you are not better in a week or so, come back to the surgery")
Outcomes	Psychological: -Assessment weekly until pain resolved (between 7 and 100 days) Physical: Not reported Adverse events: Not reported
Notes	Funding: Not stated

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Telephone randomisation
Allocation concealment (selection bias)	Unclear risk	All unclear whether allocation was concealed.
Blinding of participants and personnel (performance bias)	Unclear risk	Unclear whether patients were blinded. Practitioners were blinded.
Blinding of outcome assessment (detection bias) Physical outcome		
Blinding of outcome assessment (detection bias) Psychological outcome	Low risk	Outcome assessors blinded.
Blinding of outcome assessment (detection bias) Harms		
Incomplete outcome data (attrition bias)	Low risk	All patients accounted for
Selective reporting (reporting bias)	Low risk	Power calculation for main outcome conducted and all

		outcomes reported in methods reported in results.
Other bias	Unclear risk	The selection of new onset versus ongoing chronic conditions might have biased the results. Somewhat contrary to what the authors' state (without any evidence), acute cases may be less placebo responsive. Also, Thomas (1987) might have been more charismatic than his Belgian and Dutch counterparts. "Many of them were not willing to tell some of their patients for research purposes that they did not themselves know precisely what the matter was and that the patients must come back if the problems did not go away. Some of those who wanted to help us with the trial told us afterwards that they had great difficulty in giving patients advice 2. Quite often, when we asked the GPs to give a negative consultation, they used instead a rather neutral formulation. Even at our own Department of General Practice at Maastricht University there was some opposition to the trial"
Selective recruitment (cluster trials only)		
Contamination		

Lauder 1995

Methods	Design: 2-armed RCT Recruitment: Women undergoing hysterectomy "were recruited at a preoperative interview by one of the authors, either before or after the preoperative visit by the clinical anaesthetist. The recruiting interview took place in a private room away from the rest of the ward. Any patient in the control group asking spontaneous questions about perioperative nausea, vomiting or antiemetics at the time of interview-recruitment was excluded...All patients were asked for consent to participate in a study of postoperative well being" (p.266) Setting: Southampton General Hospital, UK Inclusion criteria: Patients undergoing hysterectomy; "patients were included in the study if there was no history of hypersensitivity or other contraindications to the use of any of the proposed agents and no history of peptic ulceration or bleeding diathesis" (p. 266) Exclusion criteria: Patients with "history of hypersensitivity or other contraindications to the use of any of the proposed agents"; "history of peptic ulceration or bleeding diathesis"; "asking spontaneous questions about perioperative nausea, vomiting or antiemetics at the time of interview recruitment". "Of those excluded from the control group, seven did not receive a standard general anaesthetic, one procedure was cancelled because of another emergency case, three did not have the proposed total abdominal hysterectomy and there were no data for one patient whose form was lost. Of those excluded from the positive suggestion group, 10 did not receive a standard general anaesthetic, three returned to theatre within the 24-h study period because of haemorrhage, two patients did not have the proposed hysterectomy and

	there were no data available for four patients" (p. 268)
Participants	Total N: 226 A total of 226 patients were recruited and allocated. 112 were allocated to the control group and 12 of these were subsequently excluded; control n=100 in final analysis. 114 patients were allocated to the positive suggestion group and 19 were later excluded; intervention group n=95 Women undergoing hysterectomy "were recruited at a preoperative interview by one of the authors, either before or after the preoperative visit by the clinical anaesthetist"
Interventions	Intervention: Positive suggestion: "During the recruiting visit, the positive suggestion group was informed of the use of two perioperative antiemetics in order to foster the belief that these drugs do reduce the incidence of emetic symptoms after operation. At induction of anaesthesia the positive suggestion group were again told they would receive an antiemetic i.v. and informed of the expected antiemetic effect, even though they would be under the influence of benzodiazepine premedication", "...patients in the positive suggestion [experimental] group were told before operation and on induction of anaesthesia that postoperative emetic sequelae would be greatly reduced by the use of two antiemetic drugs" (p. 266) Control: "The control group was informed that this was a study of postoperative well being and there were no discussions or suggestions concerning perioperative nausea and vomiting." "Control patients were simply asked to participate in a study of post-operative well being with no mention of nausea or vomiting" (p. 266)
Outcomes	Psychological: Patient assessment of nausea reported on a 0-10 point nausea scale, 24 hours after surgery Physical: Post-operative antiemetic use over a 24 hour period. Adverse events: Patient experience of vomiting or retching (yes/no)
Notes	Funding: Not stated The experimental intervention was intended to induce positive expectations, "Patients were allocated to a study (positive suggestion) or control group by means of random numbers generated by a computer program." (p. 266)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated random allocation
Allocation concealment (selection bias)	Low risk	Computer generated allocation sequence, however unclear whether practitioners were blinded
Blinding of participants and personnel (performance bias)	Unclear risk	Unclear whether patients were blinded. Unclear whether practitioners were blinded.
Blinding of outcome assessment (detection bias) Physical outcome	Low risk	Outcome assessors blinded.
Blinding of outcome assessment (detection bias) Psychological outcome	Low risk	Outcome assessors blinded.
Blinding of outcome assessment (detection bias) Harms	Unclear risk	Unclear whether harm assessors were blinded.
Incomplete outcome data (attrition bias)	Unclear risk	A total of 226 patients were recruited; 112 patients were allocated to the control group and 114 patients to the positive suggestion group. Patients excluded from the study included 12 from the control group (10.7%) and 19 from the positive suggestion group (16.7%)
Selective reporting (reporting bias)	Low risk	Power calculation for main outcome reported and all outcomes described in methods reported in results.
Other bias	Low risk	None obvious

Selective recruitment (cluster trials only)		
Contamination		

Little 2015

Methods	Design: Cluster parallel group trial Recruitment: Any adult aged ≥16 years attending general practices close to the study coordinating centres in Southampton (with any primary care health concern) Setting: Primary Care, Southampton, UK Inclusion criteria: "Any adult patient attending their GP who had agreed to participate in the study and were able and willing to consent to study procedures Exclusion criteria: Patients unable to consent or complete questionnaires (for example, because of severe mental illness, severe distress, very unwell generally, and difficulty reading or writing)
Participants	Total N: 224 Patients: Eligible - not reported, Randomized - 224, Completed - 190 Gender: Not reported Mean age: Intervention 51 (SD 23), Control 56 (SD 21)
Interventions	Intervention: Brief training intervention for enhancing physician non-verbal communication with patients Control: No behavioral intervention was given to control group practitioners
Outcomes	Psychological: Questionnaire MISS (Medical Interview Satisfaction Scale, mean item score from 1-7 overall) immediately after the consultation (although questionnaire could be taken home and returned via freepost) Physical: Not reported Adverse events: Not reported
Notes	Funding: "Scientific Foundation of the RCGP and the NIHR South West Regional R+D panel for partly funding this work (Reference number SFB 2003/44)" Ethical approval: "The study was approved by the Salisbury and South East Hampshire local research ethics committees (Southampton Local Research Ethics Committee number: 230/97)" (p. e355)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated random sequence generation
Allocation concealment (selection bias)	Low risk	Reported as concealed
Blinding of participants and personnel (performance bias)	Unclear risk	Patients blinded Personnel not blinded
Blinding of outcome assessment (detection bias) **Physical outcome**		
Blinding of outcome assessment (detection bias) **Psychological outcome**	Unclear risk	Unclear whether outcome assessment was blinded
Blinding of outcome assessment (detection bias) **Harms**		
Incomplete outcome data (attrition bias)	Unclear risk	26 patients (21%) from the intervention group and 8 (8%) from control group dropped out; ITT with complete data with no imputation of missing value; no explanation on attrition
Selective reporting (reporting bias)	Unclear risk	Power calculation reported but not described, secondary outcomes (enablement) described in text as 'non-significant' but no quantitative data provided.
Other bias	Low risk	None obvious
Selective recruitment (cluster trials only)		No evidence of selective recruitment
Contamination		No evidence of contamination

Olsson 1989

Methods	Design: 2-armed RCT Recruitment: "Patients aged 16 years and older, with subjective acute infectious throat symptoms, when the counselling nurse, on the basis of the introductory verbal contact with the patient, considered it probable that the patient was suffering from acute streptococcal tonsillitis and that immediate screening for mononucleosis with Monosticon was negative" Setting: Knuten health centre, Sandviken, Sweden Inclusion criteria: "The criteria for inclusion in the study were that the counselling nurse, on the basis of the introductory verbal contact with the patient, considered it probable that the patient was suffering from acute streptococcal tonsillitis and that immediate screening for mononucleosis with Monosticon was negative" (p. 189) Exclusion criteria: Not stated (implied within inclusion criteria)
Participants	Total N: 100 Patients who contacted the Knuten health centre in Sandviken with subjective acute infectious throat symptoms
Interventions	Intervention: -"The doctor met the patient in the corridor, introduced himself and took the patient to a dark-room. After a brief history had been taken the patient underwent an ear, nose and throat examination (inspection of the pharynx with a lamp and head mirror, anterior rhinoscopy, otoscopy). After the examination the patient was taken to the doctor's office for a conversation, and was given information about the diagnosis, treatment (phenoxymethylpenicillin capsules 25 mg per kg body weight per day divided into two doses for 10 days) and the prognosis, the doctor emphasizing that the patient would probably feel well after about 24 hours. The prescription was written by hand in the patient's presence on an ordinary, not pre-printed, prescription form. The patient was informed that a study was being made of the symptoms in tonsillitis and was asked to fill in linear scales with an evaluation both of the current throat symptoms and of his or her confidence in pharmacological treatment in general. In addition the patient was told that he or she would be telephoned after two days and would be asked about the throat condition. The mean length of consultation for this group was about 10 minutes. The conversation was ended and the patient was given an opportunity to ask any further questions. A medical certificate was not offered spontaneously by the doctor, but on request he wrote one for a week and emphasized that when the patient felt well he or she could report the recovery to the social insurance office 'prematurely'." (p. 189) Control: -Less detailed information about prognosis: "The doctor met the patient in the corridor but did not introduce himself, and took the patient to an ordinary examination room. A brief history was taken and the patient's throat was then examined with a torch and spatula. The patient was informed about the diagnosis and treatment but not about the prognosis. The doctor had written out a prescription for phenoxymethylpenicillin in advance on a pre-printed form, in the same dosage as in group 1. A medical certificate had been filled in beforehand and was available if the patient should ask for one. The patient was given the prescription and, if requested a medical certificate, was then told that he or she would be telephoned after two days and asked about the throat condition. The mean length of consultation for this group was about six minutes. The patient's name, the date of the consultation and the group to which the patient had been allocated were noted on a list at the clinic. An interview form with information as to when the patient was to be contacted was sent to the interviewer. After two days the patient was telephoned and interviewed according to a standardized and structured schedule. At that time the interviewer did not know to which group the patient belonged. The main questions asked were: For how many days had the symptoms been present before you contacted the health centre? How severe are the throat symptoms now compared with the day of consultation? Has the treatment helped? Did you think that information about the disease and the treatment was sufficient?" (p. 189)
Outcomes	Psychological: Patients' opinion about the severity of their throat symptoms after two days compared with the day of consultation, phone survey; "How is your throat now compared with the day when you contacted the health centre". Physical: Not reported Adverse events: Not reported
Notes	Funding: Not stated

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number tables
Allocation concealment (selection bias)	Unclear risk	Unclear whether allocation was concealed.
Blinding of participants and personnel (performance bias)	Unclear risk	Patients blinded Practitioners not blinded
Blinding of outcome assessment (detection bias) **Physical outcome**		

Blinding of outcome assessment (detection bias) Psychological outcome	High risk	Outcome assessors not blinded since "all interview forms were sent to the doctor who had treated the patient"
Blinding of outcome assessment (detection bias) Harms		
Incomplete outcome data (attrition bias)	Low risk	All patients accounted for
Selective reporting (reporting bias)	Low risk	All outcomes described in methods reported in results.
Other bias	Low risk	None obvious
Selective recruitment (cluster trials only)		
Contamination		

Petersen 2012

Methods	Design: 6 group crossover trial Recruitment: "The patients were recruited from the Department of Cardiothoracic and Vascular Surgery, Aarhus University Hospital, Denmark, from January 2000 to December 2009...Patients were contacted for further screening if they had reported an average score of pain intensity >3 on a numerical rating scale (NRS) in a hospital questionnaire about their postsurgical pain" (p. 1293) Setting: Department of Cardiothoracic and Vascular Surgery, Aarhus, Denmark Inclusion criteria: "Patients age 18 years or older with neuropathic pain after unilateral thoracotomy 1 to 10 years before their participation, reported an average score of pain intensity >3 on a numerical rating scale (NRS) in a hospital questionnaire about their postsurgical pain. Exclusion criteria: "Other neurological or psychiatric disorders, known allergies to local anesthetics, skin disease in the upper part of the body, or treatment with class 1 antiarrhythmic drugs"
Participants	Total N: 19 Patient having undergone thoracotomy with postsurgical pain
Interventions	Intervention: Positive message: "An active medication that has been shown to be effective for some types of pain will be tested", The active medication was given in full view of the patients, and the patients were told: "The agent you have just been given is known to powerfully reduce pain in some patients". The mean length of consultation was 10 min for intervention group. Control: "In the control condition, no medication was applied to the disinfecting napkin", "In the baseline-control condition, patients were told: 'We will test your response to different types of stimuli in order to get a better understanding of how (your) pain is processed'." The mean length of consultation was 6 min for control group.
Outcomes	Psychological: Patient-reported differences in pain intensity measured on a mechanical visual analogue scale (M-VAS) Physical: None reported Adverse events: Not reported
Notes	Funding: "This work is part of the Europain project and is funded by the Innovative Medicines Initiative Joint Undertaking (IMI JU) Grant No. 115007. It was also supported by the MINDLab UNIK initiative at Aarhus University, which is funded by the Danish Ministry of Science, Technology and Innovation" (p. 1299)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random sequence generation performed by rolling of dice
Allocation concealment (selection bias)	Unclear risk	Unclear whether allocation was concealed.
Blinding of participants and personnel (performance bias)	Unclear risk	Patients blinded Practitioners not blinded.
Blinding of outcome assessment (detection bias) Physical outcome		
Blinding of outcome assessment (detection bias) Psychological outcome	Low risk	Blinded patients assessed their own pain.
Blinding of outcome assessment (detection bias) Harms		
Incomplete outcome data (attrition bias)	Low risk	All included patients

		accounted for
Selective reporting (reporting bias)	Unclear risk	Some secondary outcomes (expectancy, pain diary results) reported in text without numerical data.
Other bias	Low risk	The study appears to be free from other sources of bias
Selective recruitment (cluster trials only)		
Contamination		

Petersen 2014

Methods	Design: 6 group crossover trial Recruitment: Patients attending the Department of Cardiothoracic and Vascular Surgery and the Danish Pain Research Center, Aarhus University Hospital, Aarhus, Denmark Setting: Hospital, Aarhus, Denmark Inclusion criteria: "Persistent ongoing neuropathic pain corresponding to an average score of pain intensity of P3 on a numeric rating scale (NRS, 0–10). Neuropathic pain is defined, according to the International Association for the Study of Pain, as 'pain caused by a lesion or disease of the somatosensory system', and we included patients with definite or probable neuropathic pain using the neuropathic pain grading system. Pain should be located in an area of sensory abnormality compatible with a nerve injury after thoracic surgery. In addition, a clinical examination was performed, including a skin inspection and evaluation of pain during movement and the presence of muscle trigger points to exclude any obvious nociceptive pain" Exclusion criteria: "The exclusion criteria were neurological or psychiatric disorders, known allergies to local anesthetics, skin disease in the upper part of the body, or treatment with class 1 antiarrhythmic drugs"
Participants	Total N: 18
Interventions	Intervention: Open administration of a painkiller Control: " 'We will test your response to different types of stimuli in order to get a better understanding of how (your) pain is processed'. Then they were told: ''This is a control condition for the active medication'. The active medication was administered without the patients' knowledge" (p. 2688)
Outcomes	Psychological: -Spontaneous pain intensity (Mechanical VAS) immediately after treatment -Pain unpleasantness (Mechanical VAS) immediately after treatment - Pinprick intensity during stimulation Physical: None reported Adverse events: Not reported
Notes	Funding: "This work is part of the Europain Collaboration and funded by the Innovative Medicines Initiative Joint Undertaking (IMI JU) (grant 115007), resources that are composed of financial contribution from the European Union's Seventh Framework Program (FP7/2007-2013) and EFPIA companies' in-kind contribution (http://www.imi.europa.eu/). It was also supported by the MINDLab UNIK initiative at Aarhus University, which is funded by the Danish Ministry of Science, Technology, and Innovation"

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Flipping a coin
Allocation concealment (selection bias)	Unclear risk	Unclear whether allocation was concealed.
Blinding of participants and personnel (performance bias)	Unclear risk	Unclear whether patients or practitioners were blinded
Blinding of outcome assessment (detection bias) Physical outcome		
Blinding of outcome assessment (detection bias) Psychological outcome	Unclear risk	Unclear whether outcome assessors were blinded.
Blinding of outcome assessment (detection bias) Harms		
Incomplete outcome data (attrition bias)	Low risk	All patients accounted for
Selective reporting (reporting bias)	Low risk	No protocol or evidence of protocol or power calculation. However, all outcomes

		reported.
Other bias	Unclear risk	The instructions given before the trial ("An active medication that has been shown to increase some types of pain will be tested.") were likely to induce negative expectations in both control and experimental groups. This would leave less room for intervention induced improvement
Selective recruitment (cluster trials only)		
Contamination		

Phillips 2006

Methods	Design: 3-armed RCT Recruitment: "At admission, all potential participants were approached by a member of the research team once they settled into the room and given a complete explanation of the research project" Setting: In-patient medical rehabilitation unit, Santa Barbara, California, USA Inclusion criteria: "All potential participants were approached admitted to rehabilitation facility Exclusion criteria: Patients "receptive or expressive aphasia and/or participants who could not realistically perform the rehabilitation activities"
Participants	Total N: 80 Medical rehabilitation patients
Interventions	Intervention: Positive suggestion, "Working hard at your rehabilitation activity will help you get home sooner (i.e., not have to eat hospital food any longer, not have to do with the lack of privacy, not have to do with the discomfort of a hospital bed, etc.)", Making a commitment to really do your rehabilitation exercises will help you regain a considerable previous level of functioning (i.e., do many of the things you used to do, engage in many of the activities you used to engage in, etc.) Control: "The UC group was visited eight times. They were asked if they have attended therapy and asked if they wanted or received any magazines or videotape movies for their reading or viewing pleasure. At the last visit they were told it is the last visit and they were offered an expression for a speedy recovery"
Outcomes	Psychological: Positive: Self-efficacy for Functional Ability (SEFA); 9-item Likert measure, 0-10 each item. Physical: Functional performance (FIM) at admission and discharge: "[FIM] is an objective rating scale in six areas of patient performance rated at levels ranging from 1 = Total assistance (complete dependence); 2 = Maximal assistance; 3 = Moderate assistance (modified dependence); 4 = Minimal assistance; 5 = Supervision; 6 = Modified independence (using a supportive device); 7 = Complete independence (timely and safely). Scores are summed for a total score. The higher the total score, the greater the degree of functionality" Adverse events: Not reported
Notes	Funding: Not stated

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated sequence generation
Allocation concealment (selection bias)	Unclear risk	Unclear whether assignment was concealed.
Blinding of participants and personnel (performance bias)	Unclear risk	Unclear whether patients blinded Personnel blinded
Blinding of outcome assessment (detection bias) **Physical outcome**		Unclear whether outcome assessors were blinded however clinicians involved in study were blinded and the outcome was observer-assessed.
Blinding of outcome assessment (detection bias) **Psychological outcome**	High risk	Unclear whether outcome assessors were blinded however

		clinicians involved in study were blinded and the outcome was observer-assessed.
Blinding of outcome assessment (detection bias) Harms		
Incomplete outcome data (attrition bias)	Low risk	All patients accounted for
Selective reporting (reporting bias)	Low risk	All outcomes described in methods section reported in results.
Other bias	Low risk	No evidence of other bias
Selective recruitment (cluster trials only)		
Contamination		

Resnick 1996

Methods	Design: 2-armed RCT Recruitment: Patients undergoing a geriatric rehabilitation program Setting: Hospital (James Lawrence Kernan Hospital), Baltimore, Maryland, USA Inclusion criteria: "Rehabilitation related to orthopedic problems including: elective total knee replacements (TKR) (n=26), elective total hip replacements (THR) (n=16), hip fractures repaired with THR (n=7), or open reduction internal fixation (ORIF) (n=14), and other orthopedic accidents/fractures (n=14)" Exclusion criteria: "Any patient who was (1) discharged from rehabilitation due to acute illness prior to completing his or her recommended rehabilitation stay or (2) did not receive the interventions 5 days per week as described below, was dropped from the study, and not included in the study sample. Patients were excluded at the outset if they (1) scored below a 20 on a Mini-Mental State Exam; (2) had receptive and/or expressive aphasia, based on inability to express basic needs, and ability to follow a 3 step command; (3) scored 5 or greater on a the Geriatric Depression Scale; (4) scored 40 or greater on the Speilberger's Trait Anxiety Scale, and (5) had fewer than 2 individuals in his or her core social network".
Participants	Total N: 77
Interventions	Intervention: -Positive, verbal persuasion (p78), physiological feedback (p78-79) Control: -Usual care (90 minutes of physical therapy given by a licensed physical therapist, and 90 minutes of occupational therapy given by a licensed occupational therapist, 5 days per week.
Outcomes	Psychological: -Functional ability or status using Functional Inventory measure (FIM), -Pain (NRS) patient's numerical rating of perceived pain, reported on a 10-point scale Physical: Objective: Direct observation to evaluate patients functional ability or status using Functional Inventory measure (FIM) Adverse events: Not reported
Notes	Funding: Not stated

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization achieved by putting the 22 treatment rooms into a container and randomly choosing 11 of them
Allocation concealment (selection bias)	Unclear risk	Unclear whether randomization was concealed.
Blinding of participants and personnel (performance bias)	Unclear risk	Unclear whether patients were blinded. Practitioners blinded
Blinding of outcome assessment (detection bias) Physical outcome	Unclear risk	Unclear whether outcome assessment was blinded.
Blinding of outcome assessment (detection bias) Psychological outcome		
Blinding of outcome assessment (detection bias) Harms		
Incomplete outcome data (attrition bias)	Low risk	All patient data were included in the final

		analysis. Explanation for patient drop-out (N=3) provided
Selective reporting (reporting bias)	Unclear risk	Protocol published and approved. All outcomes described in methods reported in results. However, unclear whether 'health status' was an outcome or baseline measure as it was described in the methods but not reported.
Other bias	Low risk	None obvious
Selective recruitment (cluster trials only)		
Contamination		

Rief 2017

Methods	Design: 3-armed RCT Recruitment: Patients on the waiting list of the Heart Surgery Center were contacted before hospital admission Setting: Either at home or at the University Department (of cardiovascular surgery), Marburg, Germany Inclusion criteria: adults older than 18 years who were scheduled for elective on pump CABG or CABG combined with valve surgery. Further inclusion criteria were ability to give informed consent and sufficient fluency in German. Exclusion criteria: "Presence of a serious comorbid non-cardiac medical condition or psychiatric condition that substantially affected disability. Current psychiatric condition was assessed with the standardized interview SCID. Out of 249 patients approached for participation, 72 (28.9%) declined because of motivational reasons, including travel problems to attend the study appointments. Patients who agreed to take part in the study were significantly younger (t(157) = 3.31; p = .001), while sex ratios were comparable to patients who declined [18]. Two patients died before admission to the hospital, while 24 patients did not fulfil the inclusion criteria (Fig. 1). Thus we started with an ITT sample of 124 patients (87% only CABG; 13% CABG plus heart valve replacement). Follow-up assessments were completed by 108 patients at 6 months follow-up (88.5 % of baseline sample; 87% of ITT sample). Seven patients died post-surgery (2 in SMC, 2 in SUPPORT, 3 in EXPECT condition)"
Participants	Total N: 78
Interventions	Intervention: Expectation-modifying intervention intended to induce realistic expectations about the benefits of surgery and the process of recovery Control: Standard medical care or psychological control intervention (SUPPORT)
Outcomes	Psychological outcome: Patient-reported changes in Pain Disability Index (PDI) range=0-70, 6 months after surgery Physical outcome: Physical quality of life measured using the SF-12 (0-100 scale). Harms: Adverse events after coronary artery bypass graft surgery (including rehospitalization), within 3 weeks after the trial.
Notes	Funding: "Role of the Funding Source: This study is part of the Transregional Research Unit FOR 1328: 'Expectation and conditioning as basic processes of the placebo and nocebo response – From neurobiology to clinical applications', funded by the German Research Foundation DFG and granted to Dr Rief et al. Funding was unconditional, and funding source had no influence on study conduct and study report" Further particulars about the intervention: -EXPECT (expectation manipulation intervention): "This intervention focused on the development of realistic expectations about the benefits of surgery and the recovery process. Patients were encouraged to develop personal ideas and images about their future after surgery, including plans about activities and how they will enjoy their life afterwards (outcome expectations). Personally relevant steps and plans for the six months after surgery were recorded for patients. Additionally, patients received a booklet containing all relevant session information, including the work sheets, and audio-CDs of their sessions. Finally, normal symptoms after surgery that could be expected were discussed, and differentiated from unlikely complications. Patients' control expectations were enhanced by discussing ways how they could manage unpleasant symptoms or sensations, and how they could positively influence the disease course after surgery. An example may further illustrate this intervention. Many patients hoped to again be able to work in their garden after surgery. In the EXPECT intervention these patients developed specific plans on how they would successfully be able to reassume gardening activities due to their expected increased exercise capacity following surgery: repotting small plants in the early stage, lawn mowing after some time, increasing to more demanding gardening tasks between 3-6 months after surgery. One patient imagined himself chopping wood in preparation for hosting a barbecue in his garden

	for his family"

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated random sequence generation
Allocation concealment (selection bias)	Low risk	Allocation concealment was verified using closed envelopes. Surgeons, hospital staff involved in patient care, and staff assessing treatment effects were blind to treatment condition
Blinding of participants and personnel (performance bias)	Unclear risk	Unclear whether patients were blinded. Practitioners blinded
Blinding of outcome assessment (detection bias) Physical outcome	Low risk	Surgeons, hospital staff involved in patient care, and staff assessing treatment effects were blind to treatment condition.
Blinding of outcome assessment (detection bias) Psychological outcome	Low risk	Surgeons, hospital staff involved in patient care, and staff assessing treatment effects were blind to treatment condition.
Blinding of outcome assessment (detection bias) Harms	Low risk	Surgeons, hospital staff involved in patient care, and staff assessing treatment effects were blind to treatment condition.
Incomplete outcome data (attrition bias)	Low risk	Used the ITT sample of 124 patients initially eligible for the trial
Selective reporting (reporting bias)	Low risk	All outcomes described in methods and pre-published protocol are reported
Other bias	Low risk	None obvious
Selective recruitment (cluster trials only)		
Contamination		

Ronel 2011

Methods	Design: 2-armed RCT Recruitment: Patients with biomarker-negative chest pain Setting: University Hospital, Munich, Germany Inclusion criteria: "Patients with an age range from 18 to 80 years, presenting with biomarker-negative chest pain, informed written consent" Exclusion criteria: "Necessity of invasive treatment of coronary artery disease (as diagnosed during angiography), acute myocardial infarction or elevation of cardiac enzymes, known history of Prinzmetal angina, regular intake of nitrates, nitrate intolerance, administration of nitrates during the course of catheterization, hypotension, pregnancy, renal insufficiency, diabetes, hyperthyroidism, acute psychiatric disorders, or cognitive deficits"
Participants	Total N: 28
Interventions	Intervention: Verbal suggestion inducing positive expectations about the procedure Control: In patients assigned to the control group "the saline solution administration was done without any verbal or visual information."
Outcomes	Psychological: Chest pain perception on a 10-point scale immediately before treatment Physical: Diameter stenosis (% DS); change from baseline; baseline data also available; final data calculated by adding change to the baseline measurement (identified by the study authors as the primary outcome).

	Adverse events: Not reported
Notes	Funding: Not stated Details of medication: "Five millilitres of physiological saline solution (0.9% NaCl) was injected intracoronarily in all study patients"

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centrally generated random allocation sequence
Allocation concealment (selection bias)	Low risk	The information about the randomization allocation was stored in sealed, opaque, and consecutively numbered envelopes
Blinding of participants and personnel (performance bias)	Unclear risk	Patients blinded Practitioners not blinded
Blinding of outcome assessment (detection bias) **Physical outcome**	Low risk	Blinded practitioners assessed outcomes.
Blinding of outcome assessment (detection bias) **Psychological outcome**	Low risk	Blinded patients assessed outcomes.
Blinding of outcome assessment (detection bias) **Harms**		
Incomplete outcome data (attrition bias)	Low risk	All patients accounted for: PP analysis; 2 dropped out from VS group with reasons provided: "There were 2 severe protocol violations, both in the VS group: In one patient, the catheter was erroneously removed after the intervention and had to be replaced before the second scan"
Selective reporting (reporting bias)	Low risk	All outcomes described in methods section reported in results.
Other bias	High risk	The main outcome measure (percentage diameter) stenosis was higher in the treatment group (10.5±4.9) compared with the control group (14.0±8.0). This could have led to an exaggeration in the perceived treatment effect.
Selective recruitment (cluster trials only)		
Contamination		

Soltner 2011

Methods	Design: 4-armed RCT Recruitment: "Unselected patients undergoing day-care gynaecologic procedure...were invited to participate while waiting for the anaesthesiologist visit, under the pretext of a satisfaction enquiry" Setting: Gynecological day-care surgery unit, Angers, France Inclusion criteria: Patients undergoing day-care gynaecologic procedure Exclusion criteria: Unclear; "Over a 6 month period from November 2009 to June 2010, we enrolled unselected patients undergoing day-care gynaecologic procedure. Patients were invited to participate while waiting for the anaesthesiologist visit, under the pretext of a

	satisfaction enquiry. All had verbally accepted to participate in the study" (p. 681)
Participants	Total N: 68
Interventions	Intervention: -Empathetic practitioner attitude: "The empathic attitude allowed for an extra 50% of time (5 min for a 10 min consultation) to elicit questions, such as: 'Are you anxious about the forthcoming anaesthesia?' In case of a positive response, a two-way discussion allowed the patient to ask questions and the anaesthesiologist to provide explanations regarding the procedure" Control: -Neutral practitioner attitude: "The neutral attitude consisted of questions asked at a standard preanaesthetic consultation, which was followed by a routine clinical examination
Outcomes	Psychological: Anxiety decrease after consultation vs before hand (DVAS, mm), -Satisfaction regarding anaesthesia (VAS, mm) Physical: None reported Adverse events: Changes in acute psychological burden (scores 0-10) before and 60 seconds after the administration of saline
Notes	Funding: Not stated

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Sequential randomisation performed combining the two pairs of randomization criteria to obtain 17 blocks of four combinations each
Allocation concealment (selection bias)	Unclear risk	Unclear, though it could be inferred that since patients did not interact with the doctors, it is of low risk ("Questionnaires were handed out to patients by the consultation secretary (Q1-Q2) or the nurse in the postoperative waiting room (Q3), and were filled out without interaction between investigators and patients.")
Blinding of participants and personnel (performance bias)	Unclear risk	Patients blinded Practitioners not blinded
Blinding of outcome assessment (detection bias) **Physical outcome**		
Blinding of outcome assessment (detection bias) **Psychological outcome**	Unclear risk	Likely blinded but unclear: "Questionnaires were handed out to patients by the consultation secretary (Q1-Q2) or the nurse in the postoperative waiting room (Q3), and were filled out without interaction between investigators and patients"
Blinding of outcome assessment (detection bias) **Harms**		
Incomplete outcome data (attrition bias)	Low risk	All randomised patients accounted for in results
Selective reporting (reporting bias)	Low risk	All outcomes described in methods are reported in results,

		however no protocol published, and no power calculation reported.
Other bias	Low risk	None obvious
Selective recruitment (cluster trials only)		
Contamination		

Suarez-Almazor 2010

Methods	Design: Nested two-stage trial (3 treatment groups and 2 communication styles) Recruitment: Patients aged 50 or older suffering from painful knee osteoarthritis Setting: Texas, USA Inclusion criteria: Patients aged 50 or over, knee osteoarthritis according to American College of Rheumatology criteria, 1) pain in the knee in the preceding 2 weeks 3/10 on a visual analogue scale (VAS), 2) no prior treatment with acupuncture, 3) stable treatment with nonsteroidal anti-inflammatory drugs and analgesics in the previous month, 4) if receiving glucosamine, a stable dose for the past 2 months, and 5) no intraarticular injections in the knee in the previous 2 months Exclusion criteria: "individuals with close relationships to participants were excluded"
Participants	Total N: 455
Interventions	Intervention: Verbal messages delivered by acupuncturist prior to treatment intended to induce either positive expectations or neutral expectations Control: Waiting list control with no intervention
Outcomes	Psychological: Joint-Specific Multidimensional Assessment of Pain (JMAP) 3 months after treatment Pain (WOMAC pain subscale) 3 months after treatment Physical: Timed get up and go test (seconds) Adverse events: "These adverse events were reported: exacerbation of knee pain, bruising at the needle site, muscle cramps, headache, infection at the needle site" Data also collected at 4 weeks, 6 weeks
Notes	Funding: Not reported

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated random sequence generation
Allocation concealment (selection bias)	Low risk	Opaque, sealed, consecutively numbered envelopes kept at a central location were used for allocation
Blinding of participants and personnel (performance bias)	Unclear risk	Patients blinded Practitioners not blinded
Blinding of outcome assessment (detection bias) **Physical outcome**	Low risk	Blinded outcome assessor
Blinding of outcome assessment (detection bias) **Psychological outcome**	Low risk	Blinded outcome assessor
Blinding of outcome assessment (detection bias) **Harms**	Unclear risk	Unclear whether harms were assessed by blinded observers.
Incomplete outcome data (attrition bias)	Low risk	9.2% and 6.3% dropouts per group
Selective reporting (reporting bias)	Low risk	All outcomes described in methods are reported in results. No protocol available. Power calculation for main outcome reported
Other bias	Unclear risk	Imbalanced randomization
Selective recruitment (cluster trials only)	Unclear risk	Not reported
Contamination	Low risk	No evidence of contamination

Szilagyi 2007

Methods	Design: 2-armed RCT Recruitment: Patients being ventilated for a minimum of 48 hours in a hospital intensive care unit (ICU) Setting: Intensive care unit of two hospitals, Budapest, Hungary Inclusion criteria: Age 50+, knee osteoarthritis according to American College of Rheumatology criteria, 1) pain in the knee in the preceding 2 weeks 3/10 on a visual analogue scale (VAS), 2) no prior treatment with acupuncture, 3) stable treatment with nonsteroidal anti-inflammatory drugs and analgesics in the previous month, 4) if receiving glucosamine, a stable dose for the past 2 months, and 5) no intraarticular injections in the knee in the previous 2 months. Exclusion criteria: “a severe hearing impairment or a serious psychiatric diagnosis”
Participants	Total N: 60 Patients being ventilated for a minimum of 48 hours in a hospital intensive care unit (ICU), % male: Not stated Mean age: 67.1
Interventions	Intervention: Variety of positive suggestions delivered by trained psychologists. For example in the following way: "To feel better your body needs some help. We will provide this by inserting a thin plastic tube into your mouth. This tube is connected to a machine that detects exactly when your lungs need fresh air so it can be delivered promptly and efficiently". "The machine will help you until your body is strong enough to breathe again on its own" Control: "Usual ICU care"
Outcomes	Psychological: None reported Physical: -Mean ventilation hours (main outcome) after treatment (roughly 2 weeks), -Length of stay (weeks) in hospital on discharge from the ICU Adverse events: Number of deaths reported
Notes	Funding: "OTKA grant No. T 043751 to Katalin Varga"

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence allocation method unspecified
Allocation concealment (selection bias)	Unclear risk	Unclear whether allocation was concealed
Blinding of participants and personnel (performance bias)	High risk	Unclear whether patients were blinded Practitioners not blinded
Blinding of outcome assessment (detection bias) Physical outcome	High risk	Reported as not blinded.
Blinding of outcome assessment (detection bias) Psychological outcome		
Blinding of outcome assessment (detection bias) Harms	High risk	Reported as not blinded.
Incomplete outcome data (attrition bias)	Low risk	All patients accounted for
Selective reporting (reporting bias)	Low risk	All outcomes reported in methods reported in results. Outcomes also reported in protocol (Varga 2007) without change.
Other bias	Low risk	None obvious
Selective recruitment (cluster trials only)		
Contamination		

Thomas 1987

Methods	Design: 2-armed RCT Recruitment: Patients presenting to GP surgery Setting: General practice, Southampton, UK Inclusion criteria: Patients with symptoms but no definite diagnosis. Exclusion criteria: Not stated (implied within inclusion criteria)
Participants	Total N: 200 Patients presenting to GP surgery with no definite diagnosis
Interventions	Intervention: -Positive consultation with or without treatment: "patient was given a firm diagnosis and told confidently that he would be better in a few days. If no prescription was to be given he was told that in the doctor's opinion he required none, and if a prescription was to be given that the treatment would certainly make him better". If no prescription was to be given the following words were added:

	"And therefore I will give you no treatment." If a prescription was to be given the patient was told: "I am not sure that the treatment I am going to give you will have an effect". "Treatment" was a prescription for tabs thiamine hydrochloride 3 mg, used as a placebo, and "no treatment" was no prescription Control: -Artificial consultation, "devised so that no firm assurance was given. This was done by the doctor making one statement: 'I cannot be certain what is the matter with you." If no prescription was to be given the following words were added: "And therefore I will give you no treatment." If a prescription was to be given the patient was told: "I am not sure that the treatment I am going to give you will have an effect." The negative consultations were brought to a close by telling the patient that if he or she was no better in a few days to return to the doctor."
Outcomes	Psychological: Questionnaire two weeks after consultation asking patients whether they feel better: "Two weeks after the consultation a card was sent to each patient asking: (1) Did you get better? (2) How many days after seeing me did you get better? (3) Did you require any further treatment. The data collected for each patient included social class, choice of doctor, and the number of times previously seen by me or one of my colleagues." Physical: Not reported Adverse events: Not reported
Notes	Funding: Not stated

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Used cards
Allocation concealment (selection bias)	Unclear risk	Unclear whether allocation was concealed.
Blinding of participants and personnel (performance bias)	Unclear risk	Patients blinded Practitioners not blinded
Blinding of outcome assessment (detection bias) **Physical outcome**		
Blinding of outcome assessment (detection bias) **Psychological outcome**	Unclear risk	Unclear whether patients (who made their assessments) were blinded. Practitioner not blinded.
Blinding of outcome assessment (detection bias) **Harms**		
Incomplete outcome data (attrition bias)	Low risk	All patient data were included in the analysis
Selective reporting (reporting bias)	Low risk	All outcomes described in methods are reported in results.
Other bias	Low risk	None obvious
Selective recruitment (cluster trials only)		
Contamination		

Vangronsveld 2012

Methods	Design: Between subject trial Recruitment: Nurses working in a geriatric unit who had experienced back pain during the last 12 months Setting: University Hospital, Örebro, Sweden Inclusion criteria: Back pain in the last 12 months nurses and fluency in Swedish Exclusion criteria: Not stated (implied within inclusion criteria)
Participants	Total N: 28 Nurses working in a geriatric unit who had experienced back pain during the last 12 months
Interventions	Intervention: Positive suggestion (active listening and validation) during a 15 min semi structured interview Control: Invalidation intervention "consisted of inappropriate body language (e.g. glancing down at papers instead of looking at the participant or not paying full attention) and the interviewer might challenge the participants, change the conversation topic or ignored expressions of feelings. The interviewer used statements to invalidate such as 'hmm, that's strange' or 'not many people report that' "
Outcomes	Psychological: Pain as a subscale within the Affect questionnaire immediately before and after the intervention Physical: Not reported Adverse events: Not reported
Notes	Funding: Not stated

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated random sequence generation
Allocation concealment (selection bias)	Low risk	The interviewer was blind to which condition was chosen until the opaque envelop was opened at the start of the day
Blinding of participants and personnel (performance bias)	Unclear risk	Patients blinded Practitioners not blinded
Blinding of outcome assessment (detection bias) Physical outcome		
Blinding of outcome assessment (detection bias) Psychological outcome	Low risk	Blinded patients assessed outcomes.
Blinding of outcome assessment (detection bias) Harms		
Incomplete outcome data (attrition bias)	Low risk	All data on all participants reported
Selective reporting (reporting bias)	High risk	Some of the outcomes appear to not have been reported, including the Roland and Morris disability score.
Other bias	Unclear risk	Rating pain and all other outcomes twice within 1 hour might influence how these were answered the second time
Selective recruitment (cluster trials only)		
Contamination		

Varelmann 2010

Methods	Design: 2-armed RCT Recruitment: Parturients requesting labor epidural analgesia or nonlaboring parturients presenting for elective caeserean section were included with waiver of informed consent Setting: General Hospital (gynecologic department), USA Inclusion criteria: Healthy parturients at term requesting labor epidural analgesia or nonlaboring parturients presenting for elective caeserean delivery under spinal anesthesia. Exclusion criteria: Administration of opioids in the 4 hours before study enrolment, IV magnesium sulfate within last 24 hours, Diabetes mellitus (I or II), More than 1 attempt at IV cannulation during current admission
Participants	Total N: 140 Parturients requesting labor epidural analgesia or nonlaboring parturients presenting for elective caeserean section were included with waiver of informed consent
Interventions	Intervention: Positive attitude statement consisting of the following messages: "We are going to inject the local anesthetic that will numb the area where we are going to do the epidural/spinal anesthesia and you will be comfortable during the procedure", "This is a medication that recently became available in the Netherlands", "This drug, according to my experience, is very effective and will decrease the pain quickly after taking it" Control (nocebo intervention) "patients were told before local anesthetic injection 'you are going to feel a big sting and burn in your back now, like a big bee sting; this the worst part of the procedure'. Hereafter lidocaine was injected intradermally and subcutaneously over 3 sec through a 25 gauge-needle 2ml lidocaine 10mg/ml. during the local anesthetic injection, only the anesthesist gave verbal instructions to the patients and the nurse was requested to remain silent throughout this portion of the procedure".
Outcomes	Physical: None reported Psychological: Pain intensity recorded on a verbal analogue scale (VAS) (0 no pain, 10 worst imaginable pain) immediately after injection Adverse events: Not reported
Notes	Funding: supported by the "department of Anesthesiology, perioperative and pain medicine, Brigham and Women's hospital, Massachusetts"

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated random sequence generation
Allocation concealment (selection bias)	Low risk	Used opaque sealed envelopes

Blinding of participants and personnel (performance bias)	High risk	Unclear whether patients were blinded Personnel not blinded
Blinding of outcome assessment (detection bias) Physical outcome		
Blinding of outcome assessment (detection bias) Psychological outcome	Low risk	Blinded observer assessed pain.
Blinding of outcome assessment (detection bias) Harms		
Incomplete outcome data (attrition bias)	Low risk	All patient data were included in the analysis
Selective reporting (reporting bias)	Low risk	All outcomes reported. No protocol. Power calculation for main outcome reported.
Other bias	Unclear risk	No pain/psychological related outcomes assessed at baseline
Selective recruitment (cluster trials only)		
Contamination		

Wang 2008

Methods	Design: 2-armed RCT Recruitment: All abdominal hysterectomy patients approached Setting: Hospital, Nanjing, China Inclusion criteria: "patients aged 18-65 approached" Exclusion criteria: "all endocrine disorders and opioid allergic patients, other chronic pain and psychiatric disorders excluded. Patients with significant post op pain were included >6/10 on subjective rating."
Participants	Total N: 241
Interventions	Intervention: - Positive suggestions: "The PCA pump was great in treating pain, especially for people who like you underwent abdominal surgeries", "You took a correct decision on using a PCA pump for your postoperative pain", and "The PCA pump was very effective in removing the postoperative pain affliction" - Negative suggestion Control: - Neutral suggestion
Outcomes	Psychological: Pain intensity on 10-point VAS (0=no pain, 10=worst pain imaginable) 6 hours after surgery Physical: Morphine consumption throughout the study Adverse events: Incidence of side-effects reported
Notes	Funding: Not stated

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated random allocation using SNOSE
Allocation concealment (selection bias)	Low risk	Used sealed opaque envelopes
Blinding of participants and personnel (performance bias)	Low risk	Patients blinded Personnel blinded
Blinding of outcome assessment (detection bias) Physical outcome	Low risk	Outcome assessors blinded.
Blinding of outcome assessment (detection bias) Psychological outcome	Low risk	Outcome assessors blinded.
Blinding of outcome assessment (detection bias) Harms	Low risk	Outcome assessors blinded.
Incomplete outcome data (attrition bias)	Unclear risk	Of the 771 patients randomized: 63 were lost to follow up, 40 retreated from study, and 22 had incoherent analgesia = 115 total not assessed, which is 14.9%, just under the 15% to be considered high risk. Hence, 614

		of the 1500 enrolled patients completed the study.
Selective reporting (reporting bias)	Low risk	Primary outcome reported as stated in methods. No protocol or power calculation reported.
Other bias	Low risk	None obvious
Selective recruitment (cluster trials only)		
Contamination		

White 2012

Methods	Design: Multifactorial mixed-methods trial Recruitment: OA patients via joint replacement waiting lists at Southampton General and Salisbury District Hospitals Setting: Western acupuncture practice, Southampton, UK Inclusion criteria: Age 18 to 80 years; Suffering chronic osteoarthritic pain from a single joint (hip or knee); Awaiting joint replacement surgery; Having a mean score of P30 mm during the baseline week (7 daily recordings) on a 100-mm visual analogue pain scale; Not on any current physical treatment (e.g., physiotherapy) Exclusion criteria: Pregnancy; Serious comorbidity (including severe back pain); History of prolonged or current steroid use; Awaiting hip/knee revision (i.e., current prosthesis); Needle phobia; Allergy to sticking plaster
Participants	Total N: 221
Interventions	Intervention: Empathic consultation: "patients were greeted in a friendly, warm manner and were free to enter into conversation with their practitioner, who in turn would willingly do so. Practitioners did their utmost to comply with participants' wishes, providing detailed answers to questions and emphasising patient comfort and well-being" Control: Non-empathetic consultation: the "encounter was 'clinical' in nature. Patients were greeted in an efficient manner and quietly shown to the treatment cubicle. Practitioners would only discuss matters directly relating to the treatment to enable them to effectively carry out that treatment, e.g., pattern of pain and side effects. Necessary explanations were kept as short as possible, and if patients attempted to enter into any discussion, the practitioner would respond using the words ' I am sorry but because this is a trial I am not allowed to discuss this with you.' Between needle stimulations, patients were left on their own in a curtained cubicle"
Outcomes	Psychological: Pain intensity measured on a 100-point scale, 7 days after treatment Physical: Not reported Adverse events: Number of adverse events (after treatment) reported for the following items: temporary increase in pain, bleed or bruise at needle site, reddening over patella, posttreatment headache, posttreatment tiredness, tearfulness after treatment
Notes	Funding: "Department of Health Postdoctoral Research Award. Additional funding from Southampton Complementary Medicine Research Trust"

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated random sequence generation
Allocation concealment (selection bias)	Low risk	Third party did the randomization
Blinding of participants and personnel (performance bias)	Unclear risk	Patients blinded Practitioners not blinded
Blinding of outcome assessment (detection bias) Physical outcome		
Blinding of outcome assessment (detection bias) Psychological outcome	Low risk	Blinded patients reported outcomes.
Blinding of outcome assessment (detection bias) Harms	Low risk	Blinded patients reported outcomes.
Incomplete outcome data (attrition bias)	Low risk	5% dropouts
Selective reporting (reporting bias)	Low risk	All outcomes described in methods reported in results. Protocol included.
Other bias	High risk	The difference between empathic and non-empathic

		consultations does not seem especially robust. Empathy included greeting patients in a friendly warm manner and permitting conversation, giving detailed answers to questions, emphasizing comfort and well-being. Non-empathy was "more clinical in nature", less conversation mainly.
Selective recruitment (cluster trials only)		
Contamination		

Wise 2009

Methods	Design: 2x2 factorial trial Recruitment: "Participants were recruited from the clinic patient populations and local advertisements" (p. 438) Setting: American Lung Association Clinical Research Centers (20 medical centres across USA) Inclusion criteria: nonsmokers 15 years or older, a history of physician diagnosed asthma with regular use of asthma medication in the preceding year, postbronchodilator FEV1 of greater than 75% of predicted value, and 1 or more indicators of poor asthma control (Asthma Control Questionnaire[ACQ] score _1.5, use of b-agonists for asthma symptoms _2 times per week, or nocturnal awakening _1 time per week). Exclusion criteria: Participants taking or intolerant of montelukast or participants with other serious health problems
Participants	Total N: 478 Education - High School: 23% / Some college: 43% / College graduate: 35% Employment status - Full-time: 49% / Part-time: 14% / Student: 16% / Not employed outside home: 12% / Retired or disabled: 9%
Interventions	Intervention: Positive message delivered by a practitioner and positive messages embedded in a computer training presentation to increase expectancy of benefit: "I am now going to show you an interactive presentation that explains how the asthma medication that is being used in this research will work to control your asthma. You are being shown this information because you have been assigned to the group of people who receive the more detailed information about how your medicine works and what you can expect to happen when your asthma is in good control", "You are eligible for this study because your asthma needs to be better controlled and because the medicine being used in this research is safe and effective for the control of asthma—to help you breathe better and to enjoy a life that is free from asthma, free from your rescue inhalers, free from emergency doctor or hospital visits, and free to do everything that you want to do without having an asthma attack" Control: Patients received "a neutral script from practitioners and an NIH booklet on controlling asthma. Script was used to introduce the neutral educational presentation "I am now going to show you an interactive presentation that talks about asthma and the asthma medication that is being used in this research study. You are being shown this information because you have been assigned to the group of people who receive information about asthma, asthma care and the study medication." "The active medicine being used in this research is montelukast. You will either receive montelukast or an inactive medicine called a placebo as part of this study. During the study your asthma may or may not get better." "Let's begin the presentation" (p. 444.e3)
Outcomes	Psychological: -Asthma quality of life questionnaire (The Asthma Quality of Life Questionnaire consists of 15 questions with scores ranging from 1 (severely impaired) to 7 (not at all impaired) from baseline over 4 weeks Physical: -Morning peak expiratory flow (PEF) from baseline over 4 weeks after treatment Adverse events: Number of headaches after the completion of trial
Notes	Funding: "American Lung Association and the National Institutes of Health (NIH)"

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer generated random sequence generation
Allocation concealment (selection bias)	Low risk	Reported as concealed 'Participants were assigned randomly to a study group at the

		time of the second visit, with prior concealment of treatment assignment through an online randomization system.'
Blinding of participants and personnel (performance bias)	Unclear risk	Patients blinded Practitioners not blinded
Blinding of outcome assessment (detection bias) Physical outcome	High risk	Outcome assessors not blinded.
Blinding of outcome assessment (detection bias) Psychological outcome	Low risk	Blinded patients assessed outcomes.
Blinding of outcome assessment (detection bias) Harms	High risk	Outcome assessors not blinded.
Incomplete outcome data (attrition bias)	Low risk	A total of 17 patients did not have enough data for follow up (3.5%). p439: "More data on follow-up are shown in Fig 1. Eleven (2%) participants terminated treatment early: 7 because of adverse events (3 in the montelukast and 4 in the placebo groups) and 4 for other reasons. Six participants did not have follow-up data on the primary outcome"
Selective reporting (reporting bias)	Low risk	No protocol, however all outcomes reported and power calculation for main outcome reported
Other bias	Low risk	None obvious
Selective recruitment (cluster trials only)		
Contamination		

eTable 3. Description of interventions within included studies

eTable 3a. Empathy interventions

Study	Description of empathy intervention delivered to participants in the intervention group
Chassany 2006	Practitioners were given "ten recommendations to improve pain management: 1. I show my patient that I believe his/her pain is genuine, 2. I explain the mechanisms of pain and reassure him/her about the causes, 3. I describe the likely evolution of his/her pain, 4. I ask him/her to quantify his/her pain using self-rating scales, 5. I ask him/her to observe and to express his/her pain using these self-rating scales, 6. I explain the need for symptomatic treatment, 7. I explain the rationale for the choice of drug, particularly the effectiveness/safety ratio, 8. I explain the way in which the drug should be taken and the frequency of dosing, 9. I make sure that the patient has said everything he/she wants to, 10. I propose the idea of a therapeutic partnership with my patient."
Fujimori 2014	"The oncologists delivered the empathetic communication based on the SHARE model. SHARE: S, setting up a supportive environment for the interview; H, considering how to deliver the bad news; A, discussing various additional information that patients would like to know; and RE, providing reassurance and addressing patients' emotions with empathic responses."
Kaptchuk 2008	Participants in group 3 (augmented consultation) … received an augmented patient-practitioner relationship that began at the initial visit (45 minutes' duration) and was structured with respect to both content (four primary discussions) and style (five primary points). Content included questions concerning symptoms, how irritable bowel syndrome related to relationships and lifestyle, possible non-gastrointestinal symptoms, and how the patient understood the "cause" and "meaning" of his or her condition. The interviewer incorporated at least five primary behaviours including: a warm, friendly manner; active listening (such as repeating patient's words, asking for clarifications); empathy (such as saying "I can understand how difficult IBS must be for you"); 20 seconds of thoughtful silence while feeling the pulse or pondering the treatment plan; and communication of confidence and positive expectation ("I have had much positive experience treating IBS and look forward to demonstrating that acupuncture is a valuable treatment in this trial"). We based this intervention model on research concerning an optimal patient-practitioner relationship. Only after completing this nine item agenda did the acupuncturist place the placebo needles and leave the participant in a quiet room for 20 minutes. On returning, the practitioner "removed" the placebo needles and exchanged a few words of encouragement. Specific cognitive and behavioural interventions that might be beneficial for irritable bowel syndrome (such as relaxation,cognitive behavioural therapy, or education/counselling) were not allowed.
Little 2015	Physicians were instructed in the KEPe Warm method, which involved: "Knowing: the patient's history, social talk; Encouraging: back channeling (hmm, ah etc); Physically engaging: hand gestures, appropriate contact, slight lean towards the patient; Warm up; Cooler and professional but supportive at the beginning of consultation."
Soltner 2011	"The empathic attitude allowed for an extra 50% of time (5 min for a 10 min consultation) to elicit questions, such as: 'Are you anxious about the forthcoming anaesthesia?' In case of a positive response, a two-way discussion allowed the patient to ask questions and the anaesthesiologist to provide explanations regarding the procedure."
Vangronsveld 2012	"Validation; involved active listening, empathic statements like 'that must have been hard', 'So, you are experiencing a lot of pain', posing follow-up questions, and using appropriate body language (such as looking at the participant, nodding when agreeing and smiling)."
White 2012	"Empathic (EMP) consultations were deemed to be normal pragmatic treatment sessions. Patients were greeted in a friendly, warm manner and were free to enter into conversation with their practitioner, who in turn would willingly do so. Practitioners did their utmost to comply with participants' wishes, providing detailed answers to questions and emphasising patient comfort and well-being."

eTable 3b. Expectation interventions

Study	Description of expectation intervention delivered to participants in the intervention group
Benedetti 2003a	"The open administration of morphine was performed at the bedside by a doctor, who told the patients that the medication was a potent painkiller, according to routine clinical practice. In other words, the patients were informed that their pain was going to subside within a few minutes."
Benedetti 2003b	(Anxiety) [The open and hidden administration of diazepam was delivered using the same procedures as that for pain (above)]
Benedetti 2003c	(Parkinson's) The patients were told that 'motor performance was going to return to normal'
de Craen 2001	"This is a medication that recently became available in the Netherlands. This drug, according to my experience, is very effective and will decrease the pain quickly after taking it."
Dutt-Gupta 2007	"I am going to apply the tourniquet on the arm. As I do this many people find the arm becomes heavy, numb and tingly. This allows the drip to be placed more comfortably."
Goodenough 1997	"We are trying out a new special cream. I am going to put some cream on your arm that might make it (the needle) hurt less."
Kemeny 2007	"Physicians who conducted the enhanced encounters were trained to transmit a positive expectation about the bronchodilator efficacy (for both of the crossover conditions) in reducing methacholine induced symptoms by using specific scripted sentences (e.g., 'You shouldn't have any symptoms'). Enhanced physician encounters also promoted authority (physicians wore a white coat and tie, were introduced as asthma experts, and were trained to speak with authority and conviction) in a supportive environment (encounters were longer, approximately 10 minutes, and included empathetic and respectful behavior, such as shaking hands with the subject)."
Knipschild 2005	"(After ascertaining there was no serious disease) patients were told: 'You probably do not have a serious underlying disease.' 'I will tell you precisely what the matter is with you' (followed by a clear explanation). 'You will be better within a week or so'."
Lauder 1995	"During the recruiting visit, the positive suggestion group was informed of the use of two perioperative antiemetics in order to foster the belief that these drugs do reduce the incidence of emetic symptoms after operation. At induction of anaesthesia the positive suggestion group were again told they would receive an antiemetic i.v. and informed of the expected antiemetic effect, even though they would be under the influence of benzodiazepine premedication." "...patients...were told before operation and on induction of anaesthesia that postoperative emetic sequelae would be greatly reduced by the use of two antiemetic drugs."
Olsson 1989	After a longer consultation and definitive diagnosis, the patient was told they 'would probably feel well after about 24 hours.'
Petersen 2012	"An active medication that has been shown to be effective for some types of pain will be tested." The active medication was given in full view of the patients, and the patients were told: "The agent you have just been given is known to powerfully reduce pain in some patients."
Petersen 2014	"The intervention...was administered openly (as opposed to covertly for the control patients)."
Phillips 2006	Patients received physiological feedback from physicians instructed as follows: -"Validate the patient's experience and explain how the experience is not uncommon relative to the illness/injury. For example, whether patients are experiencing pain or anxiety, explain that what they are experiencing may not be an uncommon symptom considering what they have been enduring with their debilitation and hospitalization. Talk about the general course for recovery and explain what the patient might anticipate in the way of additional or ongoing symptoms, as well as *how he/she can anticipate an abatement of symptoms.*"
Resnick 1996	Participants "received three self-efficacy enhancing interventions: (1) role modelling; (2) verbal persuasion, and (3) physiological feedback."
Rief 2017	"Patients were encouraged to develop personal ideas and images about their future after surgery, including plans about activities and how they will enjoy their life afterwards (outcome expectations). Personally relevant steps and plans for the six months after surgery were recorded for patients. …Patients' control expectations were enhanced by discussing ways how they could manage unpleasant symptoms or sensations, and how they could positively influence the disease course after surgery. An example may further illustrate this intervention. Many patients hoped to again be able to work in their garden after surgery...patients developed specific plans on how they would successfully be able to reassume gardening activities due to their expected increased exercise capacity following surgery: reporting small plants in the early stage, lawn mowing after some time, increasing to more demanding gardening tasks between 3-6 months after surgery."
Ronel 2011	"Mrs./Mr. XYZ, we are now injecting a drug through the catheter which will widen your coronary vessels. This procedure will improve the blood flow in your heart. This drug is very effective and starts its action immediately. It is possible that you might feel some agreeable warmness or formication after only a few seconds."
Suarez-Almazor 2010	"I think this will work for you," "I've had a lot of success with treating knee pain," and "Most of my patients get better."
Szilagyi 2007	Patients were given a variety of positive suggestions: -"The patient is recommended to direct his/her attention to the pleasant feelings or experiences (instead of the painful, uncomfortable ones): 'What was the most comfortable moment of this morning?' " -"The discomfort of endotracheal suctioning can be considerably reduced by appropriate explanation (preferably before performing it): 'While the machine is helping you in breathing, it is usually difficult to cough up all that mucus normally produced in the lungs. You know, the usual way of cleaning the lungs is

	that we cough a bit (demonstrate), and that is it. While you are ventilated, we need to clean your lung from the outside.' 'This will be done by inserting a thin soft tube through that bigger tube that is already in your throat. You will feel it only when it is deep down, deep enough to reach the place it will clear up. Please indicate by a small cough when it is down there! (reframing the reflexive coughing). With the help of this, you can transfer the phlegm from the more distant parts of your lung to the end of the tube so we can remove it easily.' Before the first suctioning it is especially important to explain that the whole procedure is very short, 'No longer than a big, deep breath...' and we can focus the patient's attention on the immediate good feelings of the clear breathing following the procedure."
Thomas 1987	Participants were given a clear diagnosis and positive messages about their recovery.
Varelmann 2010	"We are going to inject the local anesthetic that will numb the area where we are going to do the epidural/spinal anesthesia and you will be comfortable during the procedure."
Wang 2008	"The PCA pump was great in treating pain, especially for people who like you underwent abdominal surgeries", "You took a correct decision on using a PCA pump for your postoperative pain", and "The PCA pump was very effective in removing the postoperative pain affliction."
Wise 2009	"SINGULAIR is a new medication that can be prescribed by your doctor to prevent asthma symptoms and make you feel better...With SINGULAIR and good asthma control, you should expect to: sleep through the night without symptoms, pursue physical activity, miss less time from work or school, avoid ER visits, minimize use of rescue inhalers".

eTAble 4. Summary of findings

eTable 4a. Empathy summary of findings table

Empathy compared to control in healthcare consultations

Patient or population: Healthcare consultations
Setting: Primary health centre, hospital, university hospital, day-care surgery unit, acupuncture practice
Intervention: Empathy
Comparison: Control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with control	Risk with Empathy				
New Outcome	The mean new Outcome was 0	SMD 0.18 lower (0.32 lower to 0.03 lower)	-	2169 (6 RCTs)	⊕⊕ ⊖⊖ LOW 1 2	

***The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).**

CI: Confidence interval; RR: Risk ratio; OR: Odds ratio;

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Footnotes
1 High risk of selective reporting in one study and high risk of other bias in one study
2 Variation in intervention methods and diverse study populations

eTable 4b. Expectations summary of findings table

Expectations compared to control in healthcare consultations

Patient or population: Healthcare consultations
Setting: University hospitals, general hospitals, specialist hospitals, primary healthcare centres, day-care surgery unit, acupuncture practices
Intervention: Expectations
Comparison: Control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)
	Risk with control	Risk with Expectations			
Physical outcomes	The mean new Outcome - Physical outcomes was 0	SMD 0.18 lower (0.31 lower to 0.05 lower)	-	1790 (11 RCTs)	⊕⊕⊕ ⊖ MODERATE [2 3]
Psychological outcomes	The mean new Outcome - Psychological outcomes was 0	SMD 0.43 lower (0.65 lower to 0.21 lower)	-	2014 (18 RCTs)	⊕⊕ ⊖⊖ LOW [2 3 4]

***The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).**

CI: Confidence interval; RR: Risk ratio; OR: Odds ratio;

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Footnotes
[1] Moderate heterogeneity
[2] Variation in intervention methods and diverse study populations
[3] Unclear risk of bias in several studies
[4] Substantial heterogeneity

eTable 4c. Harms summary of findings table

Harms compared to placebo in healthcare consultations

Patient or population: Healthcare consultations
Setting: University hospitals, general hospitals, specialist hospitals, primary healthcare centres, day-care surgery unit,

acupuncture practices Intervention: Empathy or Expectations Comparison: Placebo						
Outcomes	**Anticipated absolute effects* (95% CI)**		**Relative effect (95% CI)**	**№ of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Risk with control	**Risk with Harms**				
Empathy	Study population		OR 1.00 (0.40 to 2.48)	1214 (2 RCTs)	⊕⊖⊖⊖ VERY LOW [4 5 6]	
	99 per 1,000	99 per 1,000 (42 to 214)				
Expectations	Study population		OR 1.05 (0.60 to 1.85)	1492 (8 RCTs)	⊕⊖⊖⊖ VERY LOW [2 3 4 7]	
	403 per 1,000	415 per 1,000 (289 to 556)				
***The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).** **CI: Confidence interval; RR: Risk ratio; OR: Odds ratio;**						
GRADE Working Group grades of evidence **High quality: We are very confident that the true effect lies close to that of the estimate of the effect** **Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different** **Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect** **Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect**						

Footnotes

[1] High risk of detection bias in two studies and high risk of other bias in two studies

[2] Substantial heterogeneity

[3] Variation in intervention methods and diverse study populations

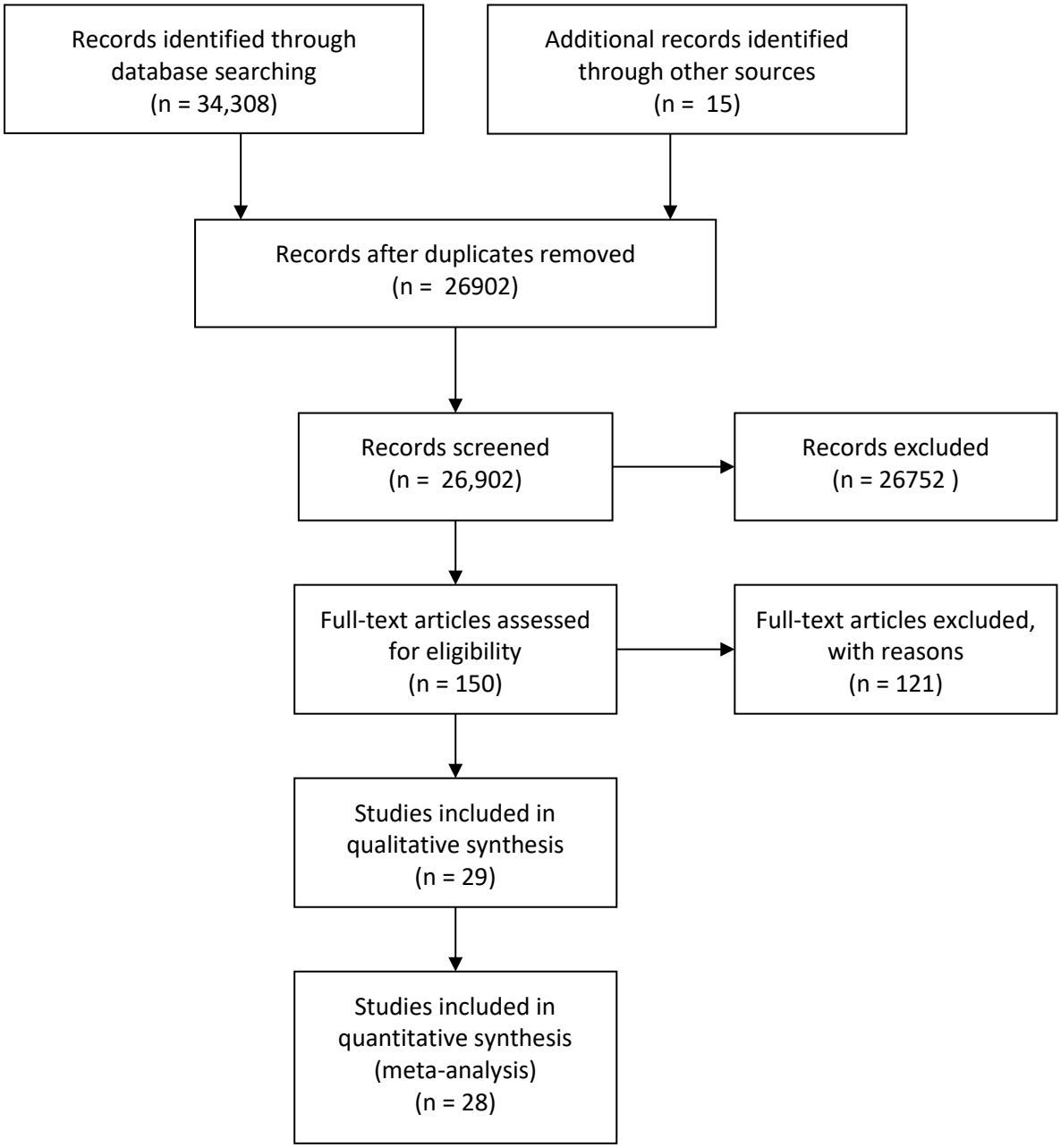
[4] Wide confidence interval

[5] High risk of other bias in one study

[6] Moderate heterogeneity

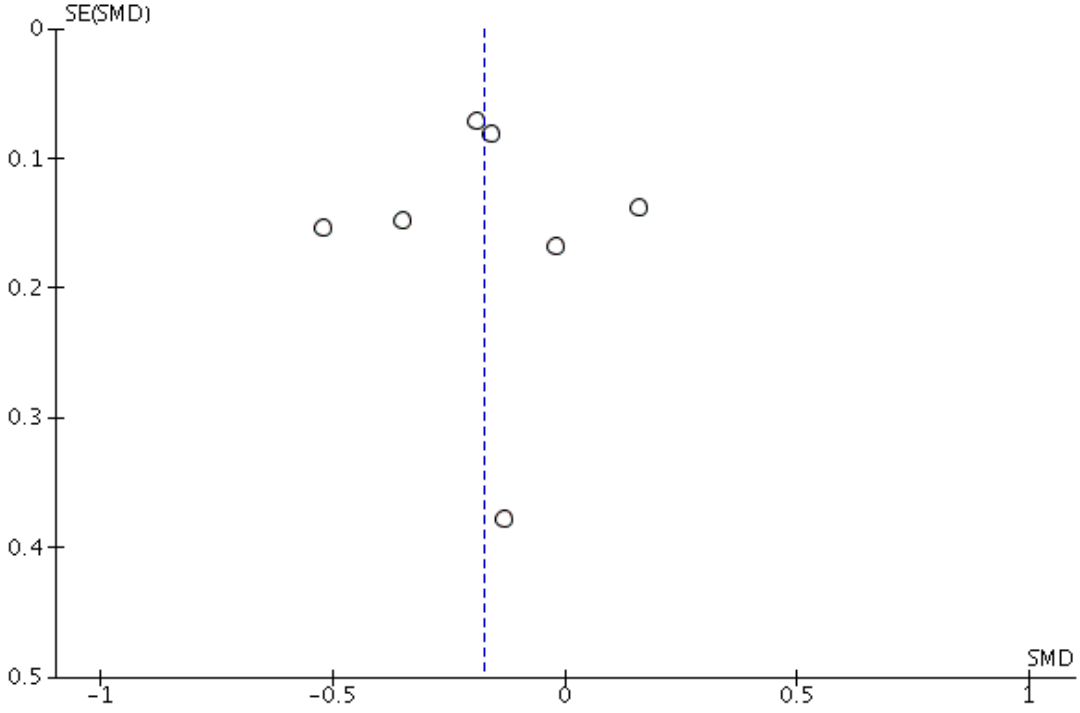
[7] High risk of detection bias in two studies and high of other bias in one study

eFigure 1. PRISMA diagram

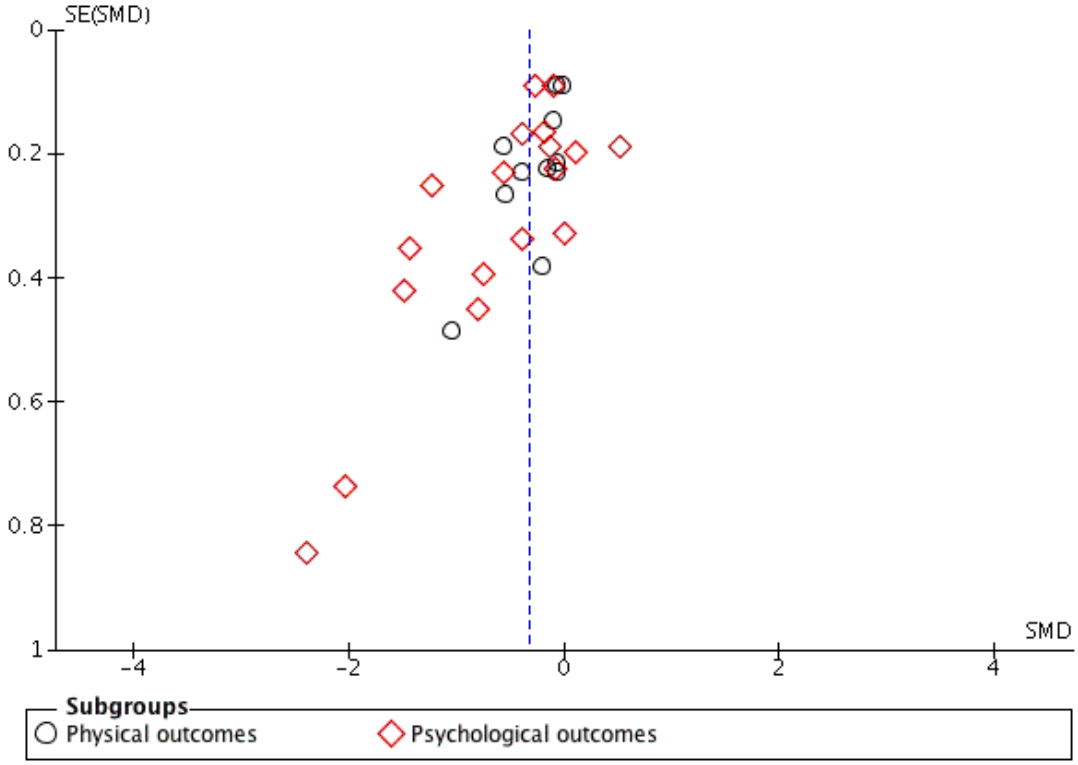


eFigure 2. Funnel Plots

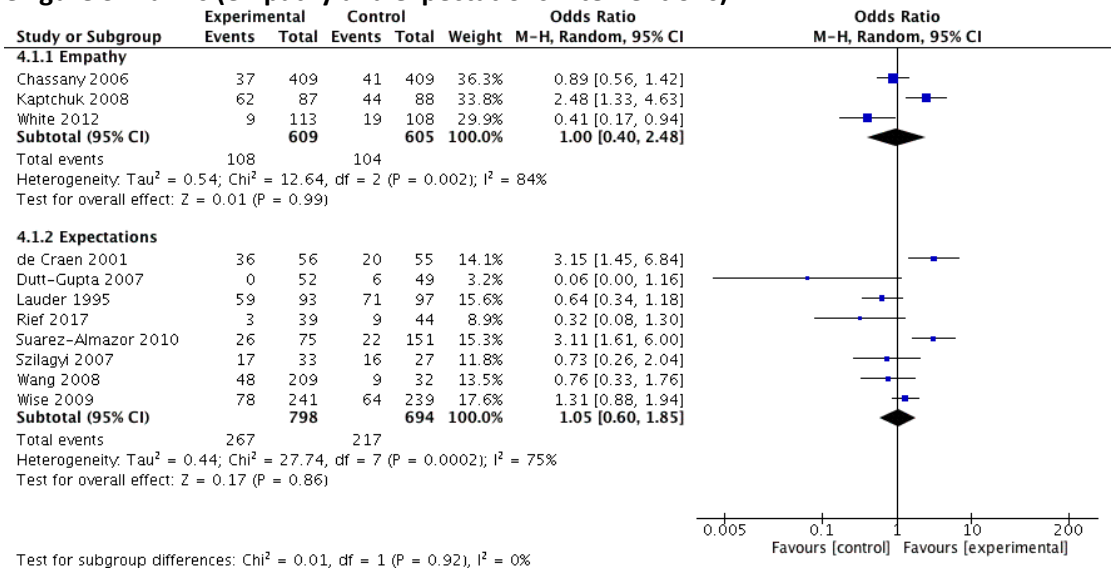
eFigure 2.a. Funnel Plot: Empathy Interventions



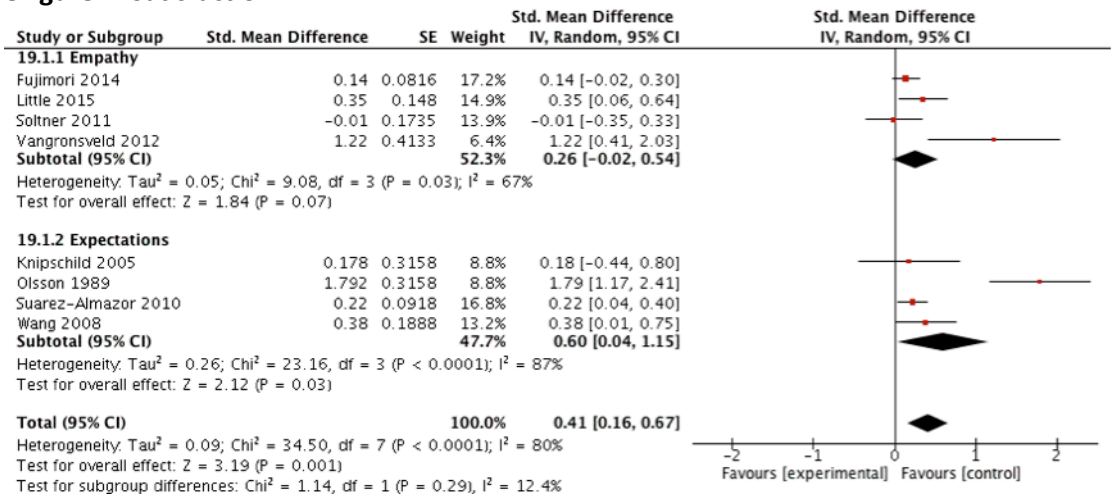
eFigure 2.b. Funnel Plot: Expectations Interventions



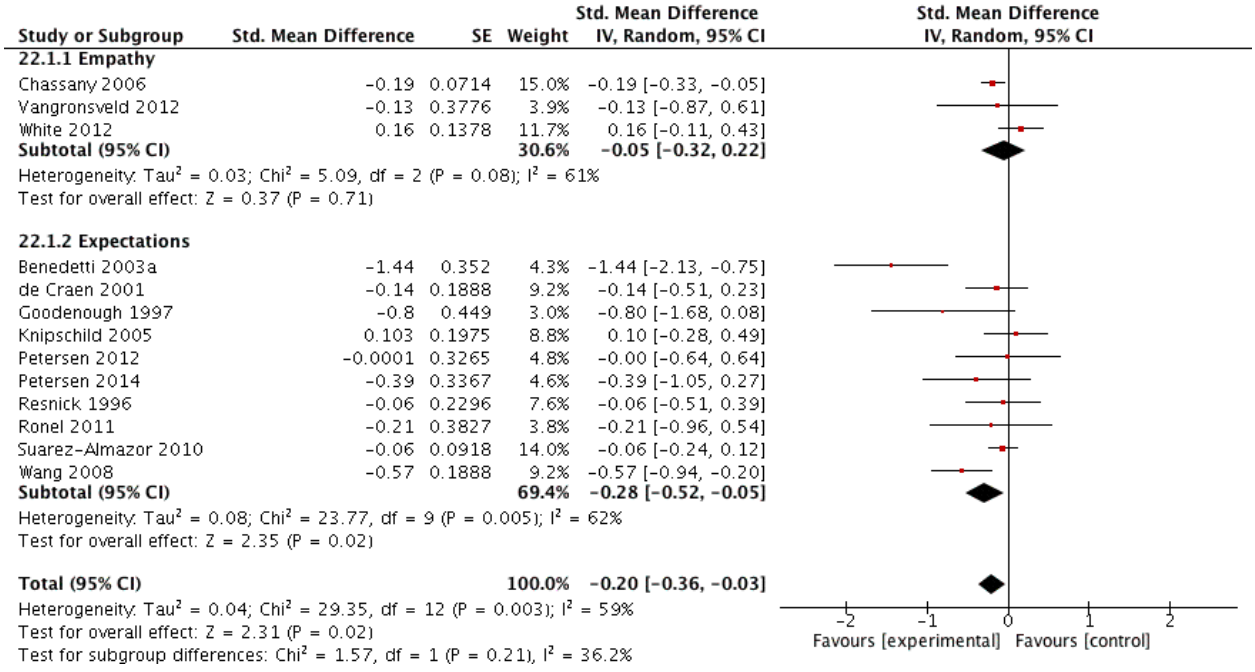
eFigure 3. Harms (empathy and expectations interventions)



eFigure 4. Satisfaction

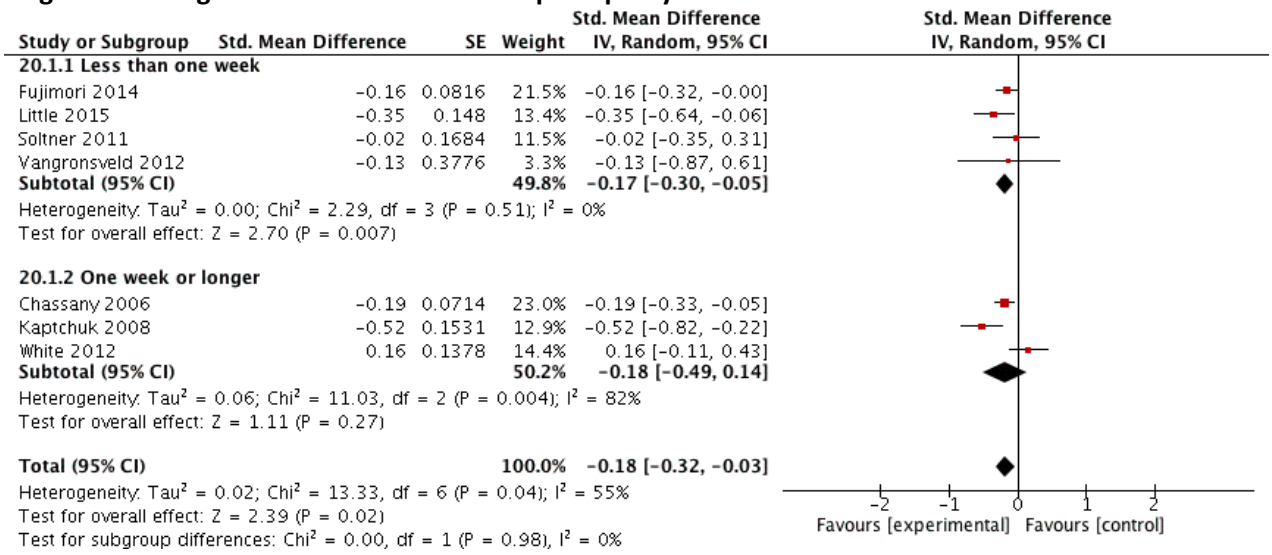


eFigure 5. Pain

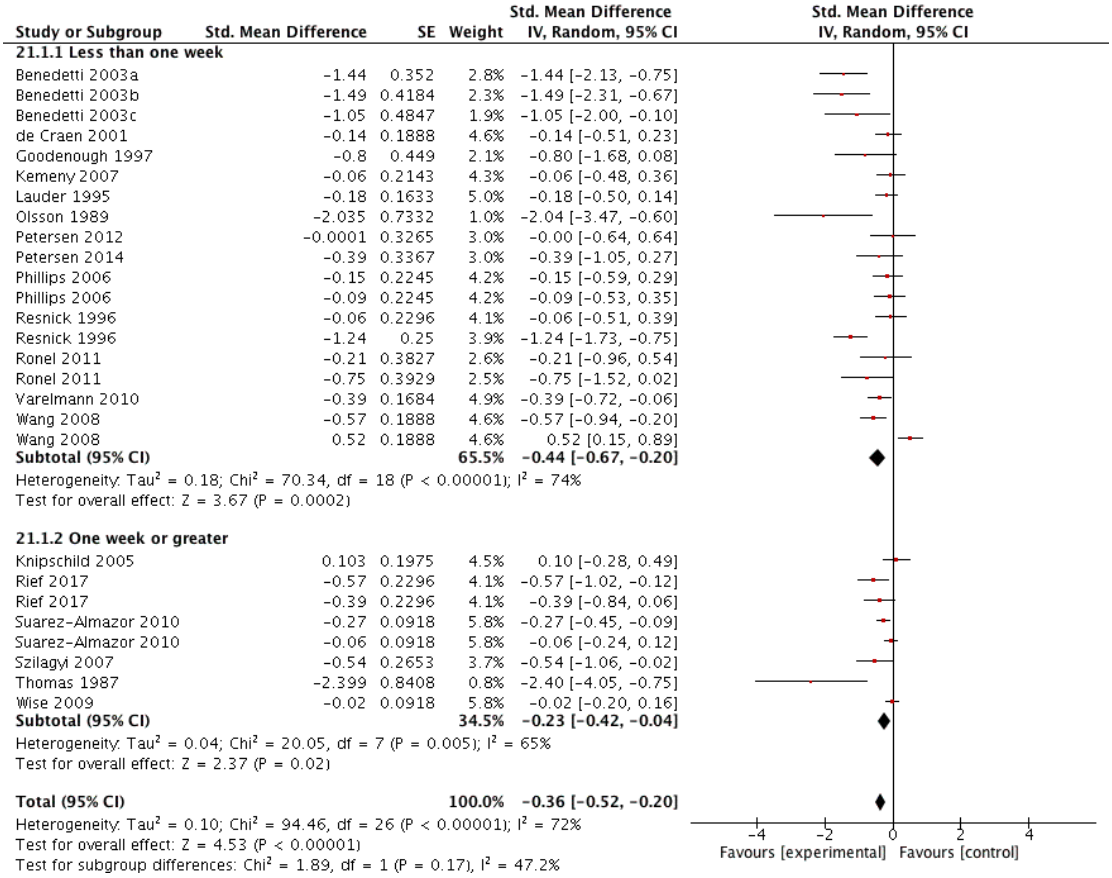


eFigure 6. Longer versus shorter follow up

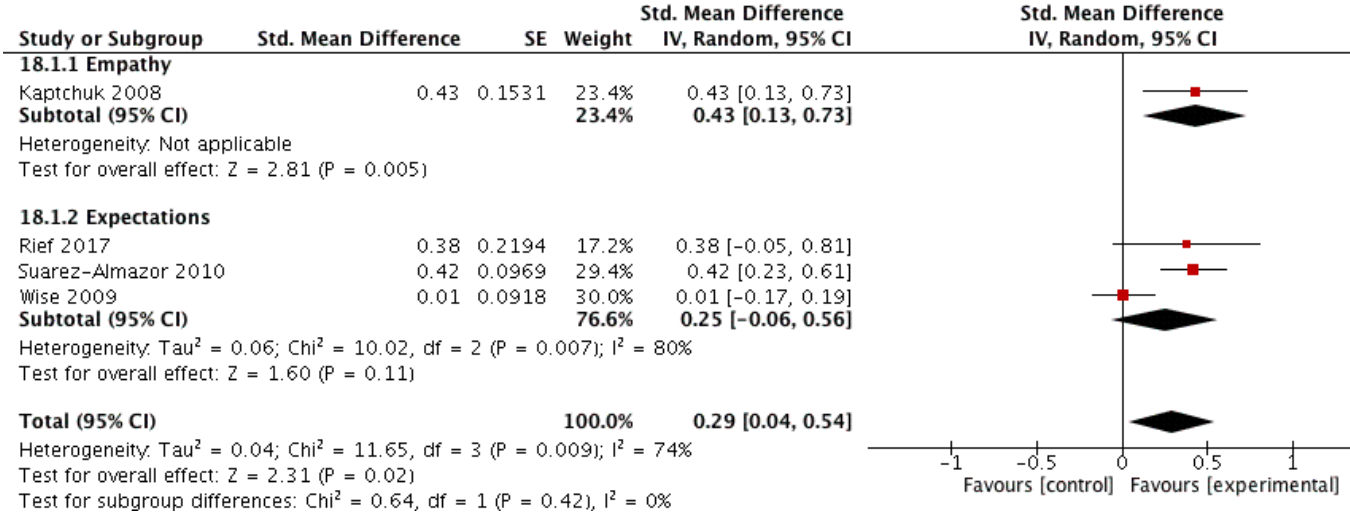
eFigure 6.a. Longer Versus Shorter Follow Up: Empathy Interventions



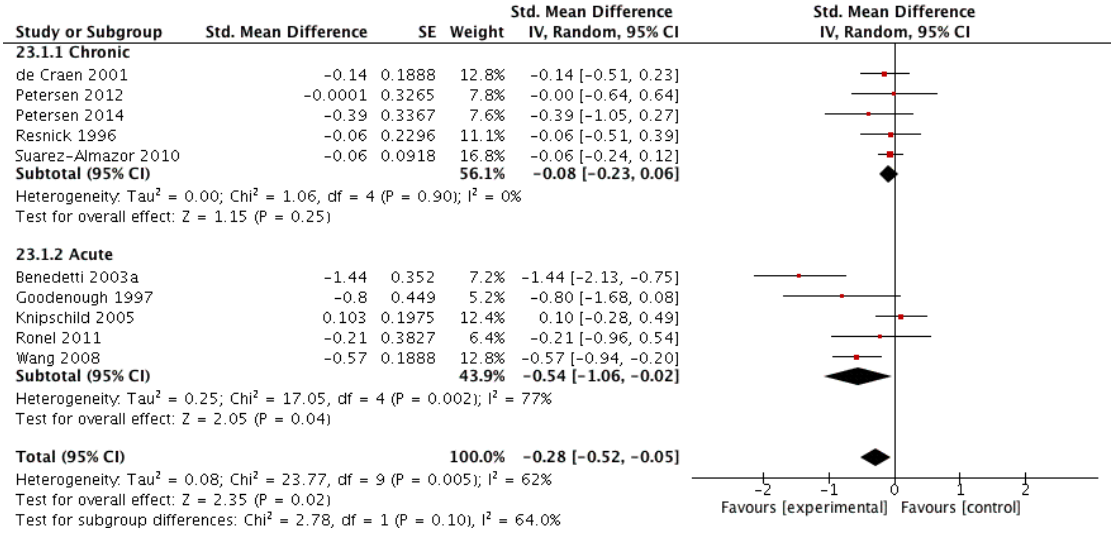
eFigure 6.b. Longer Versus Shorter Follow Up: Expectations interventions



eFigure 8. Quality of Life

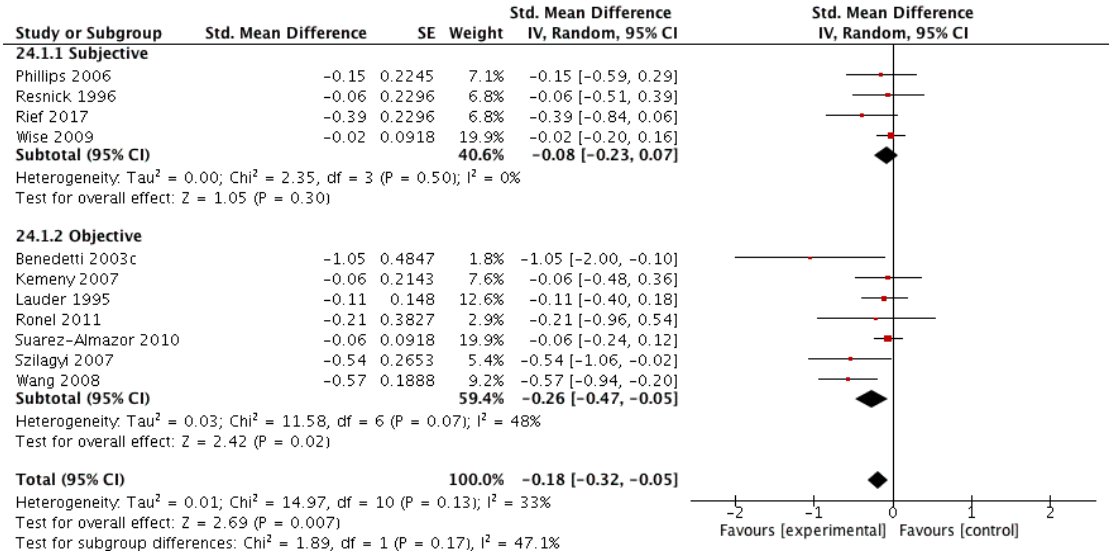


eFigure 9. Chronic Versus Acute Pain in expectations interventions



Study or Subgroup	Std. Mean Difference	SE	Weight	Std. Mean Difference IV, Random, 95% CI
23.1.1 Chronic				
de Craen 2001	-0.14	0.1888	12.8%	-0.14 [-0.51, 0.23]
Petersen 2012	-0.0001	0.3265	7.8%	-0.00 [-0.64, 0.64]
Petersen 2014	-0.39	0.3367	7.6%	-0.39 [-1.05, 0.27]
Resnick 1996	-0.06	0.2296	11.1%	-0.06 [-0.51, 0.39]
Suarez-Almazor 2010	-0.06	0.0918	16.8%	-0.06 [-0.24, 0.12]
Subtotal (95% CI)			**56.1%**	**-0.08 [-0.23, 0.06]**
Heterogeneity: Tau² = 0.00; Chi² = 1.06, df = 4 (P = 0.90); I² = 0%				
Test for overall effect: Z = 1.15 (P = 0.25)				
23.1.2 Acute				
Benedetti 2003a	-1.44	0.352	7.2%	-1.44 [-2.13, -0.75]
Goodenough 1997	-0.8	0.449	5.2%	-0.80 [-1.68, 0.08]
Knipschild 2005	0.103	0.1975	12.4%	0.10 [-0.28, 0.49]
Ronel 2011	-0.21	0.3827	6.4%	-0.21 [-0.96, 0.54]
Wang 2008	-0.57	0.1888	12.8%	-0.57 [-0.94, -0.20]
Subtotal (95% CI)			**43.9%**	**-0.54 [-1.06, -0.02]**
Heterogeneity: Tau² = 0.25; Chi² = 17.05, df = 4 (P = 0.002); I² = 77%				
Test for overall effect: Z = 2.05 (P = 0.04)				
Total (95% CI)			**100.0%**	**-0.28 [-0.52, -0.05]**
Heterogeneity: Tau² = 0.08; Chi² = 23.77, df = 9 (P = 0.005); I² = 62%				
Test for overall effect: Z = 2.35 (P = 0.02)				
Test for subgroup differences: Chi² = 2.78, df = 1 (P = 0.10), I² = 64.0%				

eFigure 10. Subjective versus Objective outcomes (in expectations studies with physical outcomes)



Study or Subgroup	Std. Mean Difference	SE	Weight	Std. Mean Difference IV, Random, 95% CI
24.1.1 Subjective				
Phillips 2006	-0.15	0.2245	7.1%	-0.15 [-0.59, 0.29]
Resnick 1996	-0.06	0.2296	6.8%	-0.06 [-0.51, 0.39]
Rief 2017	-0.39	0.2296	6.8%	-0.39 [-0.84, 0.06]
Wise 2009	-0.02	0.0918	19.9%	-0.02 [-0.20, 0.16]
Subtotal (95% CI)			**40.6%**	**-0.08 [-0.23, 0.07]**
Heterogeneity: Tau² = 0.00; Chi² = 2.35, df = 3 (P = 0.50); I² = 0%				
Test for overall effect: Z = 1.05 (P = 0.30)				
24.1.2 Objective				
Benedetti 2003c	-1.05	0.4847	1.8%	-1.05 [-2.00, -0.10]
Kemeny 2007	-0.06	0.2143	7.6%	-0.06 [-0.48, 0.36]
Lauder 1995	-0.11	0.148	12.6%	-0.11 [-0.40, 0.18]
Ronel 2011	-0.21	0.3827	2.9%	-0.21 [-0.96, 0.54]
Suarez-Almazor 2010	-0.06	0.0918	19.9%	-0.06 [-0.24, 0.12]
Szilagyi 2007	-0.54	0.2653	5.4%	-0.54 [-1.06, -0.02]
Wang 2008	-0.57	0.1888	9.2%	-0.57 [-0.94, -0.20]
Subtotal (95% CI)			**59.4%**	**-0.26 [-0.47, -0.05]**
Heterogeneity: Tau² = 0.03; Chi² = 11.58, df = 6 (P = 0.07); I² = 48%				
Test for overall effect: Z = 2.42 (P = 0.02)				
Total (95% CI)			**100.0%**	**-0.18 [-0.32, -0.05]**
Heterogeneity: Tau² = 0.01; Chi² = 14.97, df = 10 (P = 0.13); I² = 33%				
Test for overall effect: Z = 2.69 (P = 0.007)				
Test for subgroup differences: Chi² = 1.89, df = 1 (P = 0.17), I² = 47.1%				