Harnessing placebo effects by targeting expectancies

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CHAPTER 3

RELIEVING PATIENTS' PAIN WITH EXPECTATION INTERVENTIONS: A META-ANALYSIS

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Abstract

Patients' expectations are important predictors of the outcome of analgesic treatments, as demonstrated predominantly in research on placebo effects. Three commonly investigated interventions that have been found to induce expectations (verbal suggestion, conditioning, and mental imagery) entail promising, brief, and easy-to-implement adjunctive procedures for optimizing the effectiveness of analgesic treatments. However, evidence for their efficacy stems mostly from research on experimentally evoked pain in healthy samples, and these findings might not be directly transferable to clinical populations. The current meta-analysis investigated the effects of these expectation inductions on patients' pain relief. Five bibliographic databases were systematically searched for studies that assessed the effects of brief verbal suggestion, conditioning, or imagery interventions on pain in clinical populations, with patients experiencing experimental, acute procedural, or chronic pain, compared with no treatment or control treatment. Of the 15,955 studies retrieved, 30 met the inclusion criteria, of which 27 provided sufficient data for quantitative analyses. Overall a medium-sized effect of the interventions on patients' pain relief was observed (Hedges' g = 0.61, I^2 = 73%), with varying effects of verbal suggestion (k = 18, g = 0.75), conditioning (always paired with verbal suggestion, k = 3, g = 0.65), and imagery (k = 6, g = 0.27). Subset analyses indicated medium to large effects on experimental and acute procedural pain, and small effects on chronic pain. In conclusion, patients' pain can be relieved with expectation interventions; particularly, verbal suggestion for acute procedural pain was found to be effective.

Introduction

Expectations are important predictors of the outcome of analgesic treatments [62,113,206,276]. As posed in response expectancy theory [158,159], expectations of pain relief can directly elicit and/or enhance actual pain relief. The importance of expectations has particularly become clear in research on placebo effects, of which expectancy is believed to be a core mechanism [23,158,159,236]. Placebos, such as sugar pills and saline injections, have repeatedly been found to provide pain relief, with effects at both subjective [298,299] and neurobiological levels [14,256]. These and other findings suggest that interventions that induce expectations of pain relief, i.e., analgesic expectation inductions, are promising for optimizing the effectiveness of standard analgesic treatments in clinical practice. However, evidence for the efficacy of expectation inductions stems mostly from laboratory research using experimental pain in samples of healthy participants, whereas research in clinical samples (e.g., patients with chronic back pain or postoperative pain) is limited. Although experimentally evoked pain in healthy samples is generally considered a good model for clinical pain, these findings might not be directly transferable to clinical populations. On the one hand, patients with pain, especially chronic pain, have a more extensive and complex history of pain and, often unsuccessful, pain treatment. This might make them more resistant to expectation interventions [95,156]. On the other hand, patients are likely to have a higher desire for pain relief, possibly making them more sensitive to expectation interventions [99,144,237,300].

Three common, brief, and easy-to-implement interventions that have been found to induce and/or enhance expectations are promising for implementation in clinical practice: verbal suggestion, conditioning, and imagery. Verbal suggestion entails instructions regarding treatment outcomes given by, for example, a health care provider. Verbal suggestions such as saying that a placebo or active treatment is an effective analgesic, can induce expectations of pain relief and produce corresponding experiences of pain relief [15,262,266]. Conditioning entails the pairing of a neutral stimulus with an unconditioned stimulus that triggers a certain response. For example, pairing a placebo treatment with reduced pain stimulation can produce expected and experienced pain relief when merely receiving the placebo treatment [4,60,160,161,208,280], especially when conditioning is paired with a verbal suggestion [20,161,181]. Mental imagery of a future event or desired outcome entails actively generating a multisensory cognitive representation of an event and often involves relatively implicit suggestions [116,133]. For example, imagining an optimal future self or health can increase general positive expectations (i.e., optimism) [202,220,224] and correspondingly reduce pain and medical care utilization [119,157]. Thus, inducing

expectations of pain relief, through verbal suggestion, conditioning, and imagery, can reduce pain. However, the comparative effectiveness of these expectation inductions, particularly in clinical populations, is mostly unclear.

The primary aim of the current meta-analysis was to investigate the effects of brief and easy-to-implement expectation interventions for relieving patients' pain. Specifically, the effects of verbal suggestion, conditioning, and imagery on pain relief in clinical populations are investigated. Furthermore, we compared the effects on experimental versus clinical pain, and acute procedural (pain during or directly following a medical procedure, e.g., postoperative pain) versus chronic (long-lasting pain associated with a medical condition, e.g., chronic back pain or recurrent migraine) clinical pain. Additional outcome analyses explored the effects on expected pain, affective pain, and anxiety.

Methods

Protocol and registration

The systematic review and meta-analysis were performed in accordance with the PRISMA Statement [204] and the recommendations of the Cochrane Collaboration [127]. The study protocol was registered in the international prospective register of systematic reviews Prospero (CRD42013006575).

Information sources and search strategy

The electronic bibliographic databases PubMed, PsycINFO, EMBASE, Cochrane CENTRAL, and the Cochrane Methodology Register were searched from inception until June 19, 2015, using search terms describing the three expectation inductions and pain (see Supplementary section 3.1 for the full search strategy). The search was restricted to humans when possible in the databases. In addition, the reference lists of eligible studies and studies that cited the eligible studies were searched for relevant articles.

Eligibility criteria

Studies were included if they assessed the effect of one of the three expectation inductions (verbal suggestion, conditioning, or imagery) on pain relief in a clinical sample (i.e., adult patients with a somatic condition and/or undergoing medical treatment). The review was restricted to studies that compared a brief intervention (verbal suggestion, conditioning, or imagery; max. 1 day) that was believed to induce expectations of pain relief to a control condition consisting of no treatment/treatment as usual, or a control

treatment that was believed to not induce expectations of pain relief. If the studied intervention consisted of multiple components (e.g., both imagery and relaxation), the expectation induction had to be the main component of the intervention (i.e., duration > 50% of intervention time). Studies in which uncertain expectations of pain relief (e.g., 50/50 chance of receiving active or inactive treatment like during blinded treatment administration) were induced in either condition were excluded. Experimental (i.e., experimentally evoked pain), acute procedural (i.e., pain during or directly following a medical procedure), or chronic (i.e., long-lasting pain associated with a medical condition) pain had to be assessed with a self-report rating scale that provided numerical values of experienced pain intensity (e.g., visual analogue scale). Only original research results that were presented in full-length English language empirical articles were included (i.e., not abstracts, case studies, reviews, and reanalyses).

Study selection

Titles and abstracts of articles retrieved using the search strategy were screened by one of two review authors (K.J.P. or S.M.K.) to identify studies that potentially met the eligibility criteria outlined above. The full texts of these articles were retrieved (online, through Dutch academic libraries, or through study authors) and assessed for eligibility (K.J.P. or S.M.K.). Full texts that were considered to be eligible for inclusion or about which doubts existed were also assessed for eligibility by a second review author (K.J.P. or S.M.K.). Any remaining doubts were resolved through discussion with other review authors (A.W.M.E., A.I.M.v.L., and L.V.).

Data extraction

A standardized form was independently used by two review authors (K.J.P. and S.M.K.) to extract data regarding the following from the included studies: expectation induction, control condition, study design, study population, type of pain, and pain outcome measure. Statistical data for meta-analysis (i.e., sample size, mean, and standard deviation (SD) of all post-intervention pain measurements and secondary outcomes, or alternative values) were extracted by one review author (K.J.P.) and accuracy was checked by a second review author (S.M.K). If it was not possible to extract sufficient data for the calculation of post-intervention effect sizes for the primary and secondary outcomes, the study authors were contacted. When sufficient data could not be acquired, alternative statistics (e.g., standard error [SE], confidence interval [CI], *t* or *F* value, *p* value, or mean change scores) were inspected. When appropriate alternative statistics were available, effect sizes were calculated using these, otherwise the study was excluded from quantitative analysis (Table 3.1).

Risk of bias assessment

Risk of bias within each of the included studies was assessed independently by two review authors (K.J.P. and S.M.K.) with the Cochrane risk of bias tool, version 5.1.0 [127]. The following items were evaluated at study level: 'Random sequence generation' (selection bias), 'Allocation concealment' (selection bias), 'Incomplete outcome data' (attrition bias), 'Selective outcome reporting' (reporting bias), and 'Other bias' (focused on differences in sample characteristics - sex, age, and baseline pain). A priori, it was decided not to judge the items 'Blinding of participants and personnel' (performance bias) and 'Blinding of outcome assessors' (detection bias), because it is not possible to blind participants to the expectation inductions or to blind outcome assessors for self-reported outcomes. Disagreements between the authors regarding judgment of the risk of bias were resolved by discussion, with involvement of a third review author (A.I.M.v.L.) where necessary.

Considerations regarding data selection

The following choices were made regarding the selection of intervention and control conditions. When a study contained multiple relevant intervention or control conditions, data were selected from the intervention most directly aimed at pain reduction [313], the comparison of the most active expectation induction (e.g., the strongest verbal suggestion) versus the most passive control condition (e.g., no treatment) [112,122,129,148,166,180,227,313], or the control condition conducted before rather than after the intervention [235]. In two studies the control condition involving hidden administration of active medication was chosen rather than a no-treatment control condition, to avoid confusion with the effect of the active medication [226,227]. With regard to the study design, between-subjects comparisons were included in the quantitative analyses if possible [52,166], because the majority of studies used a between-subjects design. With regard to the outcome measures, in the four studies that included several pain measures [52,226,227,300], the data of the most clinically relevant type of pain were included (e.g., evoked visceral pain rather than evoked heat pain in patients with irritable bowel syndrome). See Supplementary Table 3.1 for an overview of the additional conditions and pain measures used in each study.

Data-analysis

All analyses were conducted by the first reviewer (K.J.P.) and checked by a second reviewer (S.M.K.), using Comprehensive Meta-Analysis software, version 3.3.070 (Biostat, Englewood, CO, USA). The effect size (Hedges' *g*) was calculated as the mean post-intervention pain intensity score for the control condition minus the mean post-

intervention pain intensity score for the intervention condition, divided by the pooled SD, and weighted according to the number of subjects in each study [127]. When pain was assessed at multiple post-intervention time points, the average effect across these time points was calculated. Positive values for *g* indicate lower post-intervention pain ratings (or secondary outcome values, e.g., expected pain) in the intervention condition than in the control condition. A value around 0.2 to 0.3 was considered a small effect, a value around 0.5 a medium effect, and a value of 0.8 or larger a large effect [55]. The pooled effects were analyzed using a random-effects model, given the variability in research characteristics (e.g., different expectation inductions and types of pain). The presence and magnitude of heterogeneity were assessed with the I^2 statistic, as well as by visual inspection of the forest plot. I^2 values of 25%, 50%, and 75% can be considered to indicate low, moderate, and high degrees of heterogeneity, respectively [128]. For within-subjects comparisons, the intervention-control condition correlation coefficient could not be derived from the included studies, therefore an *r* of 0.5 was imputed. For subset analyses, τ^2 was not pooled because we did not expect the between-study variance to be the same for all subsets. The effect sizes in the subsets were compared descriptively rather than with statistical tests, given the small number of studies in most subsets (i.e., insufficient statistical power). Meta-analysis was only conducted when the data of at least three studies were available.

The pooled effects of all three expectation inductions (verbal suggestion, conditioning, and imagery) were analyzed together and separately. Planned subset analyses compared the effects on different types of pain (experimental vs. clinical pain, and acute procedural vs. chronic clinical pain), which also served as a proxy for differential effects depending on the patient type (patients with somatic condition vs. those undergoing medical treatment). Post hoc subset analyses assessed the influence of the route of treatment administration (oral, injection, cutaneous, and other) and compared studies using active (e.g., analgesic medication) versus placebo (e.g., saline injection) treatments. Additional outcome analyses explored the effects of the expectation inductions on expected pain, affective pain, and anxiety. Sensitivity analyses assessed the stability of the overall effect size in relation to: 1) the risk of bias within studies (by removing studies for which at least one item was judged to involve a high risk of bias); 2) publication bias (inspection of funnel plot and trim and fill method); 3) the comparison with a control condition with or without a control treatment, as well as the inclusion of control treatments that might have induced some expectations; 4) the inclusion of both between-subjects and within-subjects comparisons; 5) the imputed intervention-control condition correlation coefficient (imputed r = 0.5, vs. $r = 0.1$ or $r = 0.9$); 6) the inclusion of post-intervention rather than change scores.

Results

Study selection

See Figure 3.1 for the flow chart of the selection process. Through the initial search in the databases 15,952 records were retrieved, three additional relevant studies were identified through other sources. Of these, 3,678 records were duplicates, 11,835 records were excluded on the basis of screening of the titles/abstracts, and the full text of 15 studies that were considered possibly relevant was not available. The full texts of 427 records were retrieved. Of the 62 full texts that were initially selected, 32 studies were excluded for various reasons (e.g., induction of negative expectations or no control condition). In total, 30 studies were included in the qualitative synthesis. For three studies a measure of variance (e.g., SD) was missing for the primary outcome (pain intensity) [129,178,181]. Sufficient data of 27 studies were available for meta-analysis.

Study characteristics

The characteristics of all included studies are reported in Table 3.1. The majority of the studies that could be included in the quantitative meta-analysis assessed the analgesic effects of verbal suggestions (67%, k = 18) such as "The agent you have just been given is known to powerfully reduce pain in some patients" [226,227,235,301] and *"This drug is a local anesthetic and we use it to reduce the pain of the next stimulus. It takes a couple of minutes to work. Rest assured, the next stimulus will be less painful"* [230]. Three studies assessed the effects of a conditioning procedure on pain, which was always combined with verbal suggestion of analgesic effects. Six studies assessed the effects of imagery, with images of pain reduction in four studies (e.g., by imagining numbness). The images used in the other two studies were not specified. Regarding the presence of multiple intervention components, we note that the intervention in four of the imagery studies incorporated relaxation instructions, to maximally engage participants in imagery. In no other studies there were indications of components of the interventions that could not be qualified as an expectation induction in themselves. Because verbal suggestions are inherently incorporated in almost all types of psychological interventions, suggestions were probably included in the studied imagery interventions. In total, 1,256 patients participated in the selected groups of the studies. The samples consisted of patients with various pathologies, e.g., patients with irritable bowel syndrome (k = 5) and patients experiencing long-lasting pain such as chronic back pain or recurrent migraine (k = 8). For most studies, measurements of clinical pain could be included: acute procedural pain (e.g., postoperative pain) was assessed in 12 studies, and chronic pain (e.g., chronic back pain, including cancer pain) in six studies. Measurements of experimentally evoked pain (e.g., electrical pain stimuli) were

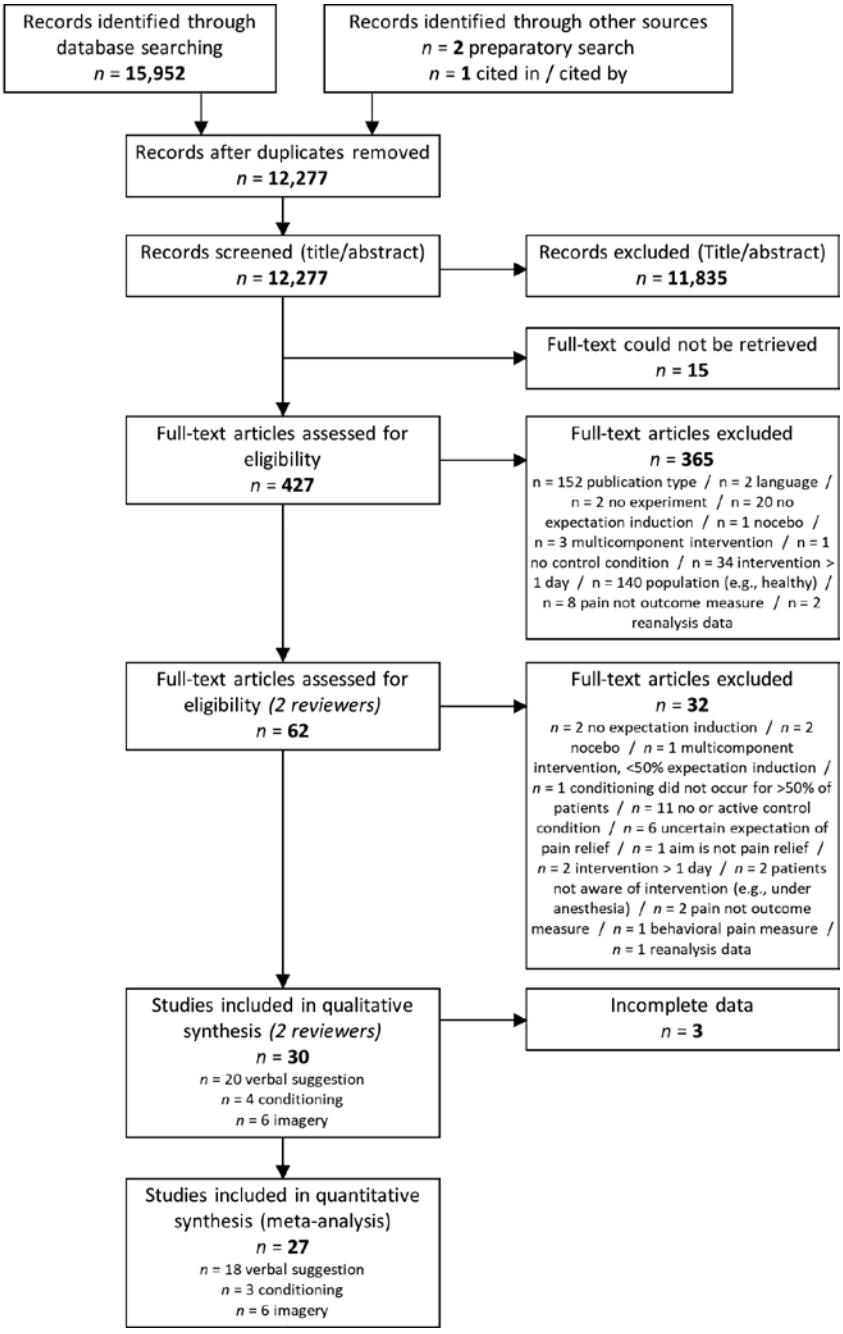

Figure 3.1. PRISMA flow diagram showing study selection process, including reasons for exclusion

Note. Selection was conducted by one reviewer unless otherwise stated.

Table 3.1. Study characteristics of all studies included in the quantitative and qualitative meta-analysis

Study	Intervention			Sample		Outcome	
Author	**Intervention (route of administration**	**Control condition**	**Compa-rison**	***N***	**Patient population**	**Pain type**	**Timing of pain measurement**
Verbal suggestion							
Amanzio et al. (2001) [5]	Verbal suggestion referring to active treatment [a] (injection)	Control treatment	Between subjects	73 / 69	Patients undergoing thoracic surgery	Acute procedural pain (postoperative pain)	15, 30, 45, and 60 min after intervention [d]
Benedetti et al. (1995) [25]	Verbal suggestion referring to placebo treatment [a] (injection)	Control treatment	Between subjects	13 / 11	Patients undergoing thoracic surgery	Acute procedural pain (postoperative pain)	15 and 60 min after intervention [f]
Benedetti et al. (2003) [30]	Verbal suggestion referring to active treatment [a] (injection)	Control treatment	Between subjects	21 / 21	Patients undergoing thoracic surgery	Acute procedural pain (postoperative pain)	30 and 60 min after intervention [d]
Benedetti et al. (2006) [28]	Verbal suggestion referring to active treatment [a] (cutaneous)	Control treatment	Within subjects	28	Patients with Alzheimer's disease	Acute procedural pain (pain after venipuncture)	15 min after intervention [g]
Bialosky et al. (2014) [35]	Verbal suggestion referring to placebo treatment (other)	No treatment	Between subjects	27 / 28	Patients with low back pain	Experimental pain (mechanical pain)	1 x post-intervention
Charron et al. (2006) [52]	Verbal suggestion referring to placebo treatment (injection)	Control treatment	Between subjects [c]	8 / 8	Patients with chronic low back pain	Chronic pain (low back pain)	every 2 min for 20 min after intervention [e,f]
De Craen et al. (2001) [70]	Verbal suggestion referring to placebo or active treatment (oral)	Control treatment	Between subjects	55 / 56	Patients with chronic pain	Chronic pain (chronic pain)	0.5, 1, 2, 4, 6, 8, and 24 h after intervention [d]
Gryll & Katahn (1978) [112]	Verbal suggestion referring to placebo treatment (oral)	No treatment	Between subjects	40 / 40	Patients undergoing dental surgery	Acute procedural pain (injection pain)	1 x post-intervention
Hashish et al. (1988) [122]	Verbal suggestion referring to placebo treatment (other)	No treatment	Between subjects	25 / 25	Patients undergoing dental surgery	Acute procedural pain (postoperative pain)	24 h post-intervention
Ho et al. (1988) [129]	*Verbal suggestion referring to placebo treatment (other)*	*No treatment*	*Between subjects*	*16 / 16*	*Patients undergoing dental surgery*	*Acute procedural pain (postoperative pain)*	*1 x post-intervention **

Table 3.1. *continued*

Study	Intervention			Sample		Outcome	
Author	**Intervention (route of administration**	**Control condition**	**Compa-rison**	***N***	**Patient population**	**Pain type**	**Timing of pain measurement**
Kam-Hansen et al. (2014) [148]	Verbal suggestion referring to placebo or active treatment (oral)	Control treatment	Within subjects	120	Patients with migraine (episodic)	Chronic pain (migraine pain)	2 h after intervention
Levine and Gordon (1984) [180]	Verbal suggestion referring to placebo treatment [a] (injection)	Control treatment	Between subjects	12 / 12	Patients undergoing dental surgery	Acute procedural pain (postoperative pain)	50 min after intervention [f]
Liberman (1964) [181]	*Verbal suggestion referring to placebo treatment (injection)*	*No treatment*	*Between subjects*	*51 / 30*	*Patients undergoing labor*	*Acute procedural pain (labor pain)*	*15 and 30 min during labor ***
Petersen et al. (2012) [227]	Verbal suggestion referring to active treatment [a] (cutaneous)	Control treatment	Within subjects	19	Patients with neuropathic pain	Chronic pain (spontaneous neuropathic pain)	1 x post-intervention
Petersen et al. (2014) [226]	Verbal suggestion referring to active treatment [a] (cutaneous)	Control treatment	Within subjects	18	Patients with neuropathic pain	Chronic pain (ongoing neuropathic pain)	1 x post-intervention
Pollo et al. (2003) [230]	Verbal suggestion referring to placebo treatment (injection)	No treatment	Between subjects	20 / 17	Patients undergoing assessment of autonomic functions	Experimental pain (electrical pain stimulus)	1 x post-intervention
Price et al. (2007) [235]	Verbal suggestion referring to placebo treatment (other)	No treatment	Within subjects	9	Patients with irritable bowel syndrome	Experimental pain (rectal distension pain)	Last 5 of 7 consecutive stimuli [e]
Schmid et al. (2015) [261]	Verbal suggestion referring to placebo treatment (injection)	Control treatment	Within subjects	17	Patients with irritable bowel syndrome	Experimental pain (rectal distension pain)	8 distensions post-intervention [d]
Vase et al. (2003) [300]	Verbal suggestion referring to placebo treatment (other)	No treatment	Within subjects	13	Patients with irritable bowel syndrome	Experimental pain (rectal distension pain)	5, 15, 20, 40, and 50 min after intervention [h]

Table 3.1. *continued*

Study	Intervention			Sample		Outcome	
Author	**Intervention (route of administration**	**Control condition**	**Compa-rison**	***N***	**Patient population**	**Pain type**	**Timing of pain measurement**
Vase et al. (2005) [301]	Verbal suggestion referring to placebo treatment (other)	No treatment	Within subjects	16	Patients with irritable bowel syndrome	Experimental pain (rectal distension pain)	5, 10, 15, 20, 25, 30, 35, and 40 min after intervention [d] (each time mean pain of 2 distensions)
Conditioning							
Hashmi et al. (2014) [123]	Conditioning with verbal suggestion referring to placebo or active treatment (other)	Control treatment	Within subjects	42	Patients with knee osteoarthritis	Experimental pain (heat pain)	2 x 6 stimuli post-intervention [e]
Klinger et al. (2007) [166]	Conditioning with verbal suggestion referring to treatment (cutaneous)	Control treatment	Between subjects [c]	12 / 12	Patients with atopic dermatitis	Experimental pain (electrical pain stimuli)	5 consecutive stimuli post-intervention [d]
Laska and Sunshine (1973) [178]	Conditioning referring to placebo treatment (after active treatment) (oral)	Control treatment	Between subjects	95 / 16	Patients with postoperative, fracture, or somatic pain	Acute procedural pain or chronic pain (postoperative, fracture, or somatic pain)	30, 60, 120, 180, 240, 300, and 360 min after intervention **
Lee et al. (2012) [179]	Conditioning with verbal suggestion referring to placebo treatment (injection)	Control treatment	Within subjects	17	Patients with irritable bowel syndrome	Experimental pain (rectal distension pain)	1 x post-intervention
Imagery							
Danhauer et al. (2007) [66]	Imagery of sending warm energy to painful areas and of a pleasant place, and relaxation instructions (audio recording)	No treatment [b]	Between subjects	56 / 58	Patients undergoing colposcopy	Acute procedural pain (pain during colposcopy)	1 x post-intervention (retrospect, i.e., pain during procedure)

Table 3.1. *continued*

Study	Intervention			Sample		Outcome	
Author	Intervention (route of administration	Control condition	Compa-rison	*N*	Patient population	Pain type	Timing of pain measurement
Foji et al. (2015) [92]	Imagery contents not reported (audio recording)	No treatment	Between subjects	31 / 31	Patients undergoing coronary angiography	Acute procedural pain (post-angiography pain)	1 x post-intervention
Gonzales et al. (2010) [105]	Imagery and progressive relaxation, biorhythmic music with positive statements (audio recording)	No treatment	Between subjects	22 / 22	Patients undergoing head and neck surgery	Acute procedural pain (postoperative pain)	1 and 2 h after intervention [d]
Jacobson (2006) [142]	Imagery of a pleasant place and cooling gloves (audio recording)	No treatment [b]	Between subjects	41 / 40	Patients undergoing peripheral i.v. therapy	Acute procedural pain (i.v. insertion pain)	1 x post-intervention
Kwekkeboom et al. (2008) [174]	Imagery using glove anesthesia technique, transferring feeling of numbness to painful areas (audio recording)	Control treatment	Within subjects	31	Patients with cancer pain	Chronic pain (cancer pain)	1 x post-intervention
Wells et al. (1989) [313]	Imagery of transferring feeling of numbness to painful area (audio recording)	Control treatment	Between subjects	10 / 10	Patients undergoing abortion	Acute procedural pain (abortion pain)	1 x worst pain during abortion, and 1 x pain in recovery room [d]

Note: [a] used open/hidden design; [b] described by study authors as treatment as usual; [c] within-subjects comparison also possible; [d] average of effect sizes across time points is calculated; [e] only average across time points available; [f] only change from baseline available; [g] post-intervention score(s) calculated; [h] only effect size (Cohen's d) available. ** Insufficient data for meta-analysis. *N* = either total sample size or sample size per condition (intervention/control condition); i.v. = intravenous

included in nine studies. In all studies, patients reported their pain on a single-item pain scale (see Supplementary Table 3.1).

Description risk of bias within studies

Figures 3.2 and 3.3 show the results of the risk of bias (RoB) assessment in all included studies. Regarding selection bias, 63% of the studies reported that treatment allocation was random, but only 27% described adequate random sequence generation (low RoB). Randomization was not mentioned in 17% of the studies (unclear RoB), and incomplete or not performed at all in 20% of the studies (high RoB). Allocation concealment was reported adequately in only 13% of the studies (low RoB), in one study allocation concealment was described, but insufficiently (unclear RoB). None of the other studies mentioned allocation concealment, but a high RoB was inferred if randomization was incomplete or not performed at all (20%). In 40% of the studies there were no signs for attrition bias due to incomplete outcome reporting (low RoB). For 10% of the studies, drop out was unbalanced and/or related to the outcome measure (high RoB). The judgment of reporting bias was challenged for the majority of studies (93%) because no preregistered study protocol could be retrieved. When disregarding the presence of a protocol in the assessment (Figures 3.2 and 3.3), 63% of the studies could be judged as having a low RoB. For 1 study, there was discordance between some measures mentioned in the methods and results section, whereas in another study, analyses did not include all available measurements of the primary outcome (high RoB). In 30% of the studies, no imbalances in sample characteristics of sex, age, and baseline

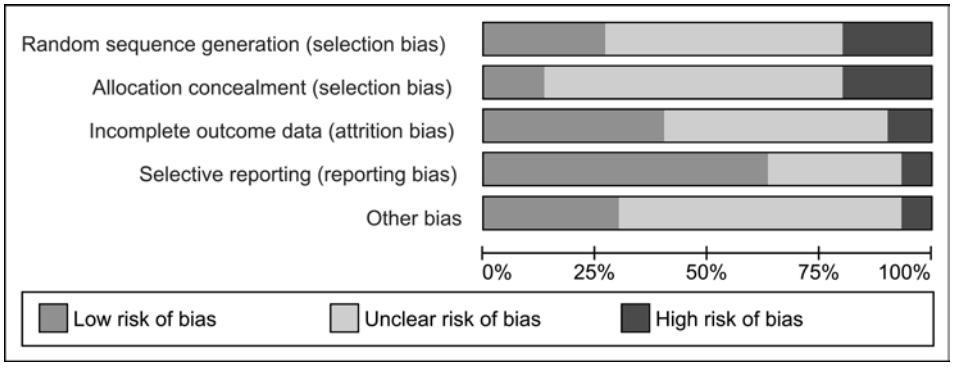

Figure 3.2. Risk of bias graph: review authors' judgments about each risk of bias item presented as percentages across all included studies

Note. For the item 'Selective outcome reporting' (reporting bias) the absence of a preregistered study protocol did not affect the judgment, because a protocol was absent for 93% of the studies.

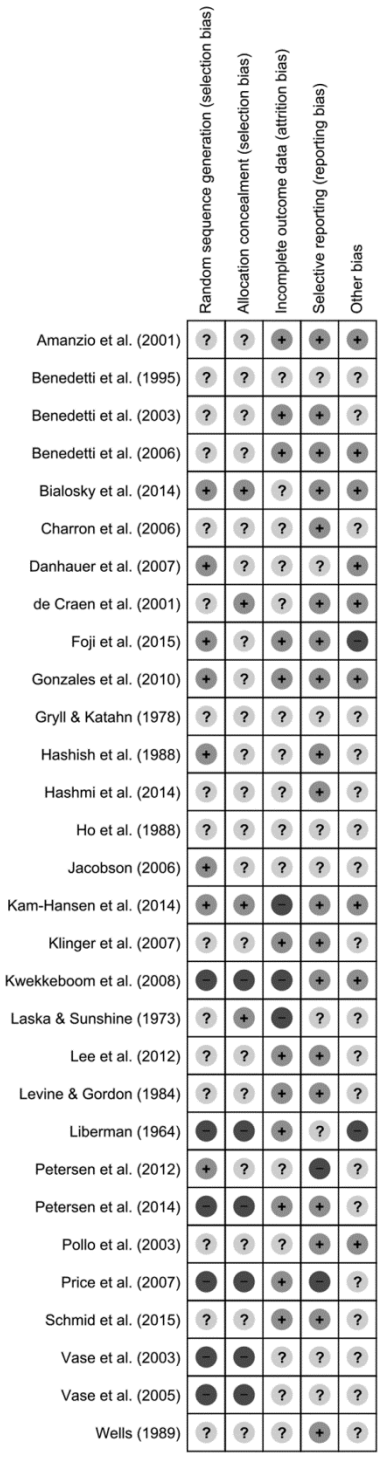

Figure 3.3. Risk of bias summary: review authors' judgments about each risk of bias item for each included study

Note. For the item 'Selective outcome reporting' (reporting bias) the absence of a preregistered study protocol did not affect the judgment, because a protocol was absent for 93% of the studies.

pain were observed (low risk of 'other bias'). All other studies (70%) reported insufficient data regarding equality of one or more of these sample characteristics (unclear RoB). Last, the risk of 'other bias' was judged to be high in one study because of different study procedures in the intervention and control condition and in another study because of the insufficient reporting of study details such as the characteristics of the pain-reporting scale.

Primary meta-analysis: Effect of expectation inductions on pain

See Figure 3.4 for the effect sizes per study and the pooled effects. Meta-analysis indicated a medium overall effect of the expectation inductions on pain in clinical samples (k = 27, g = 0.61, 95% CI 0.42-0.79). A high degree of heterogeneity was observed (I^2 = 73%), with the study effect sizes ranging between g = -0.58 and g = 1.85. The effect sizes for the different expectation inductions varied from a medium to large pooled effect of verbal suggestion (k = 18, g = 0.75, 95% CI 0.50-1.00, I^2 = 78%), to a medium pooled effect of conditioning (always paired with verbal suggestion; k = 3, g = 0.65, 95% CI 0.18-1.11, I^2 = 56%), and to a small pooled effect of imagery (k = 6, g = 0.27, 95% CI 0.02-0.53, I^2 = 42%).

The overall effect of the expectation inductions corresponded with an average pain reduction of 1.16 points on a scale of 0-10 (95% CI 0.77-1.54). Verbal suggestion reduced pain with 1.39 points (95% CI 0.85-1.93), conditioning with 1.03 points (95% CI 0.30-1.76), and imagery with 0.62 points (95% CI 0.10-1.15).

The results of the studies for which sufficient data for meta-analyses were not available, were in line with the observed pooled effects. Ho et al. [129] found a mean difference of 18.3 on a scale of 0-100 between a verbal suggestion condition and a no-treatment condition. Liberman [181] observed that patients reported significantly less labor, postpartum, and experimental pain in a verbal suggestion condition compared with a control condition (p < .001). Laska and Sunshine [178] found that participants reported less pain when a placebo followed an active analgesic (i.e., conditioning) rather than when it followed a placebo (i.e., no conditioning; difference between 0.5 and 3.6 on a sum of pain intensity differences scale).

Subset analyses

Effects on different types of pain. A comparison of the effects of the expectation inductions on different types of pain (see Table 3.1 for specifications) indicated a medium to large pooled effect on experimental pain (k = 9, g = 0.72, 95% CI 0.43-1.01, I^2 = 52%) and a medium pooled effect on clinical pain (k = 18, g = 0.55, 95% CI 0.33-0.78, I^2 = 77%). A further comparison of acute procedural versus chronic clinical pain indicated

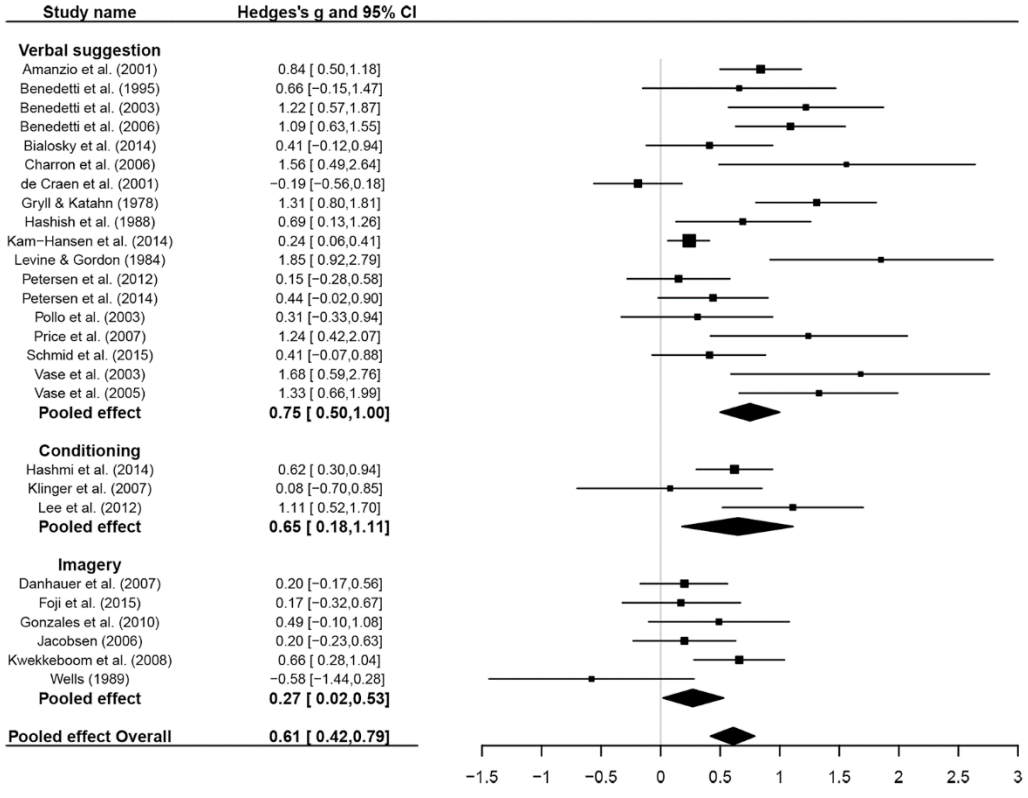

Figure 3.4. Forest plot of the random-effects meta-analysis indicating the effects of the expectation inductions (verbal suggestion, conditioning, and imagery) on pain relief in clinical samples

Note. Positive values for *g* indicate lower post-intervention pain ratings in the intervention condition than in the control condition.

a medium pooled effect on acute procedural pain (k = 12, g = 0.67, 95% CI 0.36-0.97, I^2 = 74%) compared with a small pooled effect on chronic pain (k = 6, g = 0.33, 95% CI 0.04-0.62, I^2 = 70%). Comparing the effects on the different types of pain for the separate expectation inductions was only possible for verbal suggestion. The effects of verbal suggestion on experimental pain were comparable to the overall effect (k = 6, g = 0.79, 95% CI 0.37-1.21, I^2 = 59%), but the difference between the effects on acute procedural and chronic pain was considerably larger (k = 7, g = 1.03, 95% CI 0.79-1.27, I^2 = 24% vs. k = 5, g = 0.25, 95% CI -0.06-0.56, I^2 = 66%, respectively).

Post hoc: Route of treatment administration. Verbal suggestions or conditioning referring to treatments that were administered via injection (see Table 3.1 for relevant studies) were associated with large pooled effects (k = 8, g = 0.90, 95% CI 0.58-1.21, I^2 = 52%), whereas oral and cutaneous treatments were associated with a small to medium pooled effect (k = 3, g = 0.42, 95% CI -0.23-1.07, I^2 = 91% and k = 4, g = 0.47, 95% CI 0.00-0.94, I^2 = 70%,respectively). When analyzing only the effects of verbal suggestion, comparable results were found (k = 7, g = 0.87, 95% CI 0.51-1.23, I^2 = 56% vs. k = 3, g = 0.42, 95% CI -0.23-1.07, I^2 = 91% vs. k = 3, g = 0.56, 95% CI 0.01-1.11, I^2 = 77%, respectively).

Post hoc: Active or placebo treatment. Studies that assessed the effects of verbal suggestion or conditioning that referred to an active treatment (see Table 3.1 for relevant studies) found a medium to large pooled effect (k = 5, g = 0.73, 95% CI 0.35-1.10, I^2 = 70%), compared with a large pooled effect in studies that used a placebo treatment (k = 13, g = 0.90, 95% CI 0.61-1.19, I^2 = 58%). When analyzing only the effects of verbal suggestion, comparable results were found (k = 5, g = 0.73, 95% CI 0.35-1.10, I^2 = 70% vs. k = 11, g = 0.95, 95% CI 0.63-1.26, I^2 = 58%, respectively). No differential effects were indicated in three studies in which both active and placebo treatments were used (g = 0.25, 95% CI -0.13-0.64, I^2 = 64% and g = 0.22, 95% CI -0.15-0.59, I^2 = 62%, respectively) [70,123,148].

Effect of expectation inductions on additional outcomes

See Figure 3.5 for the effect sizes per study and the pooled effects for each of the additional outcomes.

Expected pain. From five (of seven) studies, sufficient data were available to analyze the effects of expectation inductions (k = 5 verbal suggestion) on self-reported expectations of pain. A medium pooled effect was observed (g = 0.66, 95% CI 0.43-0.90, I^2 = 0%).

Affective pain. From seven (of ten) studies, sufficient data were available to analyze the effects of expectation inductions (k = 4 verbal suggestion, k = 3 imagery) on affective

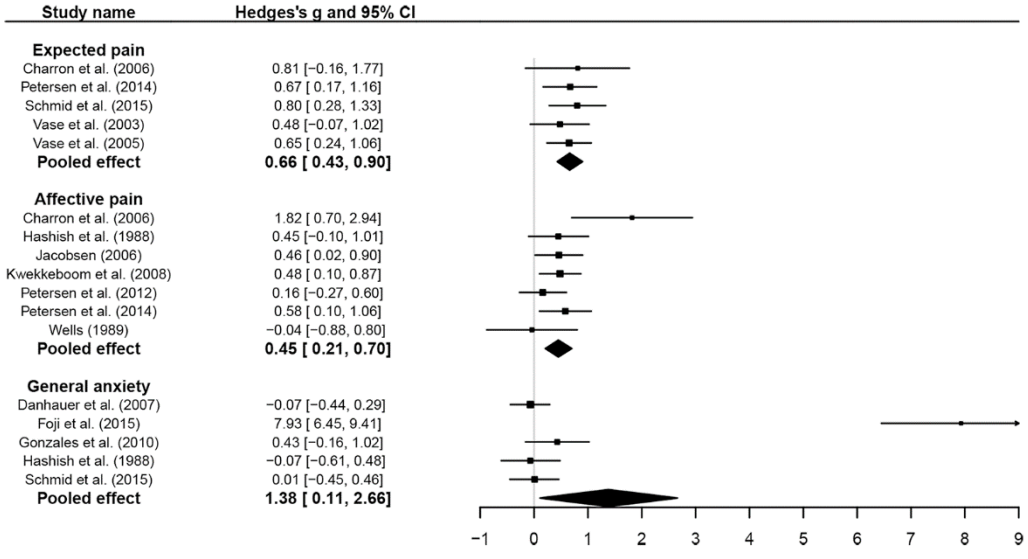

Figure 3.5. Forest plot of the random-effects meta-analysis indicating the effects of the expectation inductions (verbal suggestion, conditioning, and imagery) on expected pain, affective pain, and anxiety in clinical samples

Note. Positive values for *g* indicate lower post-intervention pain ratings in the intervention condition than in the control condition.

pain (i.e., pain unpleasantness or pain distress). A medium pooled effect was observed (g = 0.45, 95% CI 0.21-0.70, I^2 = 34%).

Anxiety. From five (of six) studies, sufficient data were available to analyze the effects of expectation inductions (k = 2 verbal suggestion, k = 3 imagery) on anxiety (measured with the state version of the State-Trait Anxiety Inventory or an anxiety visual analogue scale). A large pooled effect was observed (g = 1.38, 95% CI 0.11-2.66, I^2 = 96%); however, when excluding an extreme outlier (g = 7.93 [92]), no effect was observed (g = 0.03, 95% CI -0.21-0.26, I^2 = 0%).

Sensitivity analyses for overall effect of expectation inductions on pain

Risk of bias within studies. Excluding studies that were judged to have a high risk of bias on one or more items (k = 9, ~~see~~ Figure 3.3) did not substantially affect the overall effect size (g = 0.63, 95% CI 0.38-0.87).

Publication bias. The funnel plot (Figure 3.6) suggests publication bias. The trim and fill method indicated that six studies demonstrating below-average effects of an expectation induction on pain relief (the black dots in the figure) were estimated to be missing. Including these studies would lower the overall effect size to g = 0.43 (95% CI 0.24-0.62).

Type of control condition. When expectation inductions were compared to a control condition with a control treatment a pooled effect of g = 0.58 (k = 16, 95% CI 0.34-0.82) was observed, whereas for studies in which a no-treatment control condition was used, a pooled effect of g = 0.65 (k = 11, 95% CI 0.35-0.94) was found. Excluding three studies that involved a control condition in which some expectations of pain relief might have been induced [70,174,313], resulted in an overall effect of g = 0.67 (95% CI 0.49-0.86).

Between- versus within-subjects comparisons. The pooled effect for studies for which between-subjects comparisons were reported was g = 0.53 (k = 16, 95% CI 0.26-0.80), compared to g = 0.70 for studies in which within-subjects comparison were used (k = 11, 95% CI 0.45-0.96). Including within- rather than between-subjects comparisons of two studies for which both comparisons could be made did not affect the overall effect size (g = 0.60, 95% CI 0.43-0.78).

Imputed correlation coefficients. Sensitivity analyses testing whether the imputed intervention – control correlation of r = 0.5 for within-subjects comparisons affected the observed effects indicated a stable overall effect size (when r = 0.1, g = 0.60, 95% CI 0.41-0.79; when r = 0.9, g = 0.61, 95% CI 0.44-0.77).

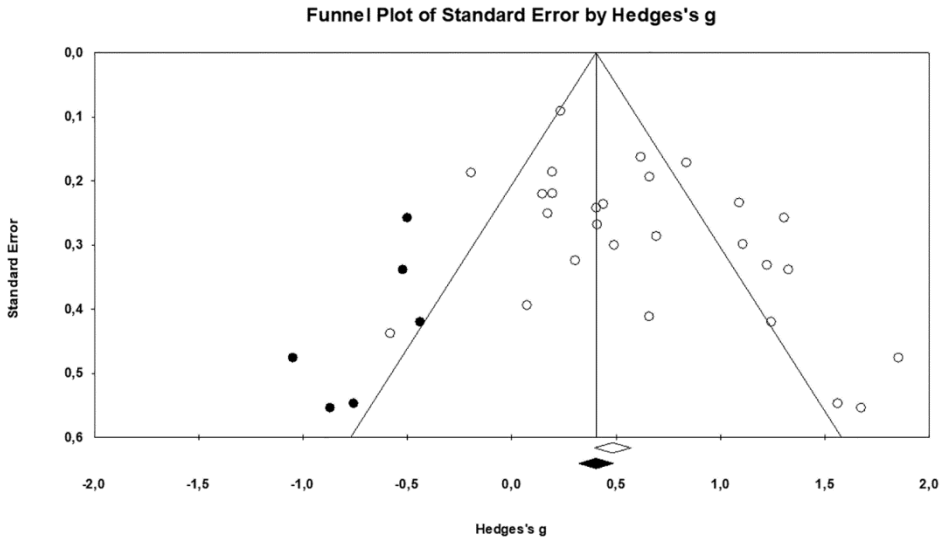

Figure 3.6. Funnel plot of SE by Hedges' g

Post-intervention versus change scores. When excluding three studies for which only change scores were available [25,52,180], rather than the preferred post-intervention scores, the overall effect size was *g* = 0.55 (95% CI 0.37-0.73). When selecting change scores rather than post-intervention scores (available for 12 studies) the overall effect size was *g* = 0.70 (95% CI 0.49-0.90).

In summary, these sensitivity analyses indicate a relatively stable overall effect size, ranging from *g* = 0.43 to *g* = 0.70.

Discussion

The current meta-analysis assessed the pain-reducing effects of three expectation interventions, i.e., verbal suggestion, conditioning, and imagery, in clinical samples. Meta-analysis of 27 studies showed an overall medium-sized (heterogeneous) effect of the interventions on patients' pain relief. The effects of verbal suggestion were most frequently studied and could be qualified as medium to large. Conditioning (always paired with verbal suggestion) and imagery were studied much less frequently, and were associated with medium and small effects, respectively. The effect sizes varied depending on the type of pain that patients experienced, with medium to large effects in the case of experimental and acute procedural pain, but small effects on chronic pain.

Thus, interventions that can induce analgesic expectations, particularly verbal suggestions for acute procedural pain, were found to relief patients' pain and can thus possibly be used to optimize the effectiveness of standard analgesic treatments in clinical practice.

The findings of this meta-analysis extend previous meta-analyses in which the pain-reducing effects of verbal suggestion and conditioning were studied in the context of placebo effects [298,299] and a meta-analysis and systematic reviews in which the pain-reducing effects of imagery were studied [231,232,291], by directly comparing the effects of these expectation inductions, while focusing on brief interventions in clinical samples. The observed medium to large effects of verbal suggestion on experimentally evoked and acute procedural pain were generally in line with the findings of a previous meta-analysis [299] and more recent studies in healthy participants [16,189,266], which supports the transferability of findings from healthy to clinical samples. In contrast, the effects of verbal suggestion on chronic pain were found to be small, possibly because of repeated negative treatment experiences in the past and consequently more negative expectations regarding pain treatment in general that cannot be easily molded by a brief verbal suggestion [95]. However, because within-study comparisons of experimental and chronic pain provided somewhat equivocal results [52,226,227], and given the heterogeneity of the studies, further research is required. Surprisingly, although conditioning procedures were always paired with corresponding verbal suggestions, their effects on pain in clinical samples were not larger than the effects of verbal suggestion alone. This finding is in contrast with previous research in healthy samples, where such procedures are generally observed to have more robust effects on pain than verbal suggestions alone [20,166,197]. However, because the effects of conditioning in clinical samples could be analyzed only in three studies and were studied only on experimental pain, and because conditioning procedures were always paired with verbal suggestion, no firm conclusions can be drawn yet about the size of conditioning effects in clinical samples. Imagery was found to have a small effect on clinical pain in our meta-analysis. This is partially in contrast with previous reviews that indicated small to large effects of imagery on pain [231,232,291]. Also, a priori, we considered that imagery might be more effective than verbal suggestion because visual thinking has been found to have a larger impact on emotions, and hence possibly also the subjective pain experience, than verbal thinking [116,133] and because imagery entails more active involvement [89]. Several factors might explain these findings. First, the selected imagery interventions were brief, maximally one day (to increase comparability between the expectation inductions). Possibly more practice time is required to obtain substantial effects (Van Kuiken, 2004a). Second, imagery instructions were always delivered through audio

recordings, whereas verbal suggestions were given by the experimenter. Personal communication might enhance the effects of expectation inductions.

Subsequent post hoc analyses demonstrated that the observed effects of verbal suggestion and conditioning varied depending on the route of administration of the medical treatment to which they referred, with larger effects for more invasive treatments (injections) than less invasive treatments (oral and cutaneous). This is in line with previous experimental placebo research and a meta-analysis of placebo arm data of clinical trials [71,152]. In addition, the effects of verbal suggestion and conditioning were slightly larger when they referred to a placebo rather than an active treatment. However, direct comparisons within three studies indicated no differential effects [70,123,148]. Also, research in healthy samples provides equivocal results regarding the relative effect sizes [15,259]. Nonetheless, these findings underscore that expectation interventions are not only relevant in the context of placebo effects, but also that they can enhance the analgesic effects of active treatments in clinical samples.

The core working mechanism of verbal suggestion, conditioning, and imagery is thought to be expectancy, as already implied by the term 'expectation inductions'. Our meta-analysis of the subset of studies in which expectations were measured demonstrated that verbal suggestion indeed induced expectations of pain relief, and the study authors showed that these expectations predicted effects on actually experienced pain [52,226,261,300,301]. Previous research in healthy samples confirmed that also conditioning and imagery induce expectations [40,119,160,161,202,224], but, because of a lack of research, this cannot yet be confirmed in clinical samples. Also, anxiety reduction has been considered as a possible psychological working mechanism [91,189,231,291]. However, our meta-analysis could not demonstrate an effect of the expectation inductions on anxiety in clinical samples, with the exception of one study in which large effects of imagery on anxiety were observed. Preliminary evidence from another study [301] suggests possible effects on pain specific anxiety. Several other psychological processes (e.g., general affect, attention, or sense of control) might be affected by the interventions, but this could not be assessed in the meta-analysis because necessary data were not available. We could not meta-analyze physiological and neuroimaging data, because of the paucity and complexity of the data. Although several previous reviews illustrate the neurobiological mechanisms of placebo effects and imagery, it was predominantly in healthy samples [14,201,256]. An inspection of the included studies in patient samples provides preliminary evidence that verbal suggestion might be able to reduce heart rate [28,230] and c-reactive protein [122], but not cortisol (possibly because of methodological issues) [122,134,261]. A study on imagery found no evidence for effects on physiological responses [92]. At a neurobiological level, the effects of verbal

suggestion and conditioning on pain have been found to be associated with pain-related brain activity and connectivity among different brain regions [28,123,179,235,261]. Further research is required to allow more conclusive inferences of the effects of expectation interventions on physiological and neurological processes in clinical populations.

When evaluating the current results, certain methodological factors that could have affected the observed effect sizes should be considered. Despite considerable heterogeneity, sensitivity analyses indicated a relatively stable overall effect size in relation to the research design (type of control condition, within- vs. between-subjects comparisons) and selected values for analyses (imputed correlation coefficients, post-intervention rather than change scores). However, there were indications for publication bias, which might have inflated the overall effect size (although the adjusted effect size could still be qualified as medium). Bias in the individual studies could frequently not be judged decisively due to insufficiently detailed reporting and the absence of preregistered study protocols. Also, response bias due to the (partial) infeasibility of blinding cannot be excluded. Nevertheless, because excluding studies with a known high risk of bias barely influenced the observed overall effect size, the influence of study bias seems minor. Last, the observed pairing of conditioning with verbal suggestion and the frequent inherent inclusion of relaxation, and possibly also verbal suggestion, in imagery interventions, could have affected the observed effects and hampers judgments of the effectiveness of the separate intervention components.

Based on this meta-analysis, several directions for future research can be considered. Most importantly, given the current positive but heterogeneous and still limited findings, future research might focus particularly on further examining the elements that determine the effectiveness of the different expectations inductions and on maximizing therapeutic effects. Research on active intervention elements (e.g., specifics of verbal suggestion and pure imagery), mediating factors (expectations, physiological and neurobiological responses, and e.g., anxiety and attention), moderating factors (e.g., previous pain experiences, pain treatment history, desire for pain relief, and personality characteristics), and outcome characteristics (e.g., type of pain) could provide insight into what determines the effects of the expectation interventions, and for whom and when they are effective. Also, combining different expectation inductions might enhance the effects, and for patients with chronic pain, more extensive interventions (e.g., also addressing general expectations regarding medical treatment and health) might be considered. Importantly, research should not only aim at inducing and/or enhancing positive expectations, but should also address negative expectations regarding adverse effects [225]. Furthermore, the current findings allow for conclusions regarding only the short-term effects of the expectation

interventions; further research is warranted to determine whether the interventions have a long-lasting clinical impact. Last, more detailed methodological reporting of the research, including preregistration, would further advance the field and facilitate future meta-analyses [127,264].

In conclusion, the current meta-analysis indicated that brief expectation interventions, especially verbal suggestion, can relief patients' acute procedural and, to a lesser extent, chronic pain. Most notably, the observed analgesic effects of verbal suggestions regarding placebo or active treatments underline the importance of the information a clinician provides when administering an analgesic treatment. Informing patients about, and emphasizing, the positive intended and expected outcomes of an analgesic intervention, without neglecting possible negative side effects, can optimize treatment effectiveness.

Acknowledgements

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Supplementary materials Chapter 3

Supplementary Section 3.1. Search strategy

PubMed
("Placebo Effect"[Mesh] OR "Conditioning (Psychology)"[Mesh:noexp] OR "Conditioning, Classical"[Mesh] OR "Imagery (Psychotherapy)"[Mesh] OR placebo effect[tiab] OR placebo effects[tiab] OR placebo analgesia[tiab] OR verbal suggestion[tiab] OR verbal suggestions[tiab] OR open-hidden [tiab] OR open-label placebo[tiab] OR (conditioning[tiab] NOT medline[sb]) OR imagery[tiab]) AND ("Pain"[Mesh] OR "Analgesia"[Mesh] OR pain[tiab] OR analgesia[tiab] OR analgesic[tiab]) NOT ("animals"[Mesh] NOT "humans"[Mesh])

PsycINFO (via OvidSP)
(exp placebo/ OR conditioning/ OR classical conditioning/ OR imagery/ OR conceptual imagery/ OR guided imagery/ OR (placebo effect OR placebo effects OR placebo analgesia OR verbal suggestion OR verbal suggestions OR open-hidden OR open-label placebo OR conditioning OR imagery).ti,ab,id.) AND (exp pain/ OR exp analgesia/ OR (pain OR analgesia OR analgesic).ti,ab,id.)

EMBASE (via OvidSP)
(placebo effect/ OR conditioning/ OR imagery/ OR guided imagery/ OR (placebo effect OR placebo effects OR placebo analgesia OR verbal suggestion OR verbal suggestions OR open-hidden OR open-label placebo OR conditioning OR imagery).ti,ab.) AND (exp pain/ OR exp analgesia/ OR (pain OR analgesia OR analgesic).ti,ab.) NOT ((nonhuman/ OR animal/) NOT human/)

Cochrane CENTRAL & Cochrane Methodology Register (via Cochrane library)
([mh "Placebo Effect"] OR [mh ^"Conditioning (Psychology)"] OR [mh "Conditioning, Classical"] OR [mh "Imagery (Psychotherapy)"] OR (“placebo effect” OR “placebo effects” OR “placebo analgesia” OR “verbal suggestion” OR “verbal suggestions” OR “open-hidden” OR “open-label placebo” OR conditioning OR imagery:ti,ab,kw)) AND ([mh Pain] OR [mh Analgesia] OR (pain OR analgesia OR analgesic:ti,ab,kw)) NOT ([mh animals] NOT [mh humans]

Supplementary Table 3.1. Additional study characteristics of all studies included in the quantitative and qualitative meta-analysis

Study	Intervention	Sample		Outcome	Additional groups and measures [e]		
Author	**Actual or suggested treatment**	**Age** [a] M (SD) *[range]*	**Sex** [a] % Male	**Pain measure** [d]	**Additional conditions**	**Additional samples**	**Additional pain intensity outcomes**
Verbal suggestion							
Amanzio et al. (2001) [5]	Active: buprenorphine, tramadol, ketorolac, or metamizol	I: 53.8 (8.1) C: 54.3 (7.9)	I: 53% M C: 57% M	NRS (0-10)	·	· first group of patients, data analyzed in terms of analgesic dose needed to obtain pain reduction of 50% · healthy sample (ischemic arm pain)	·
Benedetti et al. (1995) [25]	Placebo: analgesic	55 [b]	56% M [b]	NRS (0-10)	· open proglumide (0.05, 0.5, or 5 mg) · hidden proglumide (0.05, 0.5, or 5 mg)	·	·
Benedetti et al. (2003) [30]	Active: morphine	I: 56.5 (9.5) C: 53.9 (11.8)	I: 52% M C: 62% M	NRS (0-10)	· open interruption morphine · hidden interruption morphine	· thoractomized patients (state anxiety) · Parkinsonian patients (movement velocity) · healthy volunteers (beta-blockade) · healthy volunteers (muscarinic antagonism)	·
Benedetti et al. (2006) [28]	Active: lidocaine	73.5 (6.8)	39% M	NRS (0-10)	·	· healthy controls · retested after 1 year (incl. 10 additional Alzheimer disease patients without reduced connectivity)	·

Supplementary Table 3.1. *continued*

Study	Intervention	Sample		Outcome	Additional groups and measures [e]		
Author	**Actual or suggested treatment**	**Age** [a] M (SD) *[range]*	**Sex** [a] % Male	**Pain measure** [d]	**Additional conditions**	**Additional samples**	**Additional pain intensity outcomes**
Bialosky et al. (2014) [35]	Placebo: spinal manipulative therapy	I: 31.6 (11.9) C: 29.9 (12.1) *[18-60]*	I: 26% M C: 32% M	M-VAS (100mm)	· placebo without verbal suggestion	·	· experimental pain: thermal pain sensitivity · clinical pain: low back pain intensity after 2 additional intervention weeks
Charron et al. (2006) [52]	Placebo: analgesic	39.8 (13.2) *[18-60]*	63% M	Numeric scale (0-100)	·	·	· experimental pain: cold pain
De Craen et al. (2001) [70]	Placebo: analgesic or Active: tramadol	I: 50.9 (14.5) C: 53.2 (15.3) *[incl ≥ 18]*	I: 42% M C: 39% M	VAS (10cm)	·	·	·
Gryll & Katahn (1978) [112]	Placebo: reduction of tension, anxiety, sensitivity to pain	33 *[incl ≥ 18]* [b]	53% M [b]	Semantic differen-tial (1-5)	· undersell, saliva suggestion · Note, a factorial design assessing multiple additional factors was used: 4 (suggestion: oversell, undersell, saliva, no pill) x 2 (status: dentist or dental technician) x 2 (warm vs neutral dentist) x 2 (warm vs neutral dental technician)	·	·
Hashish et al. (1988) [122]	Placebo: ultrasound	*[16-70]* [b]	F & M [b]	VAS (100mm)	· ultrasound · stationary ultrasound · self-massage	·	·

Supplementary Table 3.1. *continued*

Study	Intervention	Sample		Outcome	Additional groups and measures [e]		
Author	**Actual or suggested treatment**	**Age** [a] M (SD) *[range]*	**Sex** [a] % Male	**Pain measure** [d]	**Additional conditions**	**Additional samples**	**Additional pain intensity outcomes**
Ho et al. (1988) [129]	Placebo: ultrasound	24 [b] *[15-44]*	30% M [b]	Scale	· ultrasound · stationary ultrasound · self-massage	·	·
Kam-Hansen et al. (2014) [148]	Placebo: maxalt or Active: maxalt	40.6 (12.7) *[incl ≥ 18]* [b,c]	15% M [b,c]	NRS (0-10)	· given placebo told "maxalt or placebo" · given maxalt told "maxalt or placebo"	·	·
Levine and Gordon (1984) [180]	Placebo: analgesic?	?	?	VAS (100mm)	· hidden placebo · open naloxone · hidden naloxone · machine naloxone · machine morphine 8 mg · machine morphine 12 mg	·	·
Liberman (1964) [181]	Placebo: analgesic	?	0% M	Verbal indications (4 points)	· verbal suggestion/control during postpartum · verbal suggestion/control 3 days after (ischemic muscle pain)	·	·
Petersen et al. (2012) [227]	Active: lidocaine	61.9 *[51-75]*	63% M	M-VAS (10cm)	· control condition (no lidocaine)	·	· experimental pain: brush-evoked, cold-evoked, pinprick, wind-up like pain
Petersen et al. (2014) [226]	Active: lidocaine	56.8 *[32-65]*	56% M	M-VAS (10cm)	· 2x control condition (no lidocaine) · open capsaicin · hidden capsaicin	·	· experimental pain: brush-evoked, pinprick, wind-up like pain

Supplementary Table 3.1. *continued*

Study	Intervention	Sample		Outcome	Additional groups and measures [e]		
Author	**Actual or suggested treatment**	**Age** [a] M (SD) *[range]*	**Sex** [a] % Male	**Pain measure** [d]	**Additional conditions**	**Additional samples**	**Additional pain intensity outcomes**
Pollo et al. (2003) [230]	Placebo: local anesthetic	I: 38.0 (15.5) C: 34.8 (13.0)	I: 18% M C: 20% M	NRS (0-10)	·	· healthy controls (ischemic arm pain)	·
Price et al. (2007) [235]	Placebo: analgesic	27.7 (9.6)	0% M	Rating scale (100 units)	· placebo match · baseline 2	·	·
Schmid et al. (2015) [261]	Placebo: analgesic	39.0 (3.4) *[incl 18-65]*	12% M	VAS (100mm)	·	· patients with ulcerative colitis in remission · healthy controls	·
Vase et al. (2003) [300]	Placebo: analgesic	30 (13) *[incl pre-menopausal]*	0% M	M-VAS (10cm)	· rectal lidocaine · oral lidocaine · rectal nocebo	·	· experimental pain: heat pain
Vase et al. (2005) [301]	Placebo: analgesic	29 (9) *[incl pre-menopausal]*	0% M	M-VAS (10cm)	· rectal lidocaine after hidden saline · rectal placebo after hidden naloxone · natural history after hidden naloxone · rectal lidocaine after hidden naloxone	·	·
Conditioning							
Hashmi et al. (2014) [123]	Placebo: acupuncture or Active: acupuncture	57.9 (7.2)	48% M	Gracely Sensory Scale (0-20)	·	·	·

Supplementary Table 3.1. *continued*

Study	Intervention	Sample		Outcome	Additional groups and measures [e]		
Author	**Actual or suggested treatment**	**Age** [a] M (SD) *[range]*	**Sex** [a] % Male	**Pain measure** [d]	**Additional conditions**	**Additional samples**	**Additional pain intensity outcomes**
Klinger et al. (2007) [166]	Placebo: analgesic	27.4 (8.2) *[17-38]* [b]	50% M [b]	NRS (0-8)	· conditioning with neutral suggestion · no conditioning with analgesic suggestion	· healthy controls	·
Laska and Sunshine (1973) [178]	Active -> placebo: propoxyphene HCL or propoxyphene napsylate, each in 3 different dosages	adult	F & M	NRS (0-3)	·	·	·
Lee et al. (2012) [179]	Placebo: analgesic	35.9 (10.8) *[incl 18-55]*	35% M	VAS (100mm)	·	· healthy controls	·
Imagery							
Danhauer et al. (2007) [66]	n.a.	I: 29.1 (10.2) C: 28.9 (9.5) *[incl ≥ 18]*	0% M	VAS (100mm)	· music	·	·
Foji et al. (2015) [92]	n.a.	I: 56.8 (1.46) C: 57.3 (1.8) *[incl 35-69]*	I: 58% M C: 61% M	NRS (0-10) ?	·	·	·
Gonzales et al. (2010) [105]	n.a.	I: 35.9 (15.1) C: 33.3 (10.8) *[18 -71]*	I: 59% M C: 59% M	VAS (100mm)	·	·	·

Supplementary Table 3.1. *continued*

Study	Intervention	Sample		Outcome	Additional groups and measures [e]		
Author	**Actual or suggested treatment**	**Age** [a] M (SD) *[range]*	**Sex** [a] % Male	**Pain measure** [d]	**Additional conditions**	**Additional samples**	**Additional pain intensity outcomes**
Jacobson (2006) [142]	n.a.	55 (16) [b] *[18-93]*	I: 22% M C: 33% M	NRS (0-10)	· music · kaleidoscope · choice between the 3 interventions	·	·
Kwekkeboom et al. (2008) [174]	n.a.	48.9 (16.3) *[18-75]*	45% M	NRS (0-10)	· progressive muscle relaxation	·	·
Wells et al. (1989) [313]	n.a.	25 *[16-35]* [b]	0% M	graphic rating scale (10cm)	· relaxation, pleasant imagery	·	·

Note. [a] Sample characteristics are reported for the experimental and control conditions together, unless otherwise indicated, I = intervention condition, C = control condition, Incl = inclusion criteria age; [b] Sample characteristics of the full sample, which also included other conditions/groups that were not included in the meta-analysis; [c] Characteristics of the sample excluding drop outs, data also available for drop outs (very similar); [d] NRS = numerical rating scale, VAS = visual analogue scale, M-VAS = mechanical visual analogue scale; [e] The data from additional groups and measures were not analyzed in the meta-analysis since they did not fit within the scope of the review.