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REVIEW ARTICLE

How do they add up? The interaction between the placebo and treatment effect: A systematic review

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[Correction added on 4 August 2022, after first online publication: The copyright line was changed.]

Aim: The placebo effect and the specific effect are often thought to add up (additive model). Whether additivity holds can dramatically influence the external validity of a trial. This assumption of additivity was tested by Kleijnen et al in 1994 but the data produced since then have not been synthetized. In this review, we aimed to systematically review the literature to determine whether additivity held.

Methods: We searched Medline and PsychInfo up to 10 January 2019. Studies using the balanced placebo design (BPD), testing two different strengths of placebos, were included. The presence of interaction was evaluated by comparing each group in the BPD with analysis of variance or covariance.

Results: Thirty studies were included and the overall risk of bias was high: four found evidence of additivity and 16 studies found evidence of interaction (seven had evidence of positive additivity).

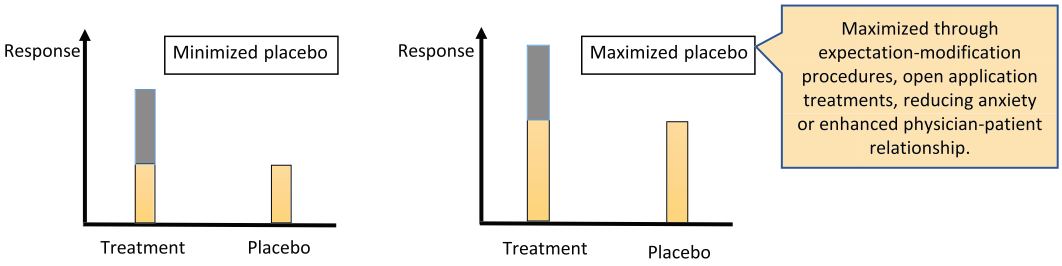
Conclusion: Evidence of additivity between placebo and specific features of treatments was rare in included studies. We suggest interventions for placebo-sensitive ailments should be tested in trials designed to take interactions seriously once an exploratory RCTs has proven their efficacy with sufficient internal validity.

KEYWORDS
clinical trials, drug effect, evidence-based practice, placebo, therapeutic alliance, treatment outcome

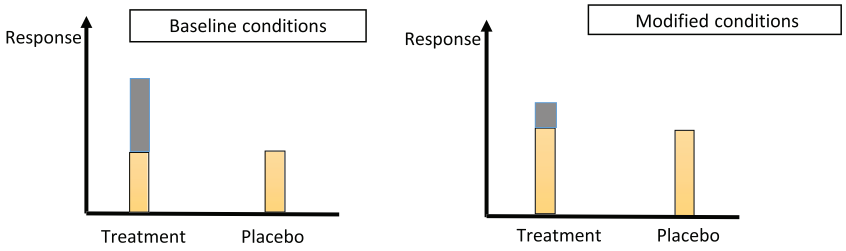
1 | INTRODUCTION

The total treatment effect is assumed to be the sum of its specific effect and of "nonspecific", or "placebo" effects.[1–3] This is known as the additive model.[4] However, it has been noted since at least the 1960s that the placebo and treatment effects can interact.[5–8] If they interact, the specific treatment and placebo effects combine in ways that can be greater than the sum of the parts of (supra-additive or synergistic), less than the sum of the parts of (subadditive or antagonistic)[9] or even reverse (qualitative interaction) the overall treatment effect.[10–14] The difference between these models is illustrated in Figure 1.

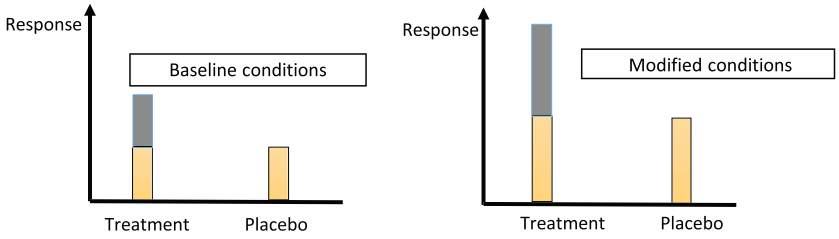
In 1994, Kleijnen et al[15] reviewed the potential evidence for interaction in 10 studies. They found that specific and nonspecific effects can at times be synergistic or antagonistic, thereby rendering overly reductive the presumed additive model of randomized clinical trials (RCTs).[4,15] For example, Bergmann et al[9] showed that the strength of the analgesic effect of naproxen depended on whether



(A) Additive model : the specific effect of treatment is the same no matter the placebo's intensity.



(B) Antagonistic interactive model : the specific effect of treatment is different according to the placebo's intensity. Here it is lower compared to the baseline situation.



(C) Synergistic interactive model : the specific effect of treatment is different according to the placebo's intensity. Here it is lower compared to the baseline situation.

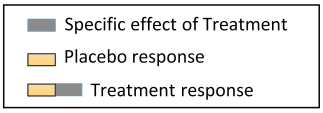


FIGURE 1 Additive versus interactive models

patients were correctly informed (and consent given) or not (*P* value interaction <0·10). Their results are illustrated in Figure 2. However, not all attempts to identify interactions found evidence of interaction.[16] In a two-by-two factorial, randomized, placebo-controlled, double-blind trial, chronic pain patients attending an outpatient clinic were randomized to receive a single oral dose of 50 mg of tramadol or placebo, and they were further randomized to receive positive or neutral information, verbally expressed by the physician, regarding the expected analgesic effect of the drug. However, the tramadol did not outperform the placebo, making it impossible to detect interactions. Overall, the clinical trials Kleijnen et al[15] identified had small populations and low quality. Also, a number of studies investigating additivity have been published since then which test the clinical pertinence of the placebo model, as discussed by Fava et al.[17] A recent review by Coleshill et al[18] tested how placebo analgesia interacted with active analgesic effects and identified seven studies suggesting that additivity did not hold in placebo analgesia. The review only included seven studies and concluded that data was unavailable to draw solid conclusions.

In this study we aimed to update the findings from Kleijnen et al by systematically reviewing the available more recent literature to determine whether the additivity model of specific and nonspecific effects may be accepted as a general model.

2 | METHODS

Our study protocol is available by contacting the study authors and is available in OSF Registries (https://osf.io/r5tzc). We followed PRISMA guidelines.

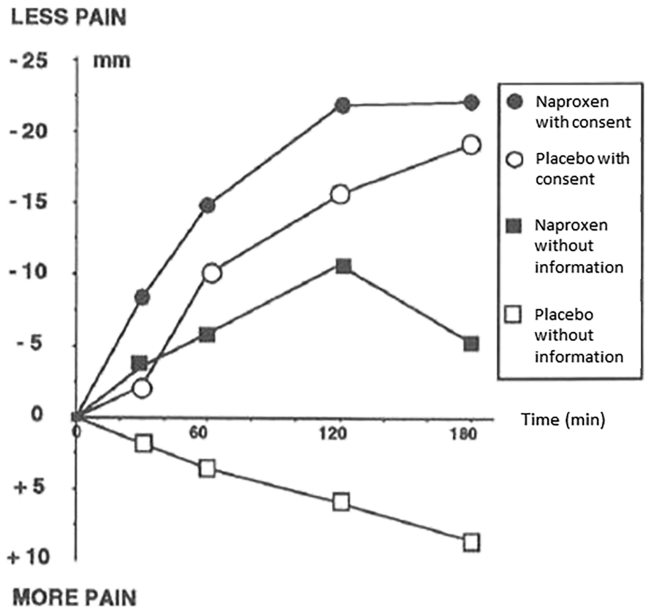


FIGURE 2 Bergmann et al results as published in 1994

TABLE 1 Balanced placebo design

	Told placebo	Told treatment
Received placebo	A	B
Received treatment	C	D

2.1 | Eligibility criteria

This review included any randomised trials using the balanced placebo design (BPD), whereby there are at least two "intensities" of placebo effects (see Table 1). We included trials with any type of participants (clinical patients or healthy volunteers). To be comparable with Kleijnen et al's earlier (1994) review, we excluded trials of alcohol, tobacco, acupuncture and homeopathy and we only included BPD trials (excluding pragmatic trials and other alternative designs). The BPD is a two-by-two factorial design and is described in Table 1.[19–22] It allows researchers to study the effect of the patient's expectation and the effect of the drug itself. In these trials, some patients in the treatment group are told they receive the treatment and others are told they receive placebo, which generates two different strengths of belief that the treatment will work. Likewise, some patients in the placebo group are told that they are receiving a placebo, while others are told they are receiving a treatment. If additivity holds, then the effect of the specific elements of the treatment should not change as a result of what patients are told, that is, (from Table 1) the difference C − A should be the same as D − B. Any statistically significant deviation from this means that additivity did not hold for that specific trial.

2.2 | Information sources

We searched Medline and PsycInfo from 1964 (inception of Medline) to the 10 January 2019.

2.3 | Search

The search equation was (["Placebo Effect"[MeSH]] OR placebos [MeSH Terms])) OR "active placebo response")) AND ((([("expectancies"] OR "expectancy") OR "expectation")))) NOT "alcohol") NOT "smoking") NOT "acupuncture") AND Clinical Trial[ptyp])) OR (drug/placebo interaction AND Clinical Trial[ptyp])) OR ("balanced placebo design" AND Clinical Trial[ptyp]).

We also searched the bibliographies of each eligible study and searched for publications by the main authors of the trials included.

2.4 | Study selection and data collection process

The searches were carried out independently by two researchers (R.Bo. and R.Ba.) and the results were pooled if possible. The two same researchers then read the full text of the selected studies and extracted the data into spreadsheets, which were then compared. In the event of doubt or disagreement a third researcher (F.G.) was intended to provide resolution, but this was not required.

2.5 | Data items

The following data were extracted: study design, treatment and placebo used, analysis of risk of bias, number of study participants, endpoints, results about interaction between the specific effect and the placebo effect, and the authors' conclusion about the existence of interactions.

2.6 | Summary measures and synthesis of results

We predicted there would be a high risk of bias on average because Kleijnen et al included 10 studies at high risk of bias in 1994. We took this into consideration when planning to pool our results: statistical analysis of interaction was planned with only low and/or intermediate risk of bias studies. The initial strategy was to calculate the effect sizes of treatments and placebos for each intensity of placebo administration (in accordance with Cochrane methods).[23] We initially planned to pool our results, but this was not possible due to lack of sufficient data in the included studies.

After the initial database search, and when analysing the data, we decided to present the results according to context (clinical context or healthy volunteers).

2.7 | Risk of bias in individual studies

Analysis of bias risk was planned for each study. We used the Revised Cochrane risk-of-bias tool for randomized trials, RoB 2.0.[24] We took into account randomization, effects of the intervention on unblinding,

missing data, primary endpoint measurement and transcription of study results. See Appendix 1 for detailed risk analysis.

2.8 | Interactive model

There are three possible types of interactions: synergistic, antagonistic and reversal (qualitative interaction). In the case of antagonistic interaction, the total effect of a treatment is inferior to the sum total of the placebo effect and the specific effect of the treatment, whereas in the synergistic model the total effect of a treatment is superior to the sum total of the placebo effect and the specific effect.[6,12,18] In the case of reversal of effect (or qualitative interaction), the placebo effect will reverse the specific effect (like when pain is experienced when a topical analgesic is applied with nocebo information in the trial by Aslaksen et al).[10]

3 | RESULTS

3.1 | Study selection

Figure 3 is a flowchart illustrating the selection process of studies for this review. Our search identified 1744 articles; only 30 studies were eligible for inclusion.[7,9,10,16,20,25–49] A considerable number of these studies (40%) were pain studies.

3.2 | Study characteristics and risk of bias within studies

Study characteristics are presented in Table 2 and a more detailed version is available Appendix 2.

3.3 | Results of individual studies

The 30 included studies were published between 1959 and 2017. Of these, 19 (63%) involved healthy volunteers,[10,20,26–35,37–40,44,48,49] with six of these using painful stimulus.[10,31–33,37,40] Eleven other studies tested symptomatic patients[7,9,16,25,36,41,43,45–47]: six for pain management,[9,16,25,36,41,45] two for psychological disorders,[7,46] two for asthma symptoms,[42,43] and one for sexual disorders.[47] Pain, whether provoked for the study or not, was the outcome in 40% of studies included (12 out of 30).

The number of patients included varied from 13 to 835 (median 70.5).

The presence or not of interaction was evaluated in most included studies by comparing the variables in each group in BPD with analysis of variance (ANOVA) or covariance (ANCOVA).[7,10,18,20,25–34,36,38,42–46,48] When it was detailed, the level of significance chosen was 0.05[10,20,25–28,30,32,33,38,39] (except for Bergmann et al at 0.10).[9] Linear regression models were also used to demonstrate interaction.[10,23,35,38–41]

Three studies did not sufficiently detail the statistical analysis.[16,37,47]

3.4 | Synthesis of results

Our review allowed us to include 22 new studies that were not included in Kleijnen et al's review. However, only eight[7,9,20,45–49] of the 10 studies included by Kleijnen et al could be reanalysed (the two others were unavailable[50,51]).

As illustrated in Tables 2, 16 studies found interaction between treatment effect and placebo effect.[7,9,27,28,30,31,33,38–42,44–46,48] Among these 16, seven described a synergistic model[7,27,33,38–40,48] and six an antagonistic model six with an antagonistic model.[9,28,30,31,41,42,44–46] Four studies provided evidence of additivity.[10,25,36,37]

There was evidence of effect reversal in two studies. In the study by Alasken et al,[10] informed participants were told that the eutectic mixture of local anaesthetics (EMLA) cream would exacerbate pain, and so it did. Similarly, in the study by Flaten et al,[35] the calming effect of a beta-blocker was reversed once participants were informed that a stimulant treatment would be applied.

The 14 other studies found no significant interaction.[10,16,20,25,26,29,32,34–37,43,47,49] The lack of evidence for interactions in some studies was due to the fact that there was no effect at all.[16,20,26,29,32,34,35,43,47] In the other studies, the hypothesis was not tested.[10,25,36,37,47]

Statistical meta-analysis of the interaction was not carried out due to lack of available data (means and standard deviation were missing).

3.5 | Risk of bias across studies

Risk of bias was evaluated as low for seven studies,[25,27,32,33,35,40,43] intermediate for four[10,31,37,41] and high for the rest.[7,16,20,26,28–30,34,36,38,39,42,44–49]

3.6 | Amendment to the initial protocol: Analysis of results according to context

This was not planned a priori but the studies were set either in clinical context (symptomatic patients) or in laboratories (healthy volunteers). Among the 19 studies carried out in laboratories,[10,20,26–35,37–40,44,48,49] 10 (52%) showed an interaction. Among the 11 studies carried out in a clinical context,[7,9,16,25,36,41–43,45–47] six (54%) showed an interaction.

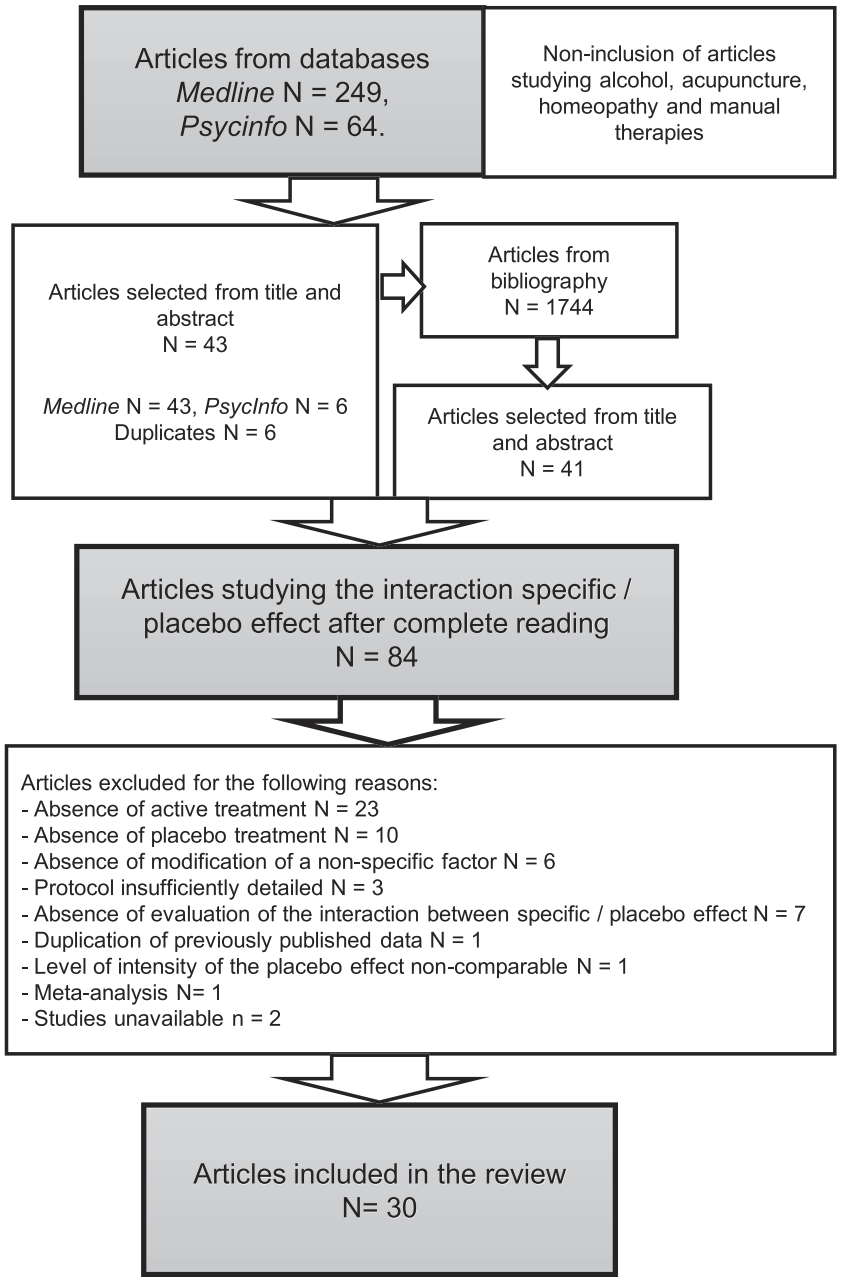


FIGURE 3 Flowchart illustrating the selection process

4 | DISCUSSION

4.1 | Summary of results

There was evidence of interaction in over half of our sample. The trials included were of poor quality overall and 18 out of 30 included healthy volunteers, making it difficult to judge the clinical pertinence of our results. Indeed, interaction can only exist if there is a specific *and* a placebo effect. On the one hand, some situations are "sensitive" to the placebo effect,[52] especially in cases of perceived disorders such as pain,[52] nausea,[52] anxiety,[52] coughing[53] and shortness of breath.[54] On the other hand, in situations where neither the drug nor the placebo is effective, no interaction (or additivity for that matter) can take place. To our knowledge, there is no direct proof showing that the placebo effect exists for hard outcomes, such as morbidity/mortality.[52] The high prevalence of studies on healthy volunteers may be the result of ethical limitations.

4.2 | Comparison with other studies

Our work confirms and adds to the earlier systematic review by Kleijnen et al[15] and a more recent literature review carried out in 2018 by Coleshill et al[18] (which only included studies pertaining to

TABLE 2 Study characteristics and results

(a) Trials including patients

Trials	Population	Information modifying the power of the placebo effect	Treatment group	Endpoints	Interaction found? (which model?)	Risk of bias
Faasse et al (2016)[41]	87 patients with chronic headaches	Oral information provided on the treatment brand administered: minimized or maximized situations	Ibuprofen	Pain	Yes (antagonistic)	Unclear
Bergmann et al (1994)[9]	49 cancer patients	Oral information provided or not on the study procedure: neutral or maximized situations	Naproxen	Pain	Yes (antagonistic)	High
Wise et al (2009)[42]	601 poorly controlled asthmatics	Oral information provided on the treatment administered, its brand and its colour: neutral or maximized situations	Montelukast	Peak expiratory flow, spirometry and four self-assessment asthma scales	Yes (antagonistic)	High
Levine et al (1984)[45]	96 patients having undergone dental extraction	Hidden administration of treatments, manually or by a machine: minimized, neutral or maximized situations	Naloxone	Pain	Yes (antagonistic)	High
Uhlenhuth et al (1959)[7]	52 psychiatric patients suffering from anxiety	Neutral or positive attitude concerning the treatments administered: neutral or maximized situations	Meprobamate or phenobarbital	Improvement perceived by patients, assessment by a psychiatrist and a scale grouping together 45 symptoms	Yes (synergistic)	High
Uhlenhuth et al (1966)[46]	138 patients referred to psychiatric clinic	Neutral or positive attitude concerning the treatments administered: neutral or maximized situations	Meprobamate in neutral or maximized situation	Modifications on different scales	Yes (antagonistic)	High
Kam-Hansen et al (2014)[25]	66 chronic migraine patients	Oral information on the treatment administered: minimized, neutral or maximized situations	Razatriptan	Pain	No (additive)	Low
Kemeny et al (2007)[43]	55 poorly controlled asthmatics	Oral information provided on the treatment administered: neutral or maximized situations	Salmeterol	Concentration of methacholine needed to induce a 20% FEV1 decrease	No (no effect)	Low
Mathews et al (1983)[47]	48 couples presenting with sexual disorders	Frequency of administration and number of therapists: weekly, monthly and at least one therapist	Testosterone	Improvement of symptoms evaluated by an outside investigator and the couples themselves	No (no effect)	High
De Craen et al (2001)[16]	112 chronic pain patients	Written information on the treatment administered: neutral or maximized situations	Tramadol	Pain	No (no effect)	High

(Continues)

TABLE 2 (Continued)

(a) Trials including patients

Trials	Population	Information modifying the power of the placebo effect	Treatment group	Endpoints	Interaction found? (which model?)	Risk of bias
Brandwhaite et al (1981)[36]	835 women with chronic headaches	Oral information provided on the "brand" of treatment administered: minimized or maximized situations	Aspirin	Pain	No (additive)	High

(b) Trials including healthy volunteers

Trials	Population	Information modifying the power of the placebo effect	Treatment group	Endpoints	Interaction found? (which model?)	Risk ok bias
Schenk et al (2013)[40]	34 healthy volunteers	Oral information provided on the treatment administered: minimized or maximized situation	Lidocaine	Pain after painful thermal stimulus	Yes (synergistic)	Low
Hammami et al (2016)[27]	480 healthy volunteers	Oral information on the treatment administered: minimized, neutral or maximized situations	Hydroxyzine	Drowsiness and dry mouth	Yes (synergistic)	Low
Berna et al (2017)[33]	100 healthy volunteers	Oral information that an analgesic yielding a dry mouth would be administered (in fact, it was atropine): minimized or maximized situations	Diclofenac	Pain after painful thermal stimulus	Yes (synergistic)	Low
Lund et al (2014)[31]	46 healthy volunteers	Oral information on the treatment administered: minimized or maximized situations	Lidocaine	Self-assessed pain duration and its maximal intensity after painful stimulus by IM injection	Yes (antagonistic)	Unclear
Kirsch et al (1993)[38]	100 healthy volunteers	Oral information on the treatment administered: minimized or maximized situation	Caffeine	Level of alertness and stress, systolic and diastolic tension and cardiac rhythm	Yes (synergistic)	High
Penick et al (1965)[39]	14 healthy volunteers	Oral information on the treatment administered: minimized or maximized situations	Epinephrine	Level of perceived stress, glucose and free fatty acid concentration and cardiac rhythm	Yes (synergistic)	High
Van Der Molen et al (1988)[48]	13 healthy volunteers	Oral information provided on the treatment administered: minimized (relaxing information) and maximized (stressful information) situations	Lactate	Anxiety, pCO_2 and respiratory rate	Yes (synergistic)	High
Rose et al (2001)[44]	53 healthy volunteers	Oral and written information on the treatment administered: minimized or maximized situations	Melatonin	12-question assessment sleeping scale	Yes (antagonistic)	High
Mitchell et al (1996)[30]	40 healthy volunteers	Oral information on the treatment administered: minimized or maximized situations	D-amphetamine	Different scales of drug response (ARCI, DEQ, POMS)	Yes (antagonistic)	High
Hammami et al (2010)[28]	180 healthy volunteers	Oral information on the treatment administered: maximized or minimized situations	Caffeine	Subjective self-assessed (energy, fatigue, nausea) and objective parameters (systolic blood pressure)	Yes (antagonistic)	High

TABLE 2 (Continued)

(b) Trials including healthy volunteers

Trials	Population	Information modifying the power of the placebo effect	Treatment group	Endpoints	Interaction found? (which model?)	Risk ok bias
Butcher et al (2012)[32]	20 healthy volunteers	Oral information on the treatment administered: minimized or maximized situations	Ibuprofen	Pain after painful electric stimulus	No (no effect)	Low
Flaten et al (2004)[35]	94 healthy volunteers	Oral information on the treatment administered: minimized, neutral or maximized situation	Carisoprodol or caffeine	Eyeblink reflex, self-assessment of level of wakefulness and calm, skin conductance, cardiac rhythm, arterial tension	No (no effect)	Low
Alasken et al (2015)[10]	142 healthy volunteers	Oral information that analgesic or hyperalgesic cream was going to be administered: minimized or maximized situations	EMLA cream	Endpoints evaluated after painful stimulus, including pain, stress and blood pressure	No (additive)	Unclear
Atlas et al (2012)[37]	14 healthy volunteers	Oral information on the treatment administered: minimized or maximized situation	Remifentanil	Pain after painful thermal stimulus	No (additive)	Unclear
Ross et al (1962)[19]	80 healthy volunteers	Hidden administration of treatments to minimize their effect: minimized or neutral situations	D-amphetamine	Mood swings (Clyde mood scale) and level of performance (tapping task and H-bar test)	No (no effect)	High
Walach et al (2009)	75 healthy volunteers	Oral information on the treatment administered	Caffeine	Objective parameters (SAT, DAT, CF, reaction time) and subjective parameters	No (no effect)	High
Bjorkedal et al (2011)[29]	20 healthy volunteers	Oral information that a powerful painkiller was administered (in fact, caffeine): minimized or maximized situations	Caffeine	Wakefulness, stress, pain, expectations and laser-evoked potentials	No (no effect)	High
Flaten et al (1999)[34]	66 healthy volunteers	Oral information on the treatment administered: minimized, neutral or maximized situations	Carisoprodol	Eyeblink reflex, skin conductance, self-assessment of level of stress and drowsiness	No (no effect)	High
Lyerly et al (1964)[49]	90 veterans and 90 young employees	Oral information provided on the treatment administered: minimized, neutral or maximized situations	Amphetamine and chloral hydrate	Mood swings (Clyde mood scale) and level of performance (tapping task and H-bar test)	No (no effect)	High

Abbreviations: ARCI, addiction research center inventory; CF, cognitive function; DAT, divided attention task; DEQ, drug effect questionnaire; EMLA, eutectic mixture of local anaesthetics; FEV1, forced expiratory volume in 1 second; IM, intramuscular; pCO_2, partial pressure of carbon dioxide; POMS, profile of mood states; SAT, spontaneous awakening trials; VAS, visual analogue scale.

pain). The evidence of effect reversal corroborates the initial experiments of Stewart Wolf in the 1950s[55] as well as those of more recent studies.[56]

4.3 | Limitations

The study had limitations. The included studies were small (only nine had over 100 participants) and of poor quality. Publication bias was also possible. Although the placebo effect is a subject that has received considerable attention, this is not the case for interaction between the placebo effect and the specific effect. However, this difficulty had been anticipated in our research protocol. We had decided to restrict our initial research to facilitate systematic analysis of the bibliographies of the included studies and of the authors of several relevant publications. For example, we identified two studies which supported the interactive model, but they were not included in our analysis because no test and no interpretation of the interaction were included in the publication.[57,58] However, negative studies may not have been published. Selective reporting was another potential problem. While several endpoints were often measured in the studies, interaction was analysed for only one endpoint.

Moreover, most (19/30, 63%) of the experimentations took place in a laboratory setting and involved healthy volunteers, a factor possibly limiting extrapolation of the results to routine clinical practice. Intensity of the placebo effect was probably higher in patients presenting with clinical symptoms such as pain.[59] However, an analysis of the data in two subgroups found that interaction presented similarly in both contexts. In the end, we were unable to undertake our planned meta-analysis, the data being too fragmented to pool. Indeed, for three-quarters of the studies, we were unable to obtain the necessary data to carry out a meta-analysis according to Cochrane standards.

4.4 | Consequences and implications

In spite of its limitations, our study shows that additivity cannot be the default assumption, at least in trials where placebo effects exist. The existence of interaction between pharmacological effect and placebo effect has consequences for medical practice, and clinical trials in particular; the effect of a treatment can no longer be considered independently of supposedly nonspecific factors. BPD trials should be carried out to better evaluate those factors that could modify the interaction, and statistical simulations could also be used to optimise the study design. Indeed, a recent expert consensus recommended a number of attitudes to be adopted in clinical practice to maximize treatment effects and minimize adverse effects.[60] In clinical practice, this reinforces the need for a biopsychosocial therapeutic model.[60,61] It becomes of utmost importance to understand how psychobiological factors affect therapeutic outcome to maintain or regain the trust of patients in medical science, as argued by Benedetti et al.[62] As suggested by Berna et al[33] and also Schenck et al,[40] a minimal placebo intensity may be necessary to get a treatment response. On the contrary, minimizing the placebo effect with an unempathetic approach[60] may decrease treatment response. At most, there may be an inverted effect of the drug depending on the information given.[10,34]

The presence of interactions also implies that the external validity of trial results (in areas that are placebo-sensitive) cannot be assumed.[63–65] This extends beyond traditional worries about external validity. Indeed, instead of focusing on the potentially different responses to interventions in trial and target populations, our analysis revealed that the very difference between intervention and placebo cannot be assumed to be stable across trial and target populations. Our sample showed that, albeit in rare cases, the effect direction of the intervention-placebo difference can be reversed.[66–68] Pragmatic trials would overcome the worries related to external validity that our analysis illustrates. In France, for example, the Haute Autorité de Santé (French National Authority for Health) has mandated post-registration meta-analyse to test glifozins (SGLT2 inhibitors, antidiabetic drugs) against older antidiabetic drugs.[69] The former have been submitted to solid placebo-controlled trials, but the latter have not. Comparing different treatment strategies, post-registration, as prescribed in clinical practice, would allow a better analysis of the treatment effect with an evaluation of the nocebo and placebo effects specific to each treatment strategy.

Moreover, interactions may explain the variability observed between RCTs and "real world evidence".[64,65,70] For example, a recent systematic review involving 347 trials (89 183 patients) compared trials that used placebo run-in periods with trials that did not.[71] In these trials, patients who respond to placebo in the run-in period are excluded from the eventual trial. The authors found that the drug-placebo difference was smaller in trials that used placebo run-in periods. Whereas an additive model would predict that the drug-placebo *difference* was constant, our results offer a plausible explanation for the findings of this systematic review. Since some patients in routine practice will be placebo responders, trials that use placebo run-in periods are not representative and, to estimate an intervention's real world effects, alternatives such as pragmatic trials or enabling technologies should be considered.

Finally, interaction between the treatment effect and the placebo effect challenges the concept of a "specific" effect of a treatment and of its "intrinsic" effect.[72–77] Any and every therapeutic intervention can be considered as "complex".[76,77]

4.5 | Conclusion

The therapeutic effect of a treatment can be increased, decreased or even reversed depending on the intensity of the placebo effect. Because placebo effects are likely to differ in trial and "real-world" contexts,[70] interventions for placebo-sensitive ailments may have very different specific effects in trials than they do in actual practice. To overcome this problem, interventions for placebo-

sensitive ailments should be tested in pragmatic trials once an exploratory RCT has proven their efficacy with sufficient internal validity.

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CONFLICT OF INTEREST

The authors declare that they have no competing interests. No funding was received.

CONTRIBUTORS

R.Bo. conceived the study, organised the research, verified the methodology, interpreted the results and wrote the initial draft. J.H. provided methodological guidance, helped interpret the results and critically reviewed the final draft of the manuscript. R.Ba. organised the database search, and helped with the methodology and the critical review of the first draft of the manuscript. F.N. participated in the critical review of the manuscript and reread the final draft, helped interpret the results and critically reviewed the final draft of the manuscript. B.F. participated in the critical review of the manuscript and reread the final draft, helped interpret the results and critically reviewed the final draft of the manuscript. G.H.-G. participated in the critical review of the manuscript and reread the final draft. W.I. participated in the critical review of the manuscript and reread the final draft. F.G. provided methodological guidance, participated in the critical review of the manuscript and reread the final draft, verified the methodology and interpreted the results. N.J. participated in the critical review of the manuscript and reread the final draft. C.B. interpreted the results, translated the initial draft into English, responded to the reviewers' critiques, managed the project and is the corresponding author. All authors read and approved the final manuscript.

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APPENDIX 1: RISK OF BIAS ANALYSIS

The following table is an example of how risk of bias was evaluated in this study using the RoB2 tool for the analysis here of Hammami et al (2010). Please see below for the detailed analysis of all the included trials.

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Description	Response options
1.1 Was the allocation sequence random? 1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?	The randomization schedule was generated by one of the authors (M.M.H.) using a program available online (http://www.randomization.com) Group assignment was concealed before randomization from participants and the study coordinators who enrolled them	Y Y
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	Baseline characteristics of study groups are shown in Table 1	N
Risk-of-bias judgement		Low

Note: N, No; Y, Yes.

Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Signalling questions	Description	Response options
2.1. Were participants aware of their assigned intervention during the trial? 2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?	None (participants) indicated that they guessed the actual study aims Study coordinators guessed that 52%, 51%, 41% and 44% of participants who received caffeine described as caffeine, caffeine described as placebo, placebo described as placebo and placebo described as caffeine, respectively, received caffeine, indicating the success of blinding	PN PN
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the experimental context?		NA
2.4. If Y/PY to 2.3: Were these deviations from intended intervention balanced between groups?		NA
2.5 If N/PN/NI to 2.4: Were these deviations likely to have affected the outcome?		NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?		PY
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		NA
Risk-of-bias judgement		Low

Note: N, No; NI, No Information; PN, Probably No; PY, Probably Yes; Y, Yes.

Domain 3: Missing outcome data

Signalling questions	Description	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	180 were equally randomized to caffeine or placebo cross-over arms We excluded from analysis participants who later withdrew from the study (three randomized to placebo, two to caffeine) or did not adequately abstain from caffeine (baseline caffeine levels in the study periods differed by ≥1 μg/mL (two randomized to placebo and five to caffeine). A flowchart is presented in Figure 2	Y
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		NA
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA
3.4 If Y/PY/NI to 3.3: Do the proportions of missing outcome data differ between intervention groups?		NA
3.5 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA
Risk-of-bias judgement		Low

Note: N, No; NI, No Information; PN, Probably No; PY, Probably Yes; Y, Yes.

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Description	Response options
4.1 Was the method of measuring the outcome inappropriate?		PN
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?		N
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		NA
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of the intervention received?		NA
Risk-of-bias judgement		Low

Note: N, No; NI, No Information; PN, Probably No; PY, Probably Yes; Y, Yes.

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Description	Response options
5.1 Was the trial analysed in accordance with a pre-specified plan that was finalized before unblinded outcome data were available for analysis?	Trial registration: ClinicalTrials.gov identification number NCT00426010 There were no changes to study outcomes after study commencement	Y
Is the numerical result being assessed likely to have been selected, on the basis of the results, from…		
5.2. … Multiple outcome measurements (e.g. scales, definitions, time points) within the outcome domain?	Measure of fatigue, energy, nausea, systolic blood pressure and conclusion according to results of energy and fatigue only, while no tests found significant difference	Y
5.3 … Multiple analyses of the data?		PN
Risk-of-bias judgement		High

Note: PN, Probably No; Y, Yes.

Overall risk of bias

Risk-of-bias judgement	High

Table of risk of bias evaluation for included trials according to RoB2

Included trials (year of publication)	Domains					Overall risk of bias
	1	2	3	4	5	
Kam-Hansen et al (2014)[25]	Low	Low	Low	Low	Low	Low
Walach et al (2009)[26]	Low	Low	Low	Low	High	High
Hammami et al (2016)[27]	Low	Low	Low	Low	Low	Low
De Craen et al (2001)[16]	Some concerns	High	Low	Some concerns	High	High
Hammami et al (2010)[28]	Low	Low	Low	Low	High	High
Bjorkedal et al (2011)[29]	Low	Low	Low	Low	High	High
Mitchell et al (1996)[30]	Low	High	Low	Low	Some concerns	High
Aslasken et al (2015)[10]	Some concerns	Some concerns	Low	Low	Low	Some concerns
Lund et al (2014)[31]	Low	Low	Low	Low	Some concerns	Some concerns
Butcher et al (2012)[32]	Low	Low	Low	Low	Low	Low
Berna et al (2017)[33]	Low	Low	Low	Low	Low	Low
Flaten et al (1999)[34]	Low	Low	Low	Low	High	High
Flaten et al (2004)[35]	Low	Low	Low	Low	Low	Low
Brandwhaite et al (1981)[36]	Low	Low	Low	Low	Some concerns	Low
Atlas et al (2012)[37]	Some concerns	Some concerns	Low	Some concerns	Some concerns	Some concerns
Kirsch et al (1993)[38]	Low	Some concerns	Low	Low	High	High

Included trials (year of publication)	Domains					Overall risk of bias
	1	2	3	4	5	
Penick et al (1965)[39]	High	High	Low	High	Low	High
Schenk et al (2014)[40]	Low	Low	Low	Low	Low	Low
Faasse et al (2016)[41]	Low	Some concerns	Low	Some concerns	Some concerns	Some concerns
Wise et al (2009)[42]	Low	Low	Low	Low	High	High
Kemeny et al (2007)[43]	Low	Low	Low	Low	Low	Low
Rose et al (2001)[44]	Low	Low	Some concerns	Some concerns	High	High
Ross et al (1962)[19]	Some concerns	Some concerns	Some concerns	Some concerns	Some concerns	High
Levine et al (1984)[45]	Low	Some concerns	Some concerns	Some concerns	Low	High
Uhlenhuth et al (1959)[7]	Low	Low	Some concerns	Some concerns	Low	High
Uhlenhuth et al (1966)[46]	Low	Some concerns	Some concerns	Low	High	High
Mathews et al (1983)[47]	Some concerns	High	Some concerns	Some concerns	Low	High
Van Der Molen et al (1988)[48]	Some concerns	Some concerns	Low	Some concerns	High	High
Lyerly et al (1964)[49]	Some concerns	Some concerns	Low	Some concerns	High	High
Bergmann et al (1994)[9]	Low	Low	Some concerns	Low	Low	Some concerns

APPENDIX 2

Trials	Hypothesis tested	Population	Modification of the power of the placebo effect	Treatments	Endpoints
Kam-Hansen et al (2014)[25]	Additive model and interactive model	66 chronic migraine patients	Oral information on the treatment administered	Treatment group (razatriptan) and placebo in minimized, neutral or maximized situation	Relief 2 h after onset of migraine symptoms and number of subjects without pain at 2.5 h
Walach et al (2009)[26]	Placebo effect depending on a nonlocal correlation with response to treatment	75 healthy volunteers	Oral information on the treatment administered	Treatment group (caffeine) and placebo in maximized or neutral situation	Objective parameters (SAT, DAT, CF, reaction time) and subjective parameters (calm, mood and alertness)
Hammami et al (2016)[27]	Interactive model	480 healthy volunteers	Oral information on the treatment administered	Treatment group (hydroxyzine) and placebo in minimized, neutral or maximized situation	Drowsiness and dry mouth, self-assessed by the participants during the 7 h following treatment
De Craen et al (2001)[16]	Interactive model	112 chronic pain patients	Written information on the treatment administered	Treatment group (tramadol) and placebo in maximized or neutral situation	Primary endpoint: pain reduction on self-assessing VAS
Hammami et al (2010)[28]	Interactive model and pharmacokinetic modification of the placebo effect	180 healthy volunteers	Oral information on the treatment administered	Treatment group (caffeine) and placebo in maximized or minimized situation	Subjective self-assessed (energy, fatigue, nausea) and objective parameters (systolic blood pressure)
Bjorkedal et al (2011)[29]	Interactive model: variation of treatment activity according to adverse effects	20 healthy volunteers	Oral information that a powerful painkiller was administered (in fact, caffeine)	Treatment (caffeine) and placebo groups in maximized or minimized situations	Wakefulness, stress, pain, expectations and laser-evoked potentials

(Continues)

Trials	Hypothesis tested	Population	Modification of the power of the placebo effect	Treatments	Endpoints
Mitchell et al (1996)[30]	Interactive model	40 healthy volunteers	Oral information on the treatment administered	Treatment group (D-amphetamine) and placebo in maximized or minimized situation	Different scales of drug response (ARCI, DEQ, POMS)
Alasken et al (2015)[10]	Interactive model: inversion of treatment effects by means of information	142 healthy volunteers	Oral information that analgesic or hyperalgesic cream was going to be administered	Treatment group (EMLA cream) and placebo in minimized or maximized situation	Endpoints evaluated after painful stimulus, including pain, stress and blood pressure
Lund et al (2014)[31]	Interactive model, being of more import with powerful placebo effect	46 healthy volunteers	Oral information on the treatment administered	Treatment group (lidocaine) and placebo in minimized or maximized situation	Self-assessed pain duration and its maximal intensity after painful stimulus by IM injection
Butcher et al (2012)[32]	Variation of the placebo effect according to gender	20 healthy volunteers	Oral information on the treatment administered	Treatment group (ibuprofen) and placebo in minimized or maximized situation	Self-assessed pain after painful electric stimulus
Berna et al (2017)[33]	Interactive model: activity variation according to adverse effects	100 healthy volunteers	Oral information that an analgesic yielding a dry mouth would be administered (in fact, it was atropine)	Treatment group (diclofenac) and placebo in minimized or maximized situation	Analgesia evaluated by VAS after painful thermal stimulus
Flaten et al (1999)[34]	Interactive model	66 healthy volunteers	Oral information on the treatment administered	Treatment group (carisoprodol) and placebo in minimized, neutral or maximized situation	Eyeblink reflex, skin conductance, self-assessment of level of stress and drowsiness
Flaten et al (2004)[35]	Interactive model	94 healthy volunteers	Oral information on the treatment administered	Treatment group (carisoprodol), caffeine and placebo in minimized, neutral or maximized situation	Eyeblink reflex, self-assessment of level of wakefulness and calm, skin conductance, cardiac rhythm, arterial tension
Brandwhaite et al (1981)[36]	Interactive model	835 women presenting with chronic headaches	Oral information provided on the "brand" of treatment administered	Treatment group (aspirin) and placebo in minimized or maximized situation	Pain self-assessment 30 min and 1 h after headaches
Atlas et al (2012)[37]	Interactive model	14 healthy volunteers	Oral information on the treatment administered	Treatment group (remifentanil) and placebo in minimized or maximized situation	Self-assessed pain after painful thermal stimulus
Kirsch et al (1993)[38]	Interactive model	100 healthy volunteers	Oral information on the treatment administered	Treatment group (caffeine) and placebo in minimized or maximized situation	Level of alertness and stress, systolic and diastolic tension and cardiac rhythm at 15, 30 and then 45 min after ingestion
Penick et al (1965)[39]	Interactive model	14 healthy volunteers	Oral information on the treatment administered	Treatment group (epinephrine) and placebo in minimized or maximized situation Endpoints: I	Level of perceived stress, glucose and free fatty acid concentration and cardiac rhythm
Schenk et al (2013)[40]	Interactive model	34 healthy volunteers	Oral information provided on the treatment administered	Treatment group (lidocaine) and placebo in minimized or maximized situation	Self-assessment of pain on VAS after painful thermal stimulus

Trials	Hypothesis tested	Population	Modification of the power of the placebo effect	Treatments	Endpoints
Faasse et al (2016)[41]	Additive model	87 patients presenting with chronic headaches	Oral information provided on the treatment brand administered	Treatment group (ibuprofen) and placebo in minimized or maximized situation	Home self-assessment of pain following headache episodes and reported adverse effects
Wise et al (2009)[42]	Interactive model	601 poorly controlled asthmatics	Oral information provided on the treatment administered, its brand and its colour	Treatment group (montelukast) and placebo in neutral or maximized situation	Improvement at 4 wk of peak expiratory flow, improvement of pulmonary functions evaluated by spirometry and asthma control evaluated by four self-assessment scales
Kemeny et al (2007)[43]	Variation of the placebo effect and its determinants	55 poorly controlled asthmatics	Oral information provided on the treatment administered	Treatment group (salmeterol) and placebo in maximized or neutral situation	Concentration of methacholine needed to induce a 20% FEV1 decrease
Rose et al (2001)[44]	Interactive model	53 healthy volunteers	Oral and written information on the treatment administered	Treatment group (melatonin) and placebo in minimized or maximized situation	Subjective sleep evaluated by a 12-question assessment scale
Ross et al (1962)[19]	Interactive model	80 healthy volunteers	Hidden administration of treatments to minimize their effect	Treatment group (D-amphetamine) and placebo in the same neutral or minimized situations	Mood swings (Clyde mood scale) and level of performance (tapping task and H-bar test)
Levine et al (1984)[45]	Placebo effect independent of the means of administration	96 patients having undergone dental extraction	Hidden administration of treatments, manually or by a machine	Treatment group (naloxone) and placebo in minimized, neutral or maximized situation	Self-assessment of pain 50 min after treatment administration
Uhlenhuth et al (1959)[7]	Interactive model	52 psychiatric patients suffering from anxieties	Neutral or positive attitude concerning the treatments administered	Treatment group (meprobamate or phenobarbital) and placebo in neutral or maximized situation	Improvement perceived by patients, assessment by a psychiatrist and a scale grouping together 45 symptoms
Uhlenhuth et al (1966)[46]	Interactive model	138 patients referred to psychiatric clinic	Neutral or positive attitude concerning the treatments administered	Treatment group (meprobamate) in neutral or maximized situations and placebo in the same situations	Modifications on different scales
Mathews et al (1983)[47]	Interactive model	48 couples presenting with sexual disorders	Frequency of administration and number of therapists	Treatment group (testosterone) and placebo with weekly or monthly administration and at least one therapist	Improvement of symptoms evaluated by an outside investigator and the couples themselves
Van Der Molen et al (1988)[48]	Hyperventilation in the event of lactate injection or stressful information	13 healthy volunteers	Oral information provided on the treatment administered	Treatment group (lactate) and placebo in minimized (relaxing information) and maximized (stressful information) situations	Anxiety, pCO_2 and respiratory rate

(Continues)

Trials	Hypothesis tested	Population	Modification of the power of the placebo effect	Treatments	Endpoints
Lyerly et al (1964)[49]	Interactive model	90 veterans and 90 young employees	Oral information provided on the treatment administered	Treatment group (amphetamine and chloral hydrate) versus placebo in minimized, neutral or maximized situation	Mood swings (Clyde mood scale) and level of performance (tapping task and H-bar test).
Bergmann et al (1994)[9]	Interactive model	49 cancer patients	Oral information provided or not on the study procedure	Treatment group (500 mg of naproxen) and placebo in neutral or maximized situation	Self-assessment of pain on VAS up to 3 h after administration

Detailed study characteristics. A minimized situation corresponds to less placebo effect power compared to a neutral or maximized situation.
Abbreviations: ARCI, addiction research center inventory; CF, cognitive function; DAT, direct antiglobulin test; DEQ, drug effect questionnaire; EMLA, eutectic mixture of local anaesthetics; FEV1, forced expiratory volume in 1 second; IM, intramuscular; pCO_2, partial pressure of carbon dioxide; POMS, profile of mood states; SAT, spontaneous awakening trials; VAS, visual analogue scale.

Interaction and risk of bias (· · ·: missing data)

Studies	Effect of the treatment	Effect of the information	Interaction	Model	Risk of bias
Hammami et al (2016)[27]	Yes	Yes	Yes	**Synergistic**	Low
Berna et al (2017)[33]	No	No	Yes	**Synergistic**	Low
Schenk et al (2013)[40]	Yes	No	Yes	**Synergistic**	Low
Lund et al (2014)[31]	Yes	Yes	Yes	**Antagonistic**	Unclear
Faasse et al (2016)[41]	Yes	Yes	Yes	**Antagonistic**	Unclear
Hammami et al (2010)[28]	Yes	Yes	Yes	**Antagonistic**	High
Wise et al (2009)[42]	Yes	Yes	Yes	**Antagonistic**	High
Rose et al (2001)[44]	No	Yes	Yes	**Antagonistic**	High
Bergmann et al (1994)[9]	Yes	Yes	Yes	**Antagonistic**	High
Van Der Molen et al 1988)[48]	Yes	Yes	Yes	**Synergistic**	High
Kirsch et al (1993)[38]	Yes	Yes	Yes	**Synergistic**	High
Penick et al (1965)[39]	...	No	Yes	**Synergistic**	High
Uhlenhuth et al (1959)[7]	...	Yes	Yes	**Synergistic**	High
Uhlenhuth et al (1966)[46]	...	Yes	Yes	**Antagonistic**	High
Levine et al (1984)[45]	No	Yes	Yes	**Antagonistic**	High
Mitchell et al (1996)[30]	Yes	Yes	Yes	**Antagonistic**	High
Kam-Hansen et al (2014)[25]	Yes	Yes	No	Additive	Low
Butcher et al (2012)[32]	No	No	No	No effect	Low
Flaten et al (2004)[35]	Yes	No	No	No effect	Low
Kemeny et al (2007)[43]	Yes	No	No	No effect	Low
Alasken et al (2015)[10]	Yes	Yes	No	Additive	Unclear
Atlas et al (2012)[37]	Yes	Yes	No	Additive	Unclear
Brandwhaite et al (1981)[36]	Yes	Yes	No	Additive	High
De craen et al (2001)[16]	No	No	No	No effect	High
Flaten et al (1999)[34]	No	Yes	No	No effect	High
Bjorkedal et al (2011)[29]	No	No	No	No effect	High
Ross et al (1962)[19]	No	No	No	No effect	High
Lyerly et al (1964)[49]	No	No	No	No effect	High
Walach et al (2009)[26]	No	No	No	No effect	High
Mathews et al (1983)[47]	No	No	No	No effect	High