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A meta-review on placebos and nocebos in pharmacological interventions: where, when and how they work

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PRISMA 2020 for Abstract Checklist

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a meta-review.	YES
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	YES
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	YES
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	YES
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	YES
Synthesis of results	6	Specify the methods used to present and synthesise results.	YES
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	YES
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	YES
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	NO
Interpretation	10	Provide a general interpretation of the results and important implications.	YES
OTHER			
Funding	11	Specify the primary source of funding for the review.	NO
Registration	12	Provide the register name and registration number.	YES

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Abstract

Objectives: Understanding placebo and nocebo effects is essential in modern medicine, as the biological mechanisms they trigger are similar to those modulated by drugs. A surge of research in this field has occurred over the past 30 years and, therefore, our aim was to present an updated picture of placebo/nocebo effects in pharmacological interventions.

Design: Meta-review, with systematic reviews appraised by using the Assessment of Multiple Systematic Reviews 2 tool.

Data sources: Five databases were searched without any time restriction for systematic reviews, narrative reviews, and original articles (very recent or addressing under-investigated topics).

Outcome measures: Mechanisms underlying placebo/nocebo effects and/or their effect sizes (Cohen's *d* or Hedges' *g*) in pharmacological interventions. Results were summarized through narrative synthesis and tables.

Results: The databases search identified 372 studies, comprising 41 systematic reviews, 312 narrative reviews, and 19 original articles. An 78% of the examined systematic reviews were of high quality (79% for those with meta-analyses and 75% for those without).

Our findings reveal that, to date, mechanisms underlying placebo and/or nocebo effects have been characterized for: pain, non-noxious somatic sensation, Parkinson's disease, migraine, sleep disorders, intellectual disability, depression, anxiety, dementia, addiction, gynaecological disorders, attention-deficit hyperactivity disorder, immune and endocrine systems, cardiovascular and respiratory systems, gastrointestinal disorders, skin diseases, flu and related vaccines, oncology, obesity, physical and cognitive performance. Their magnitude ranges from small to large.

Significant responses to open-label placebo administration were documented for pain (low back pain and ischemic arm pain), depression, menopausal hot flushes, attention-deficit hyperactivity disorder, allergic rhinitis, irritable bowel syndrome, psoriasis, and cancer-related fatigue.

Conclusions: This meta-review provides a valuable reference tool for clinicians and researchers seeking to understand placebo and nocebo mechanisms and their related effects. It can also guide the selection of outcome measures for specific settings.

Protocol registration number: PROSPERO, CRD42023392281

Keywords

placebo effect, placebo response; placebo-related effect; nocebo effect; nocebo response; nocebo-related response; mind-body relationship.

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Strengths and limitations of this study

- The meta-review followed strict PRISMA guidelines to minimise bias in literature selection.
- It provides, to our knowledge, the most updated valuable reference tool for clinicians and researchers seeking to understand the biological mechanisms underlying placebo and nocebo effects and their effect sizes. It can also guide the selection of outcome measures for specific settings.
- By only analysing placebo and nocebo effects in pharmacological interventions, it was possible to circumscribe the area of investigation and reduce the degree of methodological variability between studies.
- Systematic reviews were appraised by using the Assessment of Multiple Systematic Reviews 2 tool, which has demonstrated satisfactory reliability and construct validity.
- While the meta-review methodology allows for a comprehensive summary of the findings, it does not permit to overcome the single study limitations, which include publication biases, and the lack of information about unpublished data and the grey literature.

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Introduction

The placebo effect is defined as the ritual of the therapeutic act as a whole.[1] It involves administering a substance or treatment that lacks intrinsic therapeutic properties within a context rich in sensory and social cues, conveying that a beneficial treatment is being given. In addition to the external context, individuals' beliefs and their memories of previous treatments also deal with the process.[2–4] The opposite phenomenon to the placebo effect is represented by the nocebo effect, which occurs in negative care settings and is associated with negative outcomes.[2–5]

Over the past 30 years, there has been a surge of research on the placebo and nocebo effects in the fields of neuroscience, medicine, psychology and genetics. What has emerged is that there are many placebo and nocebo effects, not just one. They occur through specific mechanisms in many clinical conditions and in the domain of physical and cognitive performance.[6] Furthermore, it has been shown that many biological mechanisms triggered by placebos and nocebos resemble those modulated by drugs, suggesting a possible interaction between psychological factors and drug action.[6]

In 2018, a consensus of experts emphasized the importance of distinguishing *placebo effects* from *placebo responses*.[7] This need comes from the pharmacological definitions of *drug effect* and *drug response*, whereby the former is the specific pharmaco-dynamic effect of a drug, whereas the latter is the global response to drug administration.[6] Accordingly, while the *placebo* and *nocebo effects* specifically refer to the changes attributable to placebo and nocebo mechanisms, which are the "actual" psychobiological phenomena, the *placebo* and *nocebo responses* include all trial outcome changes resulting from the administration of an inactive treatment, including natural history and regression to the mean.[7]

Besides classical placebo/nocebo effects, today we can also differentiate between placebo/nocebo effects and placebo- and nocebo-related effects. Although the psychosocial context around the treatment plays a key role in both cases, in the former case, an inert (placebo) treatment is administered, while in the latter case, it is not.[8] These strict definitions remind us that it is not always necessary to administer a placebo to obtain a therapeutic effect, as sometimes the doctor's or health care professionals' words, their attitudes, and the therapeutic rituals are enough.[8]

Another important term used in clinical research is the Hawthorne effect, which refers to changes in baseline conditions that occur in response to a participant's awareness of being under study. Improvements that occur after recruitment but before the start of treatment could be attributable to several factors, including increased expectations of health benefits, better observation, better compliance, and treatment adherence.[9]

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With the exponential increase in the placebo and nocebo literature,[10] novel interpretative approaches have arisen (i.e., Pagnini et al.[11], Ongaro and Kaptchuk[12]), along with the concept of open-label placebos, in which patients are informed that they have been prescribed inert treatments.[13]

It is therefore highly important to incorporate new insights with the existing knowledge. The meta-review methodology provides a unique approach to knowledge integration, enabling the aggregation and synthesis of many reviews into a single document,[14] and exploring the consistency of findings across reviews.[15,16] This meta-review aims to present an updated picture of both placebo/nocebo effects and placebo/nocebo-related effects in pharmacological treatments. Our threefold goal was to define: 1) where robust placebo/nocebo effects or placebo/nocebo-related effects have been documented so far (i.e., in which medical and physiological conditions); 2) when they occur (i.e., any particular circumstances such as clinical or laboratory setting); 3) how they work (i.e., what do we know about the biological underpinnings).

Methods

Review selection

The study was developed according to the PRISMA guidelines,[17] with methods established prior to conducting the meta-review. The protocol was registered on the international prospective register for systematic reviews PROSPERO (record no. CRD42023392281, see Supplementary appendix 1A). The objective was to capture systematic (according to the PRISMA statement, with or without meta-analyses)[17] and narrative reviews mapping placebo and nocebo effects, or related effects, in pharmacological interventions, along with both their underlying mechanisms and their effect sizes (expressed as Cohen's *d* or Hedges' *g*).

The electronic bibliographic databases PubMed, Scopus, Web of Science, PsycINFO, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched according to the search equation (see Supplementary appendix 1B). The search was conducted applying the Population, Intervention, Comparison, Outcomes, and Study (PICOS) criteria reported in table 1, and no time restrictions were set.

Regarding the interventions, we excluded the investigation of placebo/nocebo effects and placebo/nocebo-related effects in non-pharmacological procedures (e.g., psychotherapy, acupuncture, surgery, neuromodulation, physical therapies, hypnosis, mindfulness training, biofeedback, neurofeedback, music) in order to circumscribe the area of investigation and reduce the degree of methodological variability among studies.

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The randomized clinical trials (RCTs) and open-label placebos (OLPs) clinical trials included in the present meta-review were required to have a three-arm design (i.e., genuine treatment, placebo, and no-treatment arms). The latter design allows participants receiving placebo treatment to be compared with those left untreated, and thus to disentangle placebo/nocebo effects from placebo/nocebo responses.[2]

To provide additional information on the biological mechanisms of placebo/nocebo effects, a first deviation from the original protocol was made for those meta-analyses based on rigorous placebo-controlled RCTs without a no-treatment group, which examined: i) different routes of placebo administration and reported improvements not attributable to spontaneous remission or regression to the mean; ii) different likelihoods of receiving active treatment or placebo; iii) the type of adverse events (AEs) occurring in both the active and placebo arms. A second deviation was made for original research articles informative about mechanisms and effect sizes that: i) addressed an under-investigated topic in the field of placebo research that missed to be included in systematic or narrative reviews; ii) were too recent to be included in systematic or narrative reviews.

Screening process and data extraction

The database search was conducted by one author (EF), who removed duplicates and screened the titles and abstracts. Two authors (EF and FP) independently reviewed the full text of potentially eligible studies (systematic review, narrative reviews and original research articles) against the inclusion and exclusion criteria. Any disagreements were resolved through discussion among all the authors. The references of the surveyed systematic and narrative reviews, and those of books or book chapters on placebo and nocebo mechanisms, were screened for potentially suitable publications. Very recent informative studies (systematic reviews and original research articles) were found through literature search. Data were entered progressively into a pre-set spreadsheet to record biological mechanisms and effect sizes, by the same authors.

Critical appraisal

EF and FP independently appraised the captured systematic reviews using the Assessment of Multiple Systematic Reviews (AMSTAR) 2 tool, which has demonstrated satisfactory reliability and construct validity.[18] In assessing the overall quality of individual studies, more weight was given to the AMSTAR 2 critical domains (i.e., 7 out 16 items).[18] About the protocol domain, an explicit statement was required that the methods had been established prior to conducting the systematic review, and/or PRISMA guidelines[17] or those for meta-analyses and systematic reviews of observational studies[19] had been adhered to, and/or any deviations from protocol had been

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reported. Supplementary appendix 2 provides the rating of critical domains for each of the examined systematic reviews, together with the final overall rating, which can be positive or negative. Moreover, results of critical appraisal were summarized as: i) the percentage of all surveyed systematic reviews that received a positive final overall assessment; ii) the percentage of systematic reviews, distinguishing between those with and without meta-analysis, that received a positive final overall assessment.

Because of the real heterogeneity in the examined conditions and in studies design included in each systematic review, we did not use funnel plots and we choose to summarize the meta-review results through narrative synthesis and tables.

Results

Meta-review outcomes

As shown in figure 1, the main search returned a total of 6215 records, which were reduced to 3725 after the exclusion of duplicates. After records were screened for title and abstract, and 3353 records were excluded, a total of 372 full text papers were retrieved, from which 357 met full inclusion criteria. Fifteen additional studies (5 systematic reviews with meta-analyses and 10 original research articles) were identified from citations or literature search, to a total of 372 studies included in the meta-review. In particular, the pool of eligible studies includes 41 systematic reviews, 312 narrative reviews, and 19 original articles, with all the examined systematic reviews and original articles published in the last 30 years.

Characteristics of the 41 systematic reviews, 33 with and 8 without meta-analyses, are presented in Table 2.[20–60] As documented in Supplementary appendix 2, 78% of the eligible systematic reviews were rated as overall high-quality, 79% for those with meta-analysis and 75% for those without. The Supplementary appendix 3 contains the list of both narrative reviews (1, A) and original articles (1, B) included in the meta-review, together with the list of systematic reviews identified from citation or literature search (1, C). The Supplementary appendix 4 contains the list of studies excluded after being read in their full length, with reason for the exclusion.

General concepts and mechanisms

Although placebos are not expected to work uniformly in all clinical conditions, a series of meta-analyses were conducted between 2001 and 2013 on three-arm RCTs across all clinical conditions (comprising mainly pharmacological interventions).[22–26] In particular, Hróbjartsson and Gøtzsche focused on the comparison between placebo and no-treatment groups. They found little evidence in general that placebo interventions had clinically important effects.[25,26] Placebos had no significant

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effects on continuous objective outcomes and subjective or objective binary outcomes, while they had possible small benefits in studies with continuous subjective outcomes, especially in the settings of pain and nausea.[23] Results obtained from Hróbjartsson and Gøtzsche's meta-analyses were inevitably constrained by the studies selected and the sensitivity of their measures. For example, binary outcomes have less power to detect effects generally than do continuous outcomes. Moreover, the authors used very broad inclusion criteria and the surveyed studies used 40 different outcome measures, some more reliable than others and some more likely to exhibit a response to placebo than others.[61]

Since the assessment of the clinical utility of placebos requires a comparison with an active treatment, in 2013 Howick and colleagues[22] extracted data about treatment effects from the last meta-analysis conducted by Hróbjartsson and Gøtzsche in 2010.[23] They showed that placebos often had a great benefit compared with no-treatment as active treatments had over placebos.[22] In trials with binary outcomes, active treatment effects were usually greater than placebo effects (n = 37, ratio of risk ratios = 0.72, 95% Confidence Interval [CI] = 0.61 to 0.86, p = 0.0003). In trials with continuous outcomes (n = 115), placebo effects were found to be higher than active treatment effects when the analysis was restricted to studies with a low risk of bias (n = 8, mean difference = 1.59, 95%CI = 0.40 to 2.77, p = 0.009).[22]

Starting from the same pool of studies used by Hróbjartsson and Gøtzsche in 2004,[25] and selecting studies that used peripherally measured parameters as outcomes, a subsequent meta-analysis showed that placebo interventions can improve physical disease processes of peripheral organs (n = 20, Hedges' pooled effect size = 0.22, 95% CI 0.07 to 0.36, p = 0.003) more easily and effectively than biochemical processes (n = 6, *g* = -0.17, 95% CI -0.31 to -0.02, p = 002).[24]

Regarding nocebo effects, manipulation of expectation, conditioning, or both has been shown to successfully evoke nocebo effects in domains such as those of pain sensation, skin dryness, nausea, and cognitive performance. Nocebo effects did not show to occur in the domains of satiety and dizziness.[27]

Despite their proven effectiveness in many conditions, prescribing placebos is considered unethical because it entails deception.[62] Yet, this idea has been challenged recently by the use of the OLP.[3,63] A positive effect for nondeceptive placebos compared with no-treatment (standardized mean difference 0.88, 95%CI 0.62 to 1.14, p < 0.00001) was recently reported in meta-analysis in which the clinical conditions analysed were depression, attention-deficit hyperactivity disorder (ADHD), irritable bowel syndrome (IBS), allergic rhinitis.[21]

The effect size of choice on the placebo effect has also recently been examined in a pool of studies that compared placebo treatment with any form of choice on its administration against placebo

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treatment without choice.[20] The fifteen eligible studies, which assessed a range of conditions including pain, discomfort, sleep difficulty, and anxiety, showed that choice did significantly enhance the placebo effect, even if with a small effect size (Hedges' g = 0.298). Also, the magnitude of the placebo effect without choice (i.e., placebo without choice versus no-treatment) was identified as the only reliable moderator of the choice effect, according to the role that larger placebo effect without choice produced smaller choice effects (i.e., placebo with choice vs. placebo without choice). Therefore, treatment choice can effectively facilitate the placebo effect, but this effect appears more pronounced in contexts where the placebo effect without choice is not prominent.[20]

From a psychobiological perspective, most knowledge about the mechanisms of placebo and nocebo effects comes from the field of pain. It shows that expectation and learning are the main mediators. Expectation is a conscious event, whereby the subject expects a future outcome. The link between expectation and clinical outcomes is twofold. First, positive expectations may reduce anxiety. Second, expectation of a positive event (i.e., a therapeutic benefit), may activate reward mechanisms, in which reward is the therapeutic benefit itself. Learning mechanisms, ranging from classical or behavioural conditioning to social learning, are crucial because prior experience toward effective treatments leads to substantial placebo effects. It is important to emphasize that expectation and learning are not mutually exclusive, since learning can lead to the reinforcement of expectations or can even create de novo expectations.[4,6,8]

A central role in placebo effects seems also to be played by the interactions between associative learning systems and appraisals, which are flexible cognitive evaluations of the personal meaning of events and situations. While learning can occur in many neural circuits, appraisal appears to be supported by a specialized system — a collection of midline cortical and temporoparietal regions associated with the so-called "default mode network". This network, involved in emotion generation, social and self-referential cognition, and value-based learning and decision making, allows individuals to simulate potential outcomes and to develop expectations about future events.[64]

In terms of predictive factors, it should be emphasized that many reasons exist why some people respond to placebos (placebo responders) while others do not (placebo non responders). Learning is certainly an important factor, as people who have had prior positive therapeutic experiences show larger placebo effects than those who have not had any.[1–3,6] Other important determinants are: personality traits; genetic variants; gender; individual differences in the efficiency of the neural mechanisms of reward, whereby the ventral striatum — i.e., the nucleus accumbens (NAcc) — is involved in motivation and reward anticipation; prefrontal functioning and connectivity.[4,65,66]

Regarding the latter factor, its importance in the placebo component of the analgesic treatments was

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demonstrated in studies on Alzheimer's disease (AD) patients, while the individual placebo analgesic effect was found to be correlated with the white matter integrity in the descending pain control system in normal subjects. Therefore, the potential disruption of placebo mechanisms should be considered in all those conditions where the prefrontal regions are involved, as occurs in vascular and frontotemporal dementia as well as in any lesion of the prefrontal cortex.[4] Regarding sex differences, males have been found to respond more strongly to placebo treatments, while females to nocebo treatments.[28] Furthermore, males respond with larger placebo effects induced by verbal information, whereas females respond with larger nocebo effects induced by conditioning procedures. The observed sex differences in placebo responding are probably due to larger stress reduction in males compared to females. Furthermore, endogenous opioid transmission has been reported to be more effective in males compared to females and may, therefore, explain the observed sex differences in placebo analgesia and nocebo hyperalgesia.[28]

Mechanisms of placebo and nocebo effects across conditions

The retrieved psychobiological mechanisms of placebo/nocebo effects and placebo-/nocebo-related effects in pharmacological interventions, together with their effect sizes, are reported in table 3. In summary, meaningful results have been found for the following clinical conditions: pain,[2,4,6,8,21,30–41,63,67–76] non-noxious somatic sensation,[77] Parkinson's disease,[2,6,42,78–80] migraine,[43–45] sleep,[46,81] intellectual disability (ID),[47] depression,[2,6,21,48,49,63,70,75,82–84] anxiety,[2,6,8,75] dementia,[2,4,50,85] addiction,[2,4,51,52,64,80,86,87] gynaecological disorders,[88,89] ADHD,[21,90] immune and endocrine systems,[2,4,21,80,91–93] cardiovascular system,[2,53,80,94,95] respiratory system,[2,80,96–98] gastrointestinal disorders,[6,21,54,63,75,99–101] skin diseases,[27,55,63,88,97,102–104] flu and related vaccines,[56,105] oncology,[21,27,54,63,97] and obesity.[9,106,107] Beyond the healing context, meaningful results have also been found for physical[2,57–60,108–110] and cognitive performance.[27,109,111] Regarding the effect sizes, they have been found to vary from small to large depending on the condition under investigation. Consistently, table 4 lists the clinical and non-clinical conditions according to the effect sizes of the placebo/nocebo effects, and for each of them indicates the outcome measures adopted (subjective and/or objective).

Interpreting the evidence

Some results about the magnitude or mechanisms of placebo and nocebo effects require interpretation and an in-depth analysis. Different settings and mechanisms present peculiarities that should be individually considered.

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In the field of pain, the difference in magnitude of placebo analgesia observed between those studies aimed at investigating placebo mechanism compared to those using placebos as control condition appears to result from different suggestions given for pain relief.[38] Moreover, magnitudes of placebo and nocebo effects in both nociceptive and idiopathic pain conditions appear to be roughly similar, supporting the hypothesis that similar mechanisms are involved in the opposite effects.[36] Regarding the difference in placebo analgesic effects according to the population type, patients show to benefit from placebo treatment to a greater extent than healthy participants do.[32] Consistently, the analysis of neurotransmitter systems involved in placebo/nocebo effects in healthy participants and chronic pain patients suggests that knowledges obtained in the former population may not necessarily be transferred to the latter.[29]

Major advances in the neuroanatomical viewpoint of placebo analgesia have also been made in the last decade. Placebos administered along with positive verbal suggestions activate and deactivate different brain regions. Many of these regions show anticipatory increases prior to pain, predicting the strength of an individual's placebo analgesic effect, and suggesting that their role in placebo analgesia may not be pain-specific but rather may be tied to broader appraisal and expectation processes.[37,71] Consistently, very small effects are elicited by placebo on the neurologic pain signature, which is a brain-based pattern that can reliably distinguish between responses to painful and nonpainful stimuli, and is sensitive and specific to pain.[31] This finding suggests that placebos might modulate nonspecific affective and cognitive processes rather than affecting nociception.[31,71] The neuroanatomy of nocebo hyperalgesia has been characterized as well.[34] Cortical systems implicated in the experience of pain have been shown to be involved in pain anticipation. Their involvement suggests that these activations have a preparatory function, whereby potentially threatening stimuli receive more attention and are reliably detected.[34,76]

In anti-migraine clinical trials, adequate controls groups are lacking. Nevertheless, the placebo-controlled RCTs in both chronic migraine prevention and acute migraine treatment trials, which examined the efficacy of different routes of drug and placebo administration, proved to be informative about placebo effects.[43,45] Indeed, as Swerts and co-workers (2022) state,[43] although their meta-analysis evaluated the placebo response deriving from different routes of administration, the methodology of the eligible trials was kept the same (all of which were double-blinded RCTs, with the natural history being kept constant). Therefore, the differences in the placebo response emerged from statistical analysis actually reflect a difference in the placebo effect, and provides a starting point for the investigation of the underlying mechanisms.[43]

The neuroanatomy of placebo effects in depression has also begun to be disclosed. It involves the activity in the ventral striatum, rostral anterior cingulate cortex and other default mode network

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regions, orbitofrontal cortex, and dorsolateral prefrontal cortex, with overlap with some of the areas involved in placebo analgesia.[49]

Dementia deserves special attention because its pathophysiology is complex and varies across the different types of dementia, of which AD is by far the most common. AD patients in moderate and later stages of the disease have shown to not benefit from certainty of receiving genuine treatment (100% certainty) compared to the uncertainty of receiving treatment or placebo (50% certainty).[50] This could be due to the nature/progression of the disease, but it could also be related to an order effect in the practice of running AD trials, where RCTs are conducted prior to open-label trials. These findings have implications for the understanding of non-specific treatment effects in AD patients as well as for the design of clinical trials that test pharmacological treatments in AD.[50]

Regarding respiratory system, expectation-induced dyspnoea in the laboratory setting by using classical conditioning shows important therapeutic perspective.[80,98] Since expectation of dyspnoea can be manipulated by an external intervention, it becomes of major importance not only to interfere with acute brain mechanisms, but also to reverse chronic conditioning to free the patient's mind from negative respiratory anticipation.[98]

In oncology, the experimental tradition in placebo and nocebo effects originated in the study of anticipatory nausea in chemotherapy, which refers to the phenomenon whereby patients develop such strong learning between their chemotherapy context and the nausea, that they begin to feel nauseous purely when re-entering this context.[54,97] There is promising preliminary evidence that latent inhibition and overshadowing procedures can be used to prevent or diminish anticipatory nausea.[54] Also, these procedures do not involve deception, so if confirmed as effective in large-scale studies they could be applied and ethically translated into practice.[54]

Placebo and nocebo effects in sport performance involve a variety of factors, such as fatigue endurance, pain tolerance, motivation, and muscle strength. Motor performance is instead a broader term, incorporating not only the execution of sport specific movements, but also including skills that are essential to normal everyday functioning, such as simple reaction time or vigilance.[57] According to the model of central command, motor performance is not limited by a failure of homeostasis in key organs, but rather it is regulated at early stages in order to ensure that exercise is completed before harm develops.[108] Consistently, placebos and nocebos might act in motor performance on the balance between an inhibitory and a facilitatory system, by altering the individual evaluation of the ongoing muscles performance. On one hand, placebos could act to increase fatigue threshold with the consequent increase of motor output and decrease of perceived fatigue; on the other hand, nocebos could act to decrease fatigue threshold.[108,109]

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Discussion

This meta-review attests the significant progress made in the past 30 years in the investigation of placebo/nocebo effects and placebo/nocebo-related effects, and it offers an updated overview on the topic. The overall high quality of the examined systematic reviews supports the reliability of both the obtained quantitative and quantitative results. Furthermore, even if overlapping meta-analyses on the same topic were found, especially in pain, each of them gave a specific contribution to the whole picture.

Many biological mechanisms have been rigorously characterized in both clinical and non-clinical contexts, as extensively described in Table 3. Moreover, the magnitude of placebo effects, ranging from small to large, has been calculated for nociceptive, idiopathic and neuropathic pain,[31–33,38–40,67] migraine,[43,45] sleep,[46] depression,[48,82] addiction,[52] respiratory system,[96] and physical performance.[58–60] A moderate placebo-related effect was calculated for intellectual disability.[47] The magnitude of nocebo effects, ranging from small to moderate and moderate to large, has been calculated for nociceptive and idiopathic pain[36,67] and for physical performance.[57,59]

Asthma and cough are known to undergo powerful placebo effects (measured as airway reactivity and cough frequency, respectively), even if their magnitudes have not yet been quantified in pools of eligible studies.[96,97]

Importantly, significant responses to OLP administration have been documented for: pain (low back pain and ischemic arm pain),[21,63,73] depression,[21,63] menopausal hot flushes,[88] ADHD,[21,90] allergic rhinitis,[21] irritable bowel syndrome,[21,63] psoriasis,[63] and cancer related fatigue.[21,63] Also, the Hawthorne effect has been documented in both dementia[85] and obesity.[9]

Many other clinical conditions exist that may contribute to the discovery of new placebo and nocebo effects in the near future. These are mainly chronic diseases in which placebos, administered in the context of classic RCTs, have been shown to induce significant improvements. These responses, however, would require the inclusion of an untreated control group in the trial to be accounted for as placebo/nocebo effects. Some of these clinical conditions include myasthenia gravis (MG)[112] and painful diabetic neuropathy (PDN).[113] Placebo and drug responses in MG trials, as assessed by means of the Quantitative Myasthenia Gravis (QMG) scores assigned by neurologists, have been shown to be small and moderate, respectively.[112] In PDN trials, the placebo response, as assessed by patients-perceived pain relief, showed a moderate effect size (with the year of study initiation as the only significant moderator), whereas the nocebo response substantially accounted for patients' reported AEs.[113]

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While the meta-review methodology allows for a comprehensive summary of the findings, it does not permit to overcome the single study limitations, which include publication biases, and the lack of information about unpublished data and the grey literature.

Concluding, scientific and clinical understanding of placebo and nocebo effects has expanded considerably over time, as evidenced by the exponential growth in research on this topic. However, these phenomena remain complex and far from being fully understood. While some studies have provided answers to certain questions, they have also given rise to new ones, necessitating further research, methods, and paradigms dedicated to exploring this subject. First and foremost, minimizing placebo and nocebo effects in clinical trials is a priority in modern clinical research. Current strategies include the double-blind placebo run-in (or lead-in) period, which allows for the identification of placebo responders and their exclusion from further random assignment.[9] However, caution should be applied to the interpretation of these approaches, as well as those of eliminating placebo-responsive subjects on the basis of genetic screening.[9] In fact, these procedures create an ideal and strictly controlled conditions (efficacy studies), which do not represent the real world (effectiveness studies). Furthermore, the degree of responsiveness to placebo could vary over time within the same individual, while random assignment of non-responders to both the placebo and active treatment arms could lead to low placebo effects in both groups, with no real benefit.

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References

1 Benedetti F. Placebo Effects: From the Neurobiological Paradigm to Translational Implications. *Neuron* 2014; 84: 623–37.
2 Finniss DG, Kaptchuk TJ, Miller F, Benedetti F. Biological, clinical, and ethical advances of placebo effects. *Lancet* 2010; 375: 686–95.
3 Colloca L, Barsky AJ. Placebo and Nocebo Effects. *N Engl J Med* 2020; 382: 554–61.
4 Benedetti F. Placebo and the New Physiology of the Doctor-Patient Relationship. *Physiol Rev* 2013; 93: 1207–46.
5 Benedetti F, Frisaldi E, Piedimonte A. The need to investigate nocebo effects in more detail. *World Psychiatry* 2019; 18: 227–8.
6 Benedetti F, Frisaldi E, Shaibani A. Thirty Years of Neuroscientific Investigation of Placebo and Nocebo: The Interesting, the Good, and the Bad. *Annu Rev Pharmacol Toxicol* 2022; 62: 323–40.
7 Evers AWM, Colloca L, Blease C, *et al.* Implications of Placebo and Nocebo Effects for Clinical Practice: Expert Consensus. *Psychother Psychosom* 2018; 87: 204–10.
8 Benedetti F. Mechanisms of placebo and placebo-related effects across diseases and treatments. *Annu Rev Pharmacol Toxicol* 2008; 48: 33–60.
9 Benedetti F, Carlino E, Piedimonte A. Increasing uncertainty in CNS clinical trials: the role of placebo, nocebo, and Hawthorne effects. *Lancet Neurol* 2016; 15: 736–47.
10 Weimer K, Buschhart C, Broelz EK, Enck P, Horing B. Bibliometric Properties of Placebo Literature From the JIPS Database: A Descriptive Study. *Front Psychiatry* 2022; 13: 853953.
11 Pagnini F, Barbiani D, Cavalera C, *et al.* Placebo and Nocebo Effects as Bayesian-Brain Phenomena: The Overlooked Role of Likelihood and Attention. *Perspect Psychol Sci* 2023; :17456916221141384.
12 Ongaro G, Kaptchuk TJ. Symptom perception, placebo effects, and the Bayesian brain. *Pain* 2019; 160: 1–4.
13 Kaptchuk TJ, Miller FG. Open label placebo: can honestly prescribed placebos evoke meaningful therapeutic benefits? *BMJ* 2018; 363: k3889.
14 Becker LA, Oxman AD. Overviews of reviews. In: Higgins JPT, Green S, eds. Cochrane handbook for systematic reviews of interventions. Chichester, John Wiley & Sons, 2008: 607–31.
15 Grant MJ, Booth A. A typology of reviews: an analysis of 14 review types and associated methodologies. *Health Inf Libr J* 2009; 26: 91–108.
16 Cooper H, Koenka AC. The overview of reviews: unique challenges and opportunities when research syntheses are the principal elements of new integrative scholarship. *Am Psychol* 2012; 67: 446–62.
17 Page MJ, McKenzie JE, Bossuyt PM, *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021; 372: n71.
18 Shea BJ, Reeves BC, Wells G, *et al.* AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ* 2017; 358: j4008.
19 Stroup DF, Berlin JA, Morton SC, *et al.* Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000; 283: 2008–12.
20 Tang B, Barnes K, Geers A, Livesey E, Colagiuri B. Choice and the Placebo Effect: A Meta-analysis. *Ann Behav Med* 2022; 56: 977–88.
21 Charlesworth JEG, Petkovic G, Kelley JM, *et al.* Effects of placebos without deception compared with no treatment: A systematic review and meta-analysis. *J Evid-Based Med* 2017; 10: 97–107.
22 Howick J, Friedemann C, Tsakok M, *et al.* Are treatments more effective than placebos? A systematic review and meta-analysis. *PloS One* 2013; 8: e62599.

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Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Erasmushogeschool .

23 Hróbjartsson A, Gøtzsche PC. Placebo interventions for all clinical conditions. *Cochrane Database Syst Rev* 2010; 2010: CD003974.
24 Meissner K, Distel H, Mitzdorf U. Evidence for placebo effects on physical but not on biochemical outcome parameters: a review of clinical trials. *BMC Med* 2007; 5: 3.
25 Hróbjartsson A, Gøtzsche PC. Is the placebo powerless? Update of a systematic review with 52 new randomized trials comparing placebo with no treatment. *J Intern Med* 2004; 256: 91–100.
26 Hróbjartsson A, Gøtzsche PC. Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. *N Engl J Med* 2001; 344: 1594–602.
27 Bagarić B, Jokić-Begić N, Sangster Jokić C. The Nocebo Effect: A Review of Contemporary Experimental Research. *Int J Behav Med* 2022; 29: 255–65.
28 Vambheim SM, Flaten MA. A systematic review of sex differences in the placebo and the nocebo effect. *J Pain Res* 2017; 10: 1831–9.
29 Skyt I, Lunde SJ, Baastrup C, Svensson P, Jensen TS, Vase L. Neurotransmitter systems involved in placebo and nocebo effects in healthy participants and patients with chronic pain: a systematic review. *Pain* 2020; 161: 11–23.
30 Daniali H, Flaten MA. A Qualitative Systematic Review of Effects of Provider Characteristics and Nonverbal Behavior on Pain, and Placebo and Nocebo Effects. *Front Psychiatry* 2019; 10: 242.
31 Zunhammer M, Bingel U, Wager TD, Placebo Imaging Consortium. Placebo Effects on the Neurologic Pain Signature: A Meta-analysis of Individual Participant Functional Magnetic Resonance Imaging Data. *JAMA Neurol* 2018; 75: 1321–30.
32 Forsberg JT, Martinussen M, Flaten MA. The Placebo Analgesic Effect in Healthy Individuals and Patients: A Meta-Analysis. *Psychosom Med* 2017; 79: 388–94.
33 Peerdeman KJ, van Laarhoven AIM, Keij SM, *et al.* Relieving patients' pain with expectation interventions: A meta-analysis. *Pain* 2016; 157: 1179–91.
34 Palermo S, Benedetti F, Costa T, Amanzio M. Pain anticipation: an activation likelihood estimation meta-analysis of brain imaging studies. *Hum Brain Mapp* 2015; 36: 1648–61.
35 Atlas LY, Wager TD. A meta-analysis of brain mechanisms of placebo analgesia: consistent findings and unanswered questions. *Handb Exp Pharmacol* 2014; 225: 37–69.
36 Petersen GL, Finnerup NB, Colloca L, *et al.* The magnitude of nocebo effects in pain: a meta-analysis. *Pain* 2014; 155: 1426–34.
37 Amanzio M, Benedetti F, Porro CA, Palermo S, Cauda F. Activation likelihood estimation meta-analysis of brain correlates of placebo analgesia in human experimental pain. *Hum Brain Mapp* 2013; 34: 738–52.
38 Vase L, Petersen GL, Riley JL, Price DD. Factors contributing to large analgesic effects in placebo mechanism studies conducted between 2002 and 2007. *Pain* 2009; 145: 36–44.
39 Sauro MD, Greenberg RP. Endogenous opiates and the placebo effect: a meta-analytic review. *J Psychosom Res* 2005; 58: 115–20.
40 Vase L, Riley JL, Price DD. A comparison of placebo effects in clinical analgesic trials versus studies of placebo analgesia. *Pain* 2002; 99: 443–52.
41 Ter Riet G, de Craen AJM, de Boer A, Kessels AGH. Is placebo analgesia mediated by endogenous opioids? A systematic review. *Pain* 1998; 76: 273–5.
42 Quattrone A, Barbagallo G, Cerasa A, Stoessl AJ. Neurobiology of placebo effect in Parkinson's disease: What we have learned and where we are going. *Mov Disord* 2018; 33: 1213–27.
43 Swerts DB, Benedetti F, Peres MFP. Different routes of administration in chronic migraine prevention lead to different placebo responses: a meta-analysis. *Pain* 2022; 163: 415–24.
44 Amanzio M, Corazzini LL, Vase L, Benedetti F. A systematic review of adverse events in placebo groups of anti-migraine clinical trials. *Pain* 2009; 146: 261–9.
45 de Craen AJ, Tijssen JG, de Gans J, Kleijnen J. Placebo effect in the acute treatment of migraine: subcutaneous placebos are better than oral placebos. *J Neurol* 2000; 247: 183–8.

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46 Yeung V, Sharpe L, Glozier N, Hackett ML, Colagiuri B. A systematic review and meta-analysis of placebo versus no treatment for insomnia symptoms. *Sleep Med Rev* 2018; 38: 17–27.
47 Jensen KB, Kirsch I, Pontén M, *et al.* Certainty of genuine treatment increases drug responses among intellectually disabled patients. *Neurology* 2017; 88: 1912–8.
48 Fernández-López R, Riquelme-Gallego B, Bueno-Cavanillas A, Khan KS. Influence of placebo effect in mental disorders research: A systematic review and meta-analysis. *Eur J Clin Invest* 2022; 52: e13762.
49 Huneke NTM, Aslan IH, Fagan H, *et al.* Functional neuroimaging correlates of placebo response in patients with depressive or anxiety disorders: A systematic review. *Int J Neuropsychopharmacol* 2022; 25: 433–47.
50 Matthiesen ST, Rosenkjær S, Pontén M, Jensen KB, Gottrup H, Vase L. Does Certainty of Genuine Treatment Increase the Drug Response in Alzheimer's Disease Patients: A Meta-Analysis and Critical Discussion. *J Alzheimers Dis JAD* 2021; 84: 1821–32.
51 Galindo MN, Navarro JF, Cavas M. The Influence of Placebo Effect on Craving and Cognitive Performance in Alcohol, Caffeine, or Nicotine Consumers: A Systematic Review. *Front Psychiatry* 2020; 11: 849.
52 McKay D, Schare ML. The effects of alcohol and alcohol expectancies on subjective reports and physiological reactivity: a meta-analysis. *Addict Behav* 1999; 24: 633–47.
53 Daniali H, Flaten MA. Placebo Analgesia, Nocebo Hyperalgesia, and the Cardiovascular System: A Qualitative Systematic Review. *Front Physiol* 2020; 11: 549807.
54 Quinn VF, Colagiuri B. Placebo interventions for nausea: a systematic review. *Ann Behav Med* 2015; 49: 449–62.
55 Meeuwis SH, van Middendorp H, van Laarhoven AIM, *et al.* Placebo and nocebo effects for itch and itch-related immune outcomes: A systematic review of animal and human studies. *Neurosci Biobehav Rev* 2020; 113: 325–37.
56 Amanzio M, Mitsikostas DD, Giovannelli F, Bartoli M, Cipriani GE, Brown WA. Adverse events of active and placebo groups in SARS-CoV-2 vaccine randomized trials: A systematic review. *Lancet Reg Health - Eur* 2022; 12: 100253.
57 Horváth Á, Köteles F, Szabo A. Nocebo effects on motor performance: A systematic literature review. *Scand J Psychol* 2021; 62: 665–74.
58 Marticorena FM, Carvalho A, Oliveira LFD, *et al.* Nonplacebo Controls to Determine the Magnitude of Ergogenic Interventions: A Systematic Review and Meta-analysis. *Med Sci Sports Exerc* 2021; 53: 1766–77.
59 Hurst P, Schipof-Godart L, Szabo A, *et al.* The Placebo and Nocebo effect on sports performance: A systematic review. *Eur J Sport Sci* 2020; 20: 279–92.
60 Bérdi M, Köteles F, Szabó A, Bárdos G. Placebo Effects in Sport and Exercise: A Meta-Analysis. *Eur J Ment Health* 2011; 6: 196–212.
61 Spiegel D, Kraemer H, Carlson RW. Is the Placebo Powerless? *N Engl J Med* 2001; 345: 1276–9.
62 Blease C, Colloca L, Kaptchuk TJ. Are open-Label Placebos Ethical? Informed Consent and Ethical Equivocations. *Bioethics* 2016; 30: 407–14.
63 Colloca L, Howick J. Placebos Without Deception: Outcomes, Mechanisms, and Ethics. *Int Rev Neurobiol* 2018; 138: 219–40.
64 Ashar YK, Chang LJ, Wager TD. Brain Mechanisms of the Placebo Effect: An Affective Appraisal Account. *Annu Rev Clin Psychol* 2017; 13: 73–98.
65 Benedetti F, Frisaldi E. Creating placebo responders and nonresponders in the laboratory: boons and banes. *Pain Manag* 2014; 4: 165–7.
66 Frisaldi E, Shaibani A, Benedetti F. Placebo responders and nonresponders: what's new? *Pain Manag* 2018; 8: 405–8.
67 Vase L, Skyt I, Hall KT. Placebo, nocebo, and neuropathic pain. *Pain* 2016; 157 Suppl 1: S98–105.

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68 Carlino E, Frisaldi E, Benedetti F. Pain and the context. *Nat Rev Rheumatol* 2014; 10: 348–55.
69 Peciña M, Zubieta J-K. Molecular mechanisms of placebo responses in humans. *Mol Psychiatry* 2015; 20: 416–23.
70 Pecina M, Zubieta J-K. Expectancy Modulation of Opioid Neurotransmission. *Int Rev Neurobiol* 2018; 138: 17–37.
71 Atlas LY. A social affective neuroscience lens on placebo analgesia. *Trends Cogn Sci* 2021; 25: 992–1005.
72 Wai-lanYeung V, Geers A, Kam SM. Merely Possessing a Placebo Analgesic Reduced Pain Intensity: Preliminary Findings from a Randomized Design. *Curr Psychol* 2019; 38: 194–203.
73 Benedetti F, Shaibani A, Arduino C, Thoen W. Open-label nondeceptive placebo analgesia is blocked by the opioid antagonist naloxone. *Pain* 2022; Publish Ahead of Print. DOI:10.1097/j.pain.0000000000002791.
74 Wrobel N, Fadai T, Sprenger C, Hebebrand J, Wiech K, Bingel U. Are Children the Better Placebo Analgesia Responders? An Experimental Approach. *J Pain* 2015; 16: 1005–11.
75 Hall KT, Loscalzo J, Kaptchuk TJ. Genetics and the placebo effect: the placebome. *Trends Mol Med* 2015; 21: 285–94.
76 Amanzio M, Palermo S. Pain Anticipation and Nocebo-Related Responses: A Descriptive Mini-Review of Functional Neuroimaging Studies in Normal Subjects and Precious Hints on Pain Processing in the Context of Neurodegenerative Disorders. *Front Pharmacol* 2019; 10: 969.
77 Fiorio M, Recchia S, Corrà F, Simonetto S, Garcia-Larrea L, Tinazzi M. Enhancing non-noxious perception: behavioural and neurophysiological correlates of a placebo-like manipulation. *Neuroscience* 2012; 217: 96–104.
78 Murray D, Stoessl AJ. Mechanisms and therapeutic implications of the placebo effect in neurological and psychiatric conditions. *Pharmacol Ther* 2013; 140: 306–18.
79 Frisaldi E, Carlino E, Lanotte M, Lopiano L, Benedetti F. Characterization of the thalamic-subthalamic circuit involved in the placebo response through single-neuron recording in Parkinson patients. *Cortex* 2014; 60: 3–9.
80 Enck P, Bingel U, Schedlowski M, Rief W. The placebo response in medicine: minimize, maximize or personalize? *Nat Rev Drug Discov* 2013; 12: 191–204.
81 Laverdure-Dupont D, Rainville P, Montplaisir J, Lavigne G. Relief expectation and sleep. *Rev Neurosci* 2010; 21: 381–95.
82 Haas JW, Rief W, Glombiewski JA, Winkler A, Doering BK. Expectation-induced placebo effect on acute sadness in women with major depression: An experimental investigation. *J Affect Disord* 2020; 274: 920–8.
83 Colagiuri B, Schenk LA, Kessler MD, Dorsey SG, Colloca L. The placebo effect: From concepts to genes. *Neuroscience* 2015; 307: 171–90.
84 Rutherford BR, Wall MM, Brown PJ, *et al.* Patient Expectancy as a Mediator of Placebo Effects in Antidepressant Clinical Trials. *Am J Psychiatry* 2017; 174: 135–42.
85 McCarney R, Warner J, Iliffe S, van Haselen R, Griffin M, Fisher P. The Hawthorne Effect: a randomised, controlled trial. *BMC Med Res Methodol* 2007; 7: 30.
86 Bailey RC, Baillie AJ. The relationship between placebo alcohol and affect: motives for drinking. *Drug Alcohol Rev* 2013; 32: 162–9.
87 Dar R, Stronguin F, Etter J-F. Assigned versus perceived placebo effects in nicotine replacement therapy for smoking reduction in Swiss smokers. *J Consult Clin Psychol* 2005; 73: 350–3.
88 Pardo-Cabello AJ, Manzano-Gamero V, Puche-Cañas E. Placebo: a brief updated review. *Naunyn Schmiedebergs Arch Pharmacol* 2022; 395: 1343–56.
89 Van Ree JM, Schagen Van Leeuwen JH, Koppeschaar HP, Te Velde ER. Unexpected placebo response in premenstrual dysphoric disorder: implication of endogenous opioids. *Psychopharmacology (Berl)* 2005; 182: 318–9.

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90 Sandler AD, Glesne CE, Bodfish JW. Conditioned placebo dose reduction: a new treatment in attention-deficit hyperactivity disorder? *J Dev Behav Pediatr JDBP* 2010; 31: 369–75.
91 Hadamitzky M, Lückemann L, Pacheco-López G, Schedlowski M. Pavlovian Conditioning of Immunological and Neuroendocrine Functions. *Physiol Rev* 2020; 100: 357–405.
92 Park C, Pagnini F, Langer E. Glucose metabolism responds to perceived sugar intake more than actual sugar intake. *Sci Rep* 2020; 10: 15633.
93 Park C, Pagnini F, Reece A, Phillips D, Langer E. Blood sugar level follows perceived time rather than actual time in people with type 2 diabetes. *Proc Natl Acad Sci* 2016; 113: 8168–70.
94 Malani A, Houser D. Expectations mediate objective physiological placebo effects. *Adv Health Econ Health Serv Res* 2008; 20: 311–27.
95 Olliges E, Schneider S, Schmidt G, *et al.* Placebo and Nocebo Effects in Patients With Takotsubo Cardiomyopathy and Heart-Healthy Controls. *Front Psychiatry* 2019; 10: 549.
96 Eccles R. The Powerful Placebo Effect in Cough: Relevance to Treatment and Clinical Trials. *Lung* 2020; 198: 13–21.
97 Wolters F, Peerdeman KJ, Evers AWM. Placebo and Nocebo Effects Across Symptoms: From Pain to Fatigue, Dyspnea, Nausea, and Itch. *Front Psychiatry* 2019; 10: 470.
98 Vinckier F, Betka S, Nion N, Serresse L, Similowski T. Harnessing the power of anticipation to manage respiratory-related brain suffering and ensuing dyspnoea: insights from the neurobiology of the respiratory nocebo effect. *Eur Respir J* 2021; 58: 2101876.
99 Elsenbruch S, Enck P. Placebo effects and their determinants in gastrointestinal disorders. *Nat Rev Gastroenterol Hepatol* 2015; 12: 472–85.
100 Enck P, Horing B, Weimer K, Klosterhalfen S. Placebo responses and placebo effects in functional bowel disorders. *Eur J Gastroenterol Hepatol* 2012; 24: 1–8.
101 Price DD, Finniss DG, Benedetti F. A comprehensive review of the placebo effect: recent advances and current thought. *Annu Rev Psychol* 2008; 59: 565–90.
102 Sondermann W, Reinboldt-Jockenhöfer F, Dissemond J, Pfaar O, Bingel U, Schedlowski M. Effects of Patients' Expectation in Dermatology: Evidence from Experimental and Clinical Placebo Studies and Implications for Dermatologic Practice and Research. *Dermatol Basel Switz* 2021; 237: 857–71.
103 Bartels DJP, van Laarhoven AIM, van de Kerkhof PCM, Evers AWM. Placebo and nocebo effects on itch: effects, mechanisms, and predictors. *Eur J Pain* 2016; 20: 8–13.
104 Sölle A, Worm M, Benedetti F, Sabine Bartholomäus T, Schwender-Groen L, Klinger R. Targeted Use of Placebo Effects Decreases Experimental Itch in Atopic Dermatitis Patients: A Randomized Controlled Trial. *Clin Pharmacol Ther* 2021; 110: 486–97.
105 Pagnini F, Cavalera C, Volpato E, Banfi P. Illness expectations predict the development of influenza-like symptoms over the winter season. *Complement Ther Med* 2020; 50: 102396.
106 Tippens KM, Purnell JQ, Gregory WL, *et al.* Expectancy, Self-Efficacy, and Placebo Effect of a Sham Supplement for Weight Loss in Obese Adults. *J Evid-Based Complement Altern Med* 2014; 19: 181–8.
107 Fontaine KR, Williams MS, Hoenemeyer TW, Kaptchuk TJ, Dutton GR. Placebo effects in obesity research. *Obesity* 2016; 24: 769–71.
108 Shaibani A, Frisaldi E, Benedetti F. Placebo response in pain, fatigue, and performance: Possible implications for neuromuscular disorders: Placebo Response. *Muscle Nerve* 2017; 56: 358–67.
109 Beedie C, Benedetti F, Barbiani D, Camerone E, Lindheimer J, Roelands B. Incorporating methods and findings from neuroscience to better understand placebo and nocebo effects in sport. *Eur J Sport Sci* 2020; 20: 313–25.
110 Davis AJ, Hettinga F, Beedie C. You don't need to administer a placebo to elicit a placebo effect: Social factors trigger neurobiological pathways to enhance sports performance. *Eur J Sport Sci* 2020; 20: 302–12.
111 Clifasefi SL, Garry M, Harper DN, Sharman SJ, Sutherland R. Psychotropic placebos create

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resistance to the misinformation effect. *Psychon Bull Rev* 2007; 14: 112–7.
112 Frisaldi E, Shaibani A, Vollert J, *et al.* The placebo response in myasthenia gravis assessed by quantitative myasthenia gravis score: A meta-analysis. *Muscle Nerve* 2019; 59: 671–8.
113 Frisaldi E, Vollert J, Husam Al S, et al. Placebo and nocebo responses in painful diabetic neuropathy: systematic review and meta-analysis. *Pain,* in press.

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Figure Legends

Fig 1. PRISMA flowchart. Trial flow of the selection process, showing both the number of events and reasons for the exclusion of most of the 6215 initially selected records.

Table 1: Description of PICOS components of meta-review

P	Human population, across different clinical conditions and beyond the healing context.
I	Placebo and nocebo effects: inert treatments undistinguishable from the matched active pharmacological interventions, administered with suggestions of improvement/worsening or according to conditioning procedures. Placebo-related and nocebo-related effects: suggestions of improvement/worsening without administration of inert treatments, or difference between expected (open) and unexpected (hidden) active pharmacological interventions.
C	No-treatment condition or control group, waiting list, pharmacological placebo not associated with expectation for symptoms improvement/worsening, baseline condition (told placebo, get placebo) according to the balanced-placebo design.
O	Biological mechanisms of placebo/nocebo effects and of placebo- nocebo-related effects, along with their effect sizes.
S	Peer-reviewed studies, published in English, informative about biological mechanisms and/or effect sizes. Specifically: - systematic-reviews and narrative reviews providing data obtained from: RCTs with a no-treatment control group, OLP trials with a no-treatment control group, placebo/nocebo mechanism studies conducted in the laboratory settings on healthy subjects and/or patients; - rigorous placebo-controlled RCTs without a no-treatment group investigating: i) different routes of placebo administration (i.e., improvements not attributable to spontaneous remission or regression to the mean); ii) different likelihoods of receiving active treatment or placebo; iii) the type of AEs occurring in both the active and placebo arms; - original research articles that: i) addressed an under-investigated topic in the field of placebo research that missed to be included in systematic or narrative reviews; ii) were too recent to be included in systematic or narrative reviews.

AEs, adverse events; OLP, open label placebo; RCTs, randomized clinical trials.

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Table 2: Summary of captured systematic reviews

	Review type	Topic	Population	Inclusion criteria for study type	Specific domain(s) of interest
1. Tang et al. (2022)[20]	SR-MA	Placebo effects	Adult individuals, both healthy volunteers and clinical patients.	Randomized design comparing having choice over placebo treatment with a placebo treatment without choice.	The impact of choice over placebo treatment on the placebo effect.
2. Charlesworth et al. (2017)[21]	SR-MA	Placebo effects	Participants with any diagnosed medical condition.	Studies that included a comparison of an open-label placebo intervention with a "no treatment" condition.	Effects of placebos without deception.
3. Howick et al. (2013)[22]	SR-MA	Placebo effects	Across clinical conditions.	Three-arm RCTs (no treatment, placebo, and active treatment).	Comparison of benefits due to placebos versus no treatments, and benefits due to active treatments versus placebos.
4. Hróbjartsson, Gøtzsche (2010)[23]	SR-MA	Placebo effects	Across clinical conditions.	Three-arm RCTs (no treatment, placebo, and active treatment).	Benefit of placebos compared to no-treatments.
5. Meissner et al. (2007)[24]	SR-MA	Placebo effects	Across clinical conditions.	We focused on the second dataset, consisting of three-arm RCTs with untreated groups (N = 26).	The impact of placebo treatment on peripheral disease processes.
6. Hróbjartsson, Gøtzsche (2004)[25]	SR-MA	Placebo effects	Across clinical conditions.	Three-arm RCTs (no treatment, placebo, and active treatment).	Magnitude and characteristics of placebos compared to no-treatments.
7. Hróbjartsson, Gøtzsche (2001)[26]	SR-MA	Placebo effects	Across clinical conditions.	Three-arm RCTs (no treatment, placebo, and active treatment).	Magnitude and characteristics of placebos compared to no-treatments.
8. Bagarić et al. (2022)[27]	SR	Nocebo effects	Predominantly young healthy adults, with one study on women suffering from breast cancer.	Studies conducted in the laboratory setting, aimed at examining the mechanisms underlying the nocebo effect. We focused on those studies including pharmacological placebos (N = 7).	State of the art of contemporary laboratory research.
9. Vambheim, Flaten (2017)[28]	SR-MA	Predictors of placebo and nocebo effects	Any condition.	Studies conducted in the laboratory setting, with a natural history control group or condition.	Sex differences in the placebo and the nocebo effect.
10. Skyt et al. (2020)[29]	SR-MA	Pain	Healthy volunteers, patients with acute or chronic pain	Placebo/nocebo mechanism studies with no-treatment group.	Neurotransmitter systems involved in placebo/nocebo effects in pain.
11. Daniali, Flaten (2019)[30]	SR	Pain	Healthy participants, patients, or animals.	Studies conducted in the laboratory setting,	Effects of experimenter/clinician characteristics and

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				including no-treatment group.	nonverbal behavior on pain, placebo, and nocebo effects.
12. Zunhammer et al. (2018)[31]	SR-MA	Pain	Healthy participants.	Studies with an experimental placebo intervention to induce placebo analgesia, plus a functional imaging measurement, plus at least one control condition (no placebo-intervention).	Placebo effects on the neurologic pain signature.
13. Forsberg et al. (2017)[32]	SR-MA	Pain	Healthy individuals and patients.	Studies conducted in the laboratory setting, including a group or a condition where a placebo treatment was administrated with information that it was a painkiller, together with a natural history/no-treatment group. Studies adopting the open/hidden design were included as well.	Investigates whether the magnitude of placebo analgesia is different in patients compared with healthy individuals, and whether placebo analgesia is different in experimentally induced pain compared with clinical pain in patients.
14. Peerdeman et al (2016)[33]	SR-MA	Pain	Adult patients with a somatic condition and/or undergoing medical treatment.	Studies that assessed the effect of expectation inductions on pain relief in a clinical sample. We focused on those studies that used verbal suggestions of pain relief referred to placebo (N = 11) or active treatment (N = 5), in both cases compared to no treatment or a control treatment that was believed to not induce expectations of pain relief.	The effect of brief expectation interventions referred to a placebo or an active treatment on patients' pain relief.
15. Palermo et al. (2015)[34]	SR-MA	Pain	Healthy participants.	Brain imaging studies conducted in the laboratory setting. Each study used one of the typical experimental paradigms for pain induction. We focused on the only experimental studies where pain anticipation was induced as a result of verbal suggestions associated with a pharmacological placebo (N = 2; we excluded cue-based expectancy studies).	Neuroanatomy of pain anticipation.

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16. Atlas, Wager (2014)[35]	SR-MA	Pain	Any human population.	Neuroimaging studies conducted in the laboratory setting. We focused on studies of placebo-based treatment expectancy (N = 17), and excluded stimulus expectancies studies.	Brain mechanisms of placebo analgesia.
17. Petersen et al. (2014)[36]	SR-MA	Pain	Mainly healthy participants, and two studies with patients (thoracoscopy or IBS).	Studies conducted in the laboratory setting, including a nocebo-treated group/condition and a no-treatment. We focused on those studies in which nocebo treatment was conceptualized as administration of an inert agent/intervention along with verbal suggestions for pain increase (N = 7).	Magnitude of nocebo effects in pain.
18. Amanzio et al. (2013)[37]	SR-MA	Pain	Mainly healthy participants, and two studies with patients (IBS, FGID).	Brain imaging studies conducted in the laboratory setting and mainly using pharmacological placebo treatments.	Brain correlates of placebo analgesia.
19. Vase et al. (2009)[38]	SR-MA	Pain	Healthy participants and patients (IBS, AD).	Studies conducted in the laboratory setting, including a placebo-treated group/condition (mainly pharmacological placebos) and a no-treatment group/condition.	Factors contributing to large analgesic effects in placebo mechanism studies conducted between 2002 and 2007.
20. Sauro, Greenberg (2005)[39]	SR-MA	Pain	Healthy participants and post-surgical/clinical patients.	Studies conducted in the laboratory setting, measuring both placebo analgesia and its reversal by naloxone administered via hidden injection or through a blinded procedure.	Investigate the ability of placebo administration to reduce self-report of pain, and examine the related mechanisms.
21. Vase et al. (2002)[40]	SR-MA	Pain	Patients affected by a variety of pain conditions.	Studies conducted in the laboratory setting, investigating placebo analgesic mechanisms (mainly through administration of pharmacological placebos) and three-arm RCTs (no treatment, placebo, and active treatment) RCTs (only some of them adopted	Comparing the magnitude of placebo effects in studies of placebo analgesia mechanisms versus clinical analgesic trials.

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				pharmacological placebos).	
22. Ter Riet et al. (1998)[41]	SR-MA	Pain	Healthy volunteers, postsurgical patients (removal of 3rd molars and posterolateral thoracotomy).	Studies employing placebo administration for clinical or experimental pain in addition to the hidden infusions with an endorphin antagonist or an endorphin synergistic drug.	Assessment of an antagonistic effect of naloxone and a synergistic effect of proglumide on placebo-induced analgesia.
23. Quattrone et al. (2018)[42]	SR	PD	PD patients.	Studies conducted in the laboratory setting, using different neuroimaging procedures and validated experimental protocols to evaluate the placebo effect.	Neurobiology of placebo effect in PD.
24. Swerts et al. (2022)*[43]	SR-MA	Migraine	Adults patients with chronic migraine and no associated comorbidities.	Placebo controlled RCTs.	Investigate the relationship between route of placebo administration and headache relief in chronic migraine preventive treatment.
25. Amanzio et al. (2009)*[44]	SR-MA	Migraine	Migraine patients with or without aura.	Anti-migraine placebo controlled RCTs.	AEs profiles of anti-migraine drugs: NSAIDs, triptans and anticonvulsants.
26. de Craen et al. (2000)*[45]	SR-MA	Migraine	Patients with acute migraine	Placebo controlled RCTs with at least one group treated with sumatriptan and one group with placebo.	Investigate the relationship between route of placebo administration and headache relief in the acute treatment of migraine.
27. Yeung et al. (2017)[46]	SR-MA	Sleep	Adult with insomnia symptoms.	Three-arm placebo controlled RCTs and experimental studies whose sole purpose was to compare placebo treatment with no treatment. All participants were blind to the possibility of receiving a placebo. Even if not all three-arm RCTs were pharmacological, the "study type" factor was shown not to moderate the placebo effect size.	Placebo effect size for insomnia symptoms.
28. Jensen et al. (2017)*[47]	SR-MA	Intellectual disability	Fragile X, Down, Prader-Willi, or Williams syndrome patients.	OLT and placebo controlled RCTs including placebo group.	To determine the placebo component (different probabilities of receiving the active treatment) of treatment responses

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					in patients with intellectual disability.
29. Fernández-López et al. (2022)[48]	SR-MA	Mental and behavioural disorders	Mental Disorders classified by DSM-V.	Three-arm placebo controlled RCTs. We focused on placebo effect in depression (i.e., the only investigated mental disorder which comprised mainly pharmacological interventions).	Placebo effects in depression.
30. Huneke et al. (2022)[49]	SR	Depression and anxiety	Adults with unipolar depression or anxiety disorders.	We focused on studies presenting neuroimaging data associated with placebo mechanisms such as learning or expectancy (N = 5).	Functional neuroanatomy of the placebo effect in patients with anxiety or depressive disorders.
31. Matthiesen et al. (2021)*[50]	SR-MA	Dementia	AD patients.	OLT and placebo controlled RCTs including placebo group.	Role of expectations (different probabilities of receiving genuine treatment) in AD clinical trials.
32. Galindo et al. (2020)[51]	SR	Addiction	Alcohol, caffeine, or nicotine consumers.	Studies conducted in the laboratory setting, whose topic was placebo effect.	The influence of placebo effect on craving and cognitive performance.
33. McKay, Schare (1999)[52]	SR-MA	Addiction	Any human population	Studies conducted in the laboratory setting, where the BPD was adopted.	Expectancy effects and their moderators in the BPD literature.
34. Daniali, Flaten (2020)[53]	SR	Cardiovascular system	Healthy subjects and patients experiencing pain.	Laboratory or clinical randomized studies including at least two comparison groups/conditions or a control group/condition (natural history).	The effects of placebo analgesia and nocebo hyperalgesia on cardiac activity.
35. Quinn, Colagiuri (2015)[54]	SR	Gastrointestinal disorders	Healthy and clinical populations (chemotherapy patients).	Instructional and conditioning interventions aimed at altering nausea via the placebo effect (most of them used nutritional or pharmacological placebos).	Determine if placebo interventions can affect nausea and which features of these interventions are effective.
36. Meeuwis et al. (2020)[55]	SR	Skin diseases	Patients with acute or chronic itching, and healthy volunteers.	Original observational/experimental studies in which placebo or nocebo effects were experimentally induced.	Placebo and nocebo effects in dermatological conditions and itch.
37. Amanzio et al. (2022)[56]	SR-MA	Flu and related vaccines	Safety population (adult, at least 1 dose of vaccine, safety data available), mainly Caucasian.	Placebo controlled RCTs, phase-III, for SARS-CoV-2 vaccines (BNT162b2, mRNA-1273, Ad26.COV2.S)	AEs in the placebo control groups associated with COVID-19 vaccines.

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				approved by EMA or FDA. The placebo control group was treated with a saline solution.	
38. Horváth et al. (2021)[57]	SR-MA	Physical performance	Any human population (mainly studies on healthy individuals and some studies on Parkinson's patients).	Studies conducted in the laboratory setting. We focused on studies that applied inert substances to evoke a nocebo effect and that included a control condition or group (N = 4). They were conducted on healthy individuals.	Nocebo effects induced by inert substances on motor performance.
39. Marticorena et al. (2021)[58]	SR-MA	Physical performance	Healthy human males and females of any age.	Any randomized and blinded, crossover, or parallel-group design requiring a supplementation protocol and including both a placebo and a no treatment group.	Estimate the size of the placebo effects associated with caffeine and buffering supplements.
40. Hurst et al. (2020)[59]	SR-MA	Physical performance	Participants described as "apparently healthy" or "athletes".	Studies conducted in the laboratory setting, assessing the effect of placebo/nocebo ergogenic aids. We focused on nutritional and pharmacological ergogenic aids (N = 20). Each study included no-treatment control or a baseline in which participants' own performance acted as a no-treatment control.	Placebo and nocebo effect on sports performance.
41. Bérdi et al. (2011)[60]	SR-MA	Physical performance	Healthy subjects at all levels of fitness.	Studies conducted in the laboratory setting, assessing the effect of placebo nutritional supplements in any sporting performance at all level of fitness. Each study included no-treatment group or baseline measurement.	Placebo effects in sport and exercise.

AD= Alzheimer's disease, AEs= Adverse events, BPD = balanced-placebo-design, EMA, European Medicine Agency, DSM-V= The Diagnostic and Statistical Manual of Mental Disorders Fifth Edition, FDA, Food and Drug Administration, FGID= functional gastrointestinal disorder, IBS= irritable bowel syndrome, OLT= open label trial, PD= Parkinson's disease, RCTs= randomized controlled trials, NSAIDs= non-steroid anti-inflammatory drugs, SR=systematic review, SR-MA=systematic review and meta-analysis.

* Based on placebo controlled RCTs without a no-treatment group, but still informative regarding placebo and nocebo mechanisms.

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Table 3: Mechanisms for placebo effects in medical conditions and physiological systems

	Magnitude of placebo effect	Magnitude of nocebo effect	Mechanisms
Pain	The magnitude of placebo analgesia (expressed as pain relief) has been found to be large in nociceptive, idiopathic, and neuropathic pain, with Cohen's *d* = 1.01, 1.63, and 2.01, respectively.[67] The magnitude of placebo analgesia in placebo mechanism studies is large (*d* = 1.00, range = 0.95-1.14), and about five times larger than placebo analgesia effects in placebo control studies (*d* = 0.15–0.27).[38,40] The magnitude of placebo effects has been found to be larger in studies that used long-term pain stimuli >20 s (*d* = 0.96) as opposed to short-term stimuli (*d* = 0.81), and the largest placebo effects were found in long-duration pain stimuli studies that involved hyperalgesic states (*d* = 1.88).[38] Patients show to benefit from placebo treatment to a greater degree than healthy participants do, with an average effect size (Hedges' *g*) equal to 1.49 for patients and 1.24 for healthy individuals. Moreover, patients' clinical pain and experimentally induced pain respond to placebo to the same degree.[32] Brief expectation interventions: studies that assessed the effects of verbal suggestion of pain relief referred to a placebo treatment found a large pooled effect (placebo, g = 0.95) compared with a medium to large pooled effect in studies that assessed the effects of verbal suggestion of pain relief referred to an active treatment (placebo-related, g = 0.73).[33] Regarding the involvement of endogenous opioid, placebo administration has been shown to be associated with a reduction in self-report of pain (*d*= 0.89, p = 0.001), while naloxone administration has been shown to be associated with the anti-analgesic effects	In nociceptive and idiopathic pain where nocebo effects were induced by verbal suggestions, the magnitude of nocebo hyperalgesic effects has been found to be moderate to large, with a Cohen's *d* around 0.66 to 0.90.[36] No nocebo hyperalgesic effects have been found in neuropathic pain.[67]	*Placebo analgesia* It is mediated by the endogenous opioid systems in some circumstances, as after pharmacological pre-exposure to μ-opioid receptor agonists. When mediated by the μ-opioid receptor, this analgesic placebo effect can be reversed by the opioid antagonist naloxone.[2,4,39,68] Proglumide (an indirect endorphin synergistic drug) has a synergistic effect of on placebo-induced analgesia.[41] After pharmacological pre-exposure to non-steroidal anti-inflammatory drugs (NSAIDs), the placebo effect is mediated by the activation of CB1 cannabinoid receptors, and can be reversed by the CB1 cannabinoid receptor antagonist rimonabant.[4,6,68] An activation of D2–D3 dopamine receptors and μ-opioid receptors in the nucleus accumbens (NAcc) occur.[2,4,6,68] In stress-induced analgesia, the increased arousal stems from an environmental stressor so that attention is diverted from the pain itself, leading to the activation of the endogenous opioid systems which, in turn, have an inhibitory effect on pain.[4,68] Genetic variants of both the fatty acid amide hydrolase (FAAH, Pro129Thr) — namely the major degrading enzyme of endocannabinoids — and the μ-opioid receptor (OPRM1, A118G) affect the magnitude of placebo analgesia.[69,70] Neuroanatomy:[35,37,68,71] reductions occur in brain regions involved in pain processing, including the dorsal anterior cingulate cortex (dACC), thalamus, and anterior insula, as well in regions implicated in studies of affect and valuation, namely in the amygdala and striatum. Activations occur in the dorsolateral prefrontal cortex, rostral ACC (rACC), and periacqueductal gray (PAG). Merely possessing a placebo analgesic (e.g. placebo cream), without using it, has been shown to reduce the intensity of acute pain sensation, which was induced using a cold compression task (placebo).[72] The open-label placebos (OLP): effective in both laboratory (i.e., ischemic arm pain)[73] and clinical setting (i.e., low back pain).[21,63] Children: the influence of previous experience on subsequent treatment outcome has been shown to be stronger in children than in adults, indicating an increased relevance of learning processes for placebo treatment outcomes in children (placebo).[74] *Nocebo hyperalgesia* The pronociceptive cholecystokinin (CCK) system antagonizes the opioid system. Activated by anticipatory anxiety,[4] it also involves the activity of hypothalamic–pituitary–adrenal (HPA) axis.[2,4] Under hypoxic conditions (using high-altitude low-oxygen pressure as a model), negative expectation about headache pain leads to the enhancement of the

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	on pain perception (d = 0.55, p = 0.001).[39] Placebos elicit a very small effects (g = −0.08) on the neurologic pain signature.[31]	cyclooxygenase (COX) – prostaglandins (PG) pathway, which, in turn, induces pain worsening. Placebo administration to headache sufferers inhibits the nocebo-related component of pain and prostaglandins synthesis, indicating that the cyclooxygenase pathway can be modulated by both nocebos and placebos.[6] Deactivation of both D2–D3 and μ receptors occur in the NAcc.[2,4,6,68] Genetic variant (high-activity Val allele) of the catechol-O-methyltransferase (COMT, rs4680) — an enzyme that metabolizes dopamine and other catecholamines — has been associated with a higher frequency of nocebo effects.[75] Neuroanatomy: In experimental pain studies where pain occur as a result of verbal suggestions in the context of inert pharmacological substances, negative expectations led to significantly increased insula and somatosensory cortex activation.[34,76] *Moderators* Experimenters/clinicians' sex, status, and nonverbal behaviours are three factors capable of altering the perception of pain.[30] *Placebo- and nocebo-related effects* Expectation of either low- or high-intensity painful stimuli has a strong influence; hidden (unexpected) injection of an active treatment is less effective than its open (expected) injection in both post-operative pain and in the experimental model of ischemic arm pain.[8]
Non-noxious somatic sensation		A top-down modulation on tactile perception has been demonstrated, probably due to an interaction between expectation and attention and which could be based on interactions between prefrontal and parietal brain regions (placebo). Changes in perception were supported by neurophysiological changes in brain-associated cortical responses (late somatosensory evoked potentials, SEP, N140, P200), whereas peripheral, subcortical and primary cortical responses (early SEP) remained stable. Possible therapeutic utility of these findings could be for those clinical conditions in which there is a pathological lack of sensation, e.g. due to a stroke.[77]
Disease of nervous system **Parkinson's disease (PD)**		Motor improvement is dependent by dopamine release in the dorsal striatum (placebo).[2,42,78–80] The magnitude of placebo-induced effects is modulated by an expectancy of improvement, which is in turn related to the release of dopamine within the ventral striatum (i.e., the NAcc) (placebo).[2,42,78–80] The functioning of the neural pathways underlying the placebo effect can be regulated by prior exposure and learning strategies (placebo and nocebo).[42,78,79] Placebo responders show a decrease in firing rate in the subthalamic nucleus, which is associated with a decrease in firing rate in the substantia nigra pars reticulata and, in turn, an increase in firing rate in the thalamic nuclei.[2,79] Also, the subthalamic nucleus neurons of all the placebo responders shift significantly from a pattern of bursting activity to a pattern of non-bursting discharge (placebo).[2,79] Strength of expectation can modulate dopamine release (placebo).[78]

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		Verbal suggestions may interfere with drug action. The supplementary motor area, source of the readiness potential, seems to be involved in this placebo effect (placebo).[6]
Disease of nervous system **Migraine**	In chronic migraine prevention trials, much of the effect of drugs (reduction in the number of days with migraine in the month) is still due to the high placebo effect, which contributes about 75% of the therapeutic gain.[43] In acute migraine treatment trials, the proportion of patients reporting adequate pain relief was 25.7% after oral placebo administration and 32.4% after subcutaneous placebo administration.[45]	Administration route impacts on placebo effects in chronic migraine preventive treatment, with the effect of application to the head being superior to the other routes (starting point for understanding placebo mechanisms).[43] In accordance with the expectation theory, adverse events (AEs) in placebo arms of clinical trials of anti-migraine medications were found to depend on the AEs of the active medication against which the placebo was compared (nocebo).[44]
Disease of nervous system **Sleep**	Placebo treatment leads to improved perceived global sleep quality (Hedges' g = 0.581), total sleep time (g = 0.322) and sleep onset latency (g = 0.272) when compared with no-treatment.[46]	Sleep seems to contribute to the consolidation of new expectations and consequently influence the generation of expectancy-mediated placebo effects (hypothetical placebo).[81] In particular, the relative duration of REM sleep can predict placebo-induced expectations of pain relief (placebo).[81]
Disease of nervous system **Intellectual disability (ID)** due to Fragile X, Down, Prader-Willi, and Williams syndromes	The effect of trial type on treatment outcomes (100% vs 50% probability of receiving genuine treatment) was statistically significant (p = 0.008). Higher effect sizes (treatment effects on core ID symptoms) were found in OLT (Hedges' g mean effect size = 0.65, placebo-related effect) compared to both the drug arm (mean g = 0.31, p = 0.043) and the placebo arm (mean g = 0.21, p = 0.009) in placebo-controlled RCTs.[47]	Certainty of genuine treatment, namely 100% likelihood of getting active drug, has been shown to increase drug responses among patients with an ID due to Fragile X, Down, Prader-Willi, and Williams syndromes compared to 50% likelihood (placebo-related).[47] In ID patients, it is likely that the expectations of surrounding parents, caretakers, and clinicians (i.e., implicit social influence of placebo by proxy) plays a role in treatment response (placebo-related).[47]
Mental and behavioural disorders **Depression**	A small placebo effect was observed in depression, whereby placebo conditions groups showed statistically significant improvements (assessed by clinical scales and number of relapses) when compared with the no-treatment or usual care (SMD 0.22, 95% CI 0.04–0.39).[48] Experimental evidence of large placebo effects on acute sadness in female depressed patients was provided: Hedge's g = 0.92. Since sadness is only one aspect of depressive affect, these results cannot be directly compared to placebo effects on symptoms of depression. Nevertheless, they're	Activity in the ventral striatum, rostral anterior cingulate cortex and other default mode network regions, orbitofrontal cortex, and dorsolateral prefrontal cortex correlates with placebo antidepressant effects (placebo), with overlap with some of the areas involved in placebo analgesia.[2,49] Regarding fluoxetine (inhibitor of serotonin re-uptake), while only a few brain areas are specifically affected by this drug, both fluoxetine and placebo treatments have been found to affect similar brain regions: orbitofrontal cortex and ventral striatum after 1 week of treatment (that is well before the clinical benefit of fluoxetine), and anterior/posterior cingulate cortex and prefrontal cortex after 6 weeks of treatment (placebo).[49] Important neurotransmitter systems could include the endogenous opioid system, dopamine, and serotonin,[49] with direct evidence for a role of the endogenous opioid system and dopamine (placebo).[70,75]

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	significant because demonstrate that experimentally induced placebo effects on mood can also prove powerful in clinical samples with depression.[82]	Regarding dopamine involvement, individuals with monoamine oxidase A (MAO-A) G/T polymorphisms (rs6323) coding for the low-activity form of the enzyme (T or T/T) and, therefore, higher basal dopamine tone, show a greater placebo-induced reduction in depressive symptoms than those with the high-activity MAOA genotypes (G o G/G) (placebo).[6,75,83] Medication (citalopram) plus expectancy (citalopram open administration, i.e. 100% chance receiving the active drug) produced greater depressive symptoms improvement in adult outpatients affected by major depressive disorder compared to the placebo-controlled group (50% chance of receiving active treatment) (placebo-related).[84] Patients affected by major depressive disorders have been shown to respond to OLP (placebo).[21,63]
Mental and behavioural disorders **Anxiety**		Genetic variation in serotonin pathway polymorphisms, namely tryptophan hydroxylase-2 (TPH2) and serotonin transporter-linked polymorphic region (5-HTTLPR), are potential biomarkers of placebo effect in social anxiety disorder.[2,6,75] In particular, the TPH2 polymorphism is a significant predictor of clinical placebo effect: the genetic effect on symptomatic improvement with placebo is mediated by its effect on amygdala activity (placebo).[75] Diazepam hidden (unexpected) administration has been shown to be less effective than its open (expected) administration (placebo-related).[4,8] In the open (expected) interruption of diazepam, anxiety increased significantly, whereas in the hidden condition it did not change (nocebo-related).[8]
Mental and behavioural disorders **Dementia**		Alzheimer's disease (AD) patients are characterized by both an impairment of prefrontal executive functions and a reduced electroencephalographic connectivity between the prefrontal lobes and the rest of the brain. This results in a reduced effectiveness of many treatments for AD patients in moderate and later stages of the disease (placebo-related).[2,4] AD patients do not benefit from certainty of receiving genuine treatment (100% certainty) compared to the uncertainty of receiving active treatment or placebo (50% certainty) (placebo-related).[50] Intensive follow-up has been shown to improve dementia patients' cognition through the Hawthorne effect. [85]
Mental and behavioural disorders **Addiction**	In the alcohol-challenge studies conducted according to the balanced-placebo design, the placebo effect size was found to range from small to moderate according to variable classes: behavioural (d = 0.221), self-report (d = 0.348), physiological (d = 0.394). When physiological variables were utilized, expectancy effects were two standard deviations greater than pharmacological effects. Also, a moderate placebo effect size	Both expectations of benefit and reward mechanisms play a crucial role in placebo effects in addiction (placebo).[2,4] According to BPD design, when methylphenidate was expected (expecting drug, receiving drug), the increases in brain glucose metabolism were about 50% larger than when it was not, and the process was mediated by cerebellum (vermis) and thalamus. Unexpected methylphenidate (expecting placebo, receiving drug) induced greater increases in left lateral orbitofrontal cortex than when it was expected (placebo-related).[2,4,64,80] Nicotine: regardless of the actual treatment received, smokers who believed they had received nicotine had significantly better outcomes after six months than

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	was found when the studies were conducted in a natural environment, defined as situations where subjects were provided with an easy chair or environments that approximated a home setting (Cohen's $d = 0.658$).[52]	those who believed they had received the placebo (placebo-related).[87] Craving and cognitive performance in alcohol, caffeine, or nicotine consumers: i) expectations of alcohol consumption under placebo conditions produce an increase in craving, as it happens with alcohol consumption; ii) expectations of caffeine or nicotine consumption under placebo conditions produce a craving reduction; iii) expectations of having consumed alcohol slows reaction time even when alcohol is not consumed, while caffeine beliefs enhance accuracy (placebo).[51] Placebo alcohol and affect: evidence has been provided of the amendable nature of alcohol motives when confronted with a negative drinking experience, with an increase in emotional lability following placebo alcohol (placebo).[86] Alcohol-challenge studies: lab setting has been found to be a moderator for both pharmacological (alcohol) and expectancy effects. The natural environment paradigm seems thus plausible for producing the largest effects since subjects are likely to experience less tension and experimental reactivity than in experimental lab situations (placebo).[52]
Mental and behavioural disorders **Gynaecological disorders**		OLP have been shown to be effective and safe in menopausal hot flushes (placebo).[88] In premenstrual dysphoric disorder, endogenous opioids seem to be involved: symptoms improvements after placebo administration are blocked by the opioid antagonist nalmefene) (placebo).[89]
Mental and behavioural disorders **Attention-deficit hyperactivity disorder (ADHD)**		Pairing stimulant medication with a visually distinctive placebo capsule administered in open-label fashion (OLP) elicits a placebo effect that allows children with ADHD to be effectively treated on 50% of their optimal stimulant dose (placebo).[21,90]
Immune and endocrine systems		*Immune response* Cellular and humoral immune functions can be modulated via associative learning protocols (placebo).[2,4,80] The strength of the association between a conditioned stimulus (CS, e.g. an olfactory, gustatory, visual, auditory, or touch stimulus) and an unconditioned stimulus (US, i.e. a drug or substance with immunological properties) is not only affected by the temporal relation between the CS and US or the number of CS/US pairings. It is also affected by the history of the stimuli used as CS or US, as well as by states such as extinction, consolidation, reconsolidation, and partial reinforcement (placebo).[91] The "Immunological road map" for Pavlovian conditioning of immune functions has been drawn. For example, the conditioned immunosuppression by cyclosporine A (US) induces decreased cytokine production (interleukin-2 (IL-2), interferon-gamma (IFN-γ), IL-4, and IL-17) and diminished numbers of peripheral blood leukocytes subsets (B and T cells) (placebo).[2,91] In asthmatic (male) patients, using grass-pollen or house dust as US and the procedure of inhalation of a

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	neutral aerosol as CS, allergic attacks can be obtained as conditioned response (CR) (nocebo).[91] Allergic rhinitis has been shown to respond to OLP (placebo).[21] Neuroanatomy: conditioned effects seem to be centrally mediated via the insular cortex and the amygdala, and peripherally mediated both via sympathetic innervation of lymphoid organs such as spleen and lymph nodes, and via noradrenaline and β-adrenoceptors on immune competent cells (placebo).[91] Predictors: Plasma noradrenaline and the subjects' state anxiety together with the baseline IL-2 levels predicted almost 60% of the variance in the conditioned IL-2 response.[91] *Endocrine response* Endocrine functions can be modulated via associative learning protocols, as demonstrated for the glucose-insulin system, HPA axis activity, growth hormone, and cortisol (placebo).[2,80] Compared to paradigms of conditioned immune responses, the basic mechanisms in endocrine system are less well understood. This is probably due to the complex temporal dynamics of HPA axis activity with its short- and long-term feedback mechanisms, and the partly pulsatile secretion of neuropeptides such as adrenocorticotropic hormone (ACTH) or corticotrophin-releasing hormone (CRH).[91] Cognition has also been found to affect glucose levels in people with type 2 diabetes, whereby blood glucose levels a) increase in accordance with how much sugar participants believe they consumed rather than how much they actually consumed;[92] b) follow perceived time rather than actual time (placebo).[93]
Cardiovascular system	Most of what we know about placebo mechanisms in the cardiovascular system is the result of placebo analgesia studies. A reduction in heart rate has been found to be associated with placebo analgesia, whereby both placebo analgesia and the concomitant reduced heart rate were completely antagonized by the opioid antagonist naloxone.[2] A spectral analysis revealed that only the β-adrenergic low frequency (0.15 Hz) spectral component, which corresponds to sympathetic activity, was reduced during placebo analgesia, an effect that was reversed by naloxone.[2] Other placebo mechanisms include changes in coronary diameter and in systolic blood pressure.[80] Using the balanced placebo design, and employing the crossover design in which participants were sequentially exposed to four possible treatments, it was shown that expectations about caffeine effects consistently affect participants' diastolic and systolic blood pressure. Specifically, the greatest mean change in blood pressure occurred with non-blinded caffeine (told caffeine, get caffeine), the least effect occurred with non-blinded placebo (told placebo, get placebo). The two blinded treatments fell somewhere between, with blinded caffeine showing a greater blood pressure effect than blinded placebo. These results are consistent with the possibility that the prefrontal cortex

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		provides external, top-down control that modulates physiological outcomes (placebo).[94] In individuals affected by the rare Takotsubo cardiomyopathy, negative verbal suggestions paired to the injection of saline solution revealed both negative subjective and objective effects (nocebo).[95] Heart rate variability has proven to be the most reliable method to study placebo-analgesic and nocebo-hyperalgesic cardiac effects. Indeed, it can account for both sympathetic and parasympathetic influences on cardiac activity (placebo and nocebo).[53]
Respiratory system	In cough, a three-arm clinical trial of acute cough associated with the common cold showed that placebo treatment consisting of a single dose of vitamin E caused a significant reduction in cough frequency (50%, objective measure) compared with a 7% reduction in the no-treatment case.[96]	Involvement of endogenous opioids at the level of the respiratory centers: placebos can mimic the depressant effects of narcotics on ventilation, and these placebo respiratory-depressant effects can be prevented by the opioid antagonist naloxone (placebo).[2,80] The effects of placebos on respiratory function appear to be independent from those on pain. Indeed, based on experimental results, it has been hypothesized that these effects might involve different subpopulations of opioid receptors. Opioid μ1 receptors could mediate the effects of placebos on pain, while μ2 receptors those on respiration ((hypothetical placebo).[2,80] Procedures that combine conditioning and verbal suggestion seem to more reliably induce a placebo effect on dyspnoea (placebo).[97] Expectation-induced dyspnoea has been reproduced in the laboratory setting by using classical conditioning (nocebo). This psychophysiological phenomenon was associated, during the expectation phase, with deactivation of the dorsomedial prefrontal cortex and the rACC (nocebo).[80,98] *Asthma* Placebo effect may be mediated by inhibition of cholinergic outflow or activation of non-adrenergic parasympathetic outflow, or even regulation of inflammatory mediators active in the central nervous system (hypothetical placebo).[80,97] *Cough* Placebo antitussives are very effective in reducing cough and the urge-to-cough in clinical settings and under experimental conditions. This placebo effect could be mediated by endogenous opioids (hypothetical placebo).[96] An increase in activity in the prefrontal cortex likely contributes to the placebo-antitussive effects (hypothetical placebo).[96] Some interaction has been hypothesized between gustatory and cough pathways in the nucleus tractus solitarius, which may influence cough by the mediation of endogenous opioids (hypothetical placebo).[96]
Gastrointestinal disorders		*Nausea* Evidence has been found that conditioning procedures can alter nausea, with gender as important variable to be taken into account (i.e., women more susceptible to conditioning) (placebo).[54] *Visceral pain in irritable bowel syndrome (IBS)* Experimental placebo and nocebo studies highlight the role of expectancies and conditioning processes in shaping gastrointestinal symptoms not only at the level of self-reports, but also within the brain and along the brain–gut axis (placebo and nocebo).[99]

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	In individuals affected by IBS, both the desire to relieve pain and the expectation to relieve pain contribute to placebo analgesia, with ratings of desire for pain reduction, expected pain, and anxiety decreasing over time as the placebo effect increases (placebo).[100,101] Brain imaging studies revealed an altered activation of the cingulate cortex (and other regions) during placebo analgesia in patients with IBS, leading to speculate that IBS might be characterized by impaired cognitive pain modulation, to which affective disturbances might contribute (hypothetical placebo).[99] The COMT functional val158met polymorphism (i.e., rs4680) is associated with the placebo effect in IBS, whereby patients homozygous for the rs4680 low-activity met allele (met/met), known to have high levels of dopamine, have the greatest placebo effect (placebo).[6,75] IBS patients have been shown to respond to OLP (placebo).[21,63]
Skin diseases	Expectations towards the benefit of a treatment — elicited by prior treatment experiences, verbal information, characteristics of the therapeutic context or intervention, social observation — have been shown to have an impact in itch, psoriasis, atopic dermatitis, allergic reactions, chronic wounds (placebo).[102] Negative product information (side-effects) paired with the administration of hydrating creams has been shown to be associated with more skin dryness (nocebo).[27] Psoriasis: positive response for placebo dose extension (OLP) was found in psoriasis patients treated with corticosteroids (placebo).[63] *Itch* Placebo and nocebo effects can be induced through similar mechanisms across animal studies, studies with healthy volunteers, and studies with patients. In accordance with placebo research on pain: i) verbal suggestions or conditioning have shown to induce placebo and nocebo effects on itch, in which the combination of both procedures seems most promising;[97,103] ii) expectations (fewer or higher itch expectations) generally predict placebo and nocebo effects for itch (placebo and nocebo).[97] In both patients and healthy participants, self-reported outcomes and scratching behavior were generally more likely to be affected by placebo and nocebo effects than physiological parameters (placebo and nocebo).[55] Brain areas likely involved in nocebo responding are those responsible for somatosensory processing of itch or are otherwise related to the itch-scratch cycle as well (nocebo). Placebo and nocebo effects may thus modulate itch through top-down processing in brain areas related to the specific condition or symptom in which they emerge (hypothetical placebo and nocebo).[55] In patients with chronic atopic dermatitis, the targeted application of placebo effects in addition to the pure pharmacological effectiveness of a drug (dimetindene) was able to improve the overall drug action (placebo).[104]

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	Moreover, placebo effects were stronger reflected on the subjective outcome "itching intensity" than on the objective outcome "wheal-size", suggesting that placebo effects in atopic dermatitis are more likely to be reflected in centrally mediated subjective experience than in peripherally mediated objective measurements (placebo).[88,104] Contagious itch: mirror neurons have been proposed to play a role in eliciting symptoms (nocebo).[55] Predictors of placebo and nocebo responding on itch and contagious itch: psychological characteristics and personality traits related to negative outcome expectancies seem to be of importance in predicting effects on itch, although evidence is mixed.[103]
Flu and related vaccines	*Influenza or influenza-like symptoms (ILS)* General expectations of getting influenza or ILS have been shown to be associated with an increased risk of developing actual symptoms over the entire winter season (nocebo).[105] The role of expectations as potential risk/protective factors remains stable even when accounting for the perception of general health and for previous ILS (nocebo).[105] Participants who expected their symptoms to be more intense and to last longer actually reported higher intensity and long duration of the illness, confirming the predictive value of expectations (nocebo).[105] *COVID-19 vaccines* A substantial proportion of AEs associated with COVID-19 vaccines are not a result of the vaccine per se, but may be related to the nocebo effect. Indeed, fatigue, headache, and pain (as local injection site reaction and myalgia) have been shown to be the most commonly reported AEs in both the active drug and the placebo arms, although in active vaccine arms they were higher.[56]
Oncology	The utility of conditioning both with and without a verbal suggestion in inducing a placebo effect on anticipatory nausea has been confirmed (placebo).[54,97] Nausea conditioning (rotation combined with cinnamon breath strips) and expectancy manipulation (instruction that cinnamon aroma would increase nausea) have been shown to lead to an exacerbation of the nausea symptom (nocebo).[27] The line of research using conditioning alone includes two strategies that are, as of yet, rarely applied in the rest of the placebo literature: overshadowing (the nausea-inducing stimulus is associated with a very salient stimulus which is then not present at test) and latent inhibition (participants are exposed to the environment where the nausea is induced several times before the nausea induction) (placebo).[97] Effective interventions tended to be those that were aimed at participants with high initial expectancies.[54] Cancer related fatigue has been shown to respond to OLP (placebo).[21,63]
Obesity	Improvements in biochemical (fasting glucose, insulin, lipids) and behavioural parameters (sleep duration/quality) occur between screening and randomization of the obese patients due to Hawthorne effect.[9]

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			Interindividual propagation of behaviours and attitudes is common in the obesity condition, whereby negative expectations spread across different individuals (nocebo).[9] Supplements without weight loss effects may have nocebo effects through diminished weight loss self-efficacy (i.e., participants' belief about being able to resist temptations and exercise more). Participants who received a daily placebo capsule and were told that i) they were taking an active weight loss supplement or ii) they had a 50% random chance of receiving either the active or placebo, they showed decreased weight loss self-efficacy and increased expectations of benefit from dietary supplements. Participants not taking capsules showed the opposite. Also, adverse events were more frequently reported in groups taking capsules than those who were not (nocebo).[106] The potentially powerful influences of placebo and placebo-related effects should be taken into account when evaluating the outcomes in diet and lifestyle modification trials (placebo and placebo-related).[107]
Physical performance	Small to moderate placebo effects were found for sham nutritional ergogenic aids (d = 0.35 ± 0.44).[59,60] Specifically, large placebo effects on sport performance were found for purported anabolic steroids and an erythropoietin like substance (d = 1.44 ± 1.01 and d = 0.81, respectively). Small to moderate effect sizes were reported for placebos described as amino acids (d = 0.36) or caffeine (d = 0.40). Small effect was found for fictitious sports supplements (d = 0.21 ± 0.17).[59] Also, using pre-conditioning procedures resulted in large placebo effects (d = 0.82 ± 0.18). Small to moderate effect sizes were found for positive (d = 0.36 ± 0.44) and negative (d = 0.37 ± 0.25) expectations.[59] Regarding placebo effects associated with both caffeine and buffering supplements, greater placebo effects have been shown with buffers and when supplements were provided in solution than in capsules (placebo).[58]	In studies on motor performance conducted on healthy individuals, where the effect of inert substances to evoke a nocebo effect was compared to a control condition or group, the mean effect size of nocebo effects has been found to be d = 0.60, suggesting a moderate effect.[57] Sports performance of healthy individuals (mainly force production and speed) seems to be the aspect of motor performance most susceptible to nocebo influences.[57] Nocebo effect on repeat-sprint performance (sprint time) has been found to have a small to moderate effect size (d = 0.32) when a dummy sports supplement thought to be detrimental to performance was administered.[59]	All available data in sport performance indicate athletes' expectations as important elements of physical performance (placebo and nocebo).[59] Regarding muscle performance and fatigue, central mechanisms would play a role through the concept of central command (placebo and nocebo).[108,109] Placebo caffeine has been found to reduce fatigue by acting at the central level on the preparatory/anticipatory phase of movement in the supplementary motor area (placebo).[109] Placebo ergogenic aid (presented as branched chain amino acids) significantly influenced frontal alpha asymmetry during maximum effort cycling (placebo).[109] Perceived fatigue has been found to be highly sensitive to placebo treatments, even more than pain. In hypoxic conditions at high altitude — differently from headache pain, perfusion, ventilation, and circulation — it is not necessary to perform a preconditioning procedure with real oxygen breathed through a mask to obtain robust placebo effects in fatigue, verbal suggestions alone being sufficient (placebo).[109] Neurotransmitter systems playing a role in fatigue: the involvement of opioid and endocannabinoid systems is intuitive considering the link between pain and fatigue (placebo).[2,109] Regarding the serotonin system, it has been most consistently linked with fatigue in sport (placebo).[109] Regarding dopamine system, it has been found to exert ergogenic effects and override inhibitory signals from the central nervous system (placebo). Conversely, a reduction of dopamine could impair activation of the basal ganglia and reduce stimulation of the motor cortex leading to central fatigue, as well as disruption of sensory inputs (nocebo).[109] Histamine release and binding to H1 receptors mediates the exercise-induced fatigue reduction (placebo).[109] Individual variability of placebo and nocebo effects in physical performance: the ergogenic effects of caffeine

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	are greater for homozygous carriers of the T allele of the adenosine A2A receptor subtype (placebo and nocebo).[109] Through mechanisms similar to those underpinning ergogenic placebo effects, also social environments that signal support and safety can reduce perceptions of pain and fatigue during physical exertion (placebo-related).[110] Social information provided by competitors and teammates can change the optimal physical output strategies for athletes and exercisers by altering the perceived costs (e.g., the consequences of resource depletion) and benefits (e.g., winning a competition) (placebo-related).[110]
Cognitive performance	Histamine release and binding to H1 receptors mediates the motivation to complete cognitive work (placebo).[109] A placebo for a psychotropic drug, i.e. R273, a mixture of baking soda and water which was described as a cognition-enhancing drug, was shown to help participants resist the misinformation effect (placebo).[111] Manipulation of cognitive performance expectation by means of the administration of an inactive nasal spray has been shown to affect the perceived change in cognitive performance and tiredness, but not the actual cognitive performance in healthy adults (placebo and nocebo).[27]

CI, confidence interval; OLP, open-label placebo; OLT, open-label trial; OR, odds ratio; RCTs, randomized clinical trials; SMD, standardized mean difference.

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Table 4: Magnitude of placebo and nocebo effects across conditions

Magnitude of the effect size	Type of effect	Condition	Outcome measures
Large	placebo	nociceptive, idiopathic, and neuropathic pain in placebo mechanism studies	validated clinical scales of pain relief, filled in by patients (subjective self-reported measure)
	placebo	chronic migraine prevention trials: strictly dependent by route of placebo administration (application to the head being superior to the other routes)	reduction in the number of days with migraine in the month (subjective self-reported measure)
	placebo	acute sadness in female depressed patients	validated clinical scale for major depression, filled in by patients (subjective measure)
	placebo	respiratory system: cough	reduction in cough frequency, recorded by means of a microphone (objective measure)
	placebo	sport performance assuming purported anabolic steroids or an erythropoietin like substance	direct measure of performance, e.g. power output, speed, or time to completion (objective measures)
Moderate to large	nocebo	nociceptive and idiopathic pain, where nocebo effects were induced by verbal suggestions	validated clinical scales of pain relief, filled in by patients (subjective self-reported measure)
Moderate	placebo	addiction: alcohol-challenge studies whereby the experimental setting consists of a natural environment (both less tension and experimental reactivity than in experimental lab situations)	self-reported measures (subjective measures); physiological or behavioural measures (objective measures)
	placebo-related	intellectual disability: effect associated to the certainty of receiving the active treatment	validated clinical scales filled in by patients (subjective measure)
	nocebo	motor performance	rotor task performance, sprint time, alertness reaction time, biceps curl total repetitions (objective measures)
Small to moderate	placebo	sleep	global sleep quality, total sleep time, sleep onset latency (patients' subjective self-reported measures)

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	placebo	addition: alcohol-challenge studies conducted according to the balanced-placebo design	self-report variables (subjective); behavioural and physiological variables (objective)
	placebo	sport performance assuming placebo described as amino acids or caffeine	direct measure of performance, e.g. power output, speed, or time to completion (objective measures)
	placebo	acute migraine treatment (small for oral placebo administration, moderate for subcutaneous placebo administration)	headache relief rate (patients' subjective self-reported measure)
	nocebo	sport performance assuming a fictitious sport supplement thought to be detrimental to performance	sprint time (objective measure)
Small	placebo	pain	activation of neurologic pain signature (NPS, objective measure)
	placebo	depression	validated clinical scale for major depression, filled in by patients (subjective measure); number of relapses (objective measure)
	placebo	sport performance assuming a fictitious sport supplement	direct measure of performance, e.g. power output, speed, or time to completion (objective measures)
	placebo	sport performance assuming the active nutritional supplements caffeine and extracellular buffers	total work done, mean power output, mean velocity, mean height, performance test/time to exhaustion

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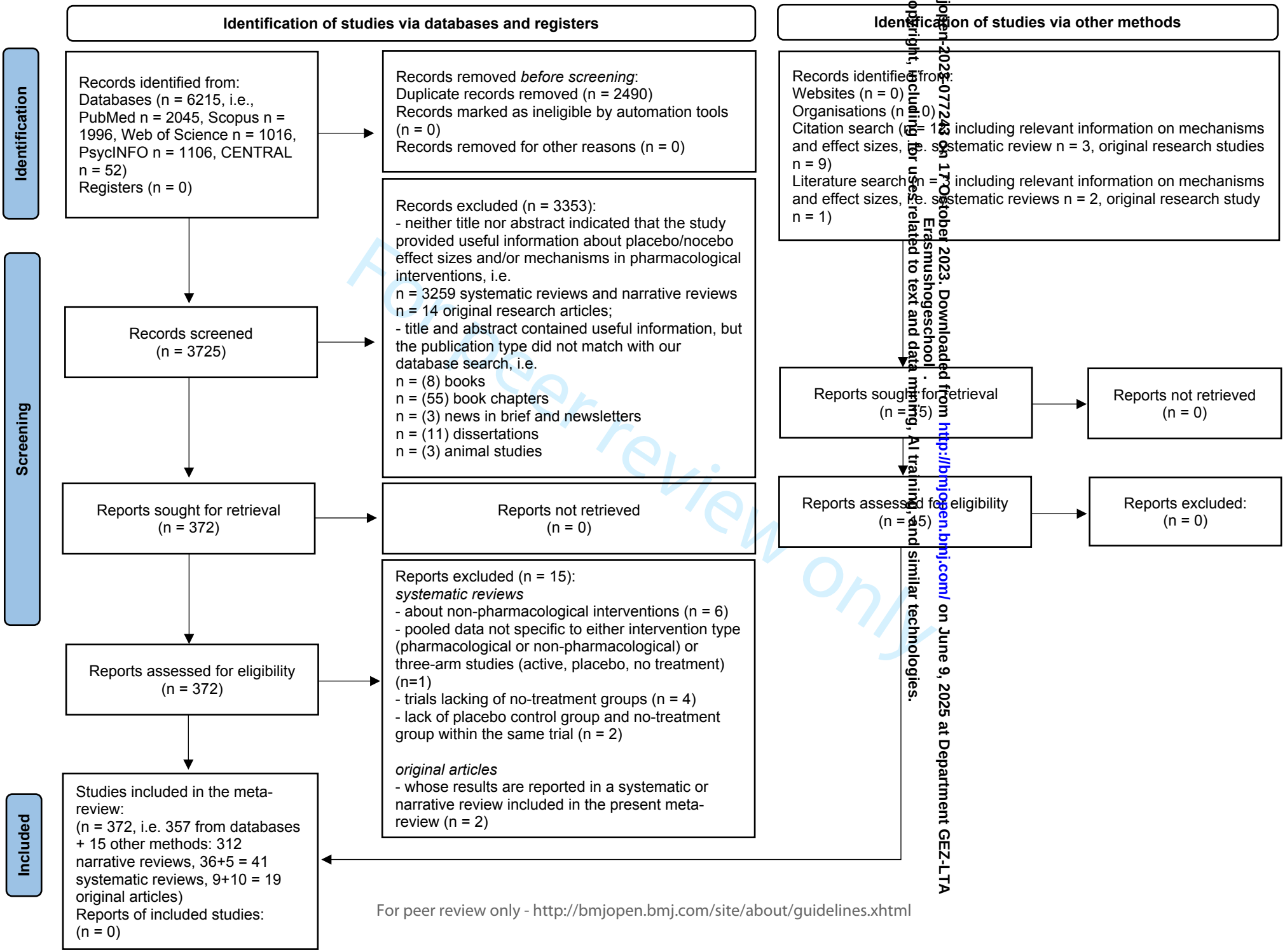

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Supplementary appendix 1

A) Protocol registration: **PROSPERO 2023 CRD42023392281**
Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023392281 and submitted as a supplementary file.

Review question
- Where (in which medical conditions) have robust placebo and nocebo effects been documented so far?
- When do they occur (any particular circumstances, such as experimental vs clinical setting)?
- How do they work (what do we know about the biological underpinnings)?

Searches
1. No time restrictions will be posed.
2. Language: English.
3. Publication stage: final.
4. Only peer-reviewed literature will be searched.
5. Databases will be used: PubMed, Scopus, Web of Science, PsycINFO, and Cochrane Central Register of Controlled Trials (CENTRAL). Search terms will be used accordingly based on different databases.
6. Relevant references cited in included reviews will also be hand-searched.
7. The search terms will have the following concepts: placebo, nocebo, placebo effect, placebo response, nocebo effect, nocebo response.

Types of study to be included
Systematic reviews, meta-analyses and reviews that:
- refer to randomized clinical trials (RCTs) with no-treatment control group, open label RCTs with no- treatment control group, experimental studies;
- are informative about biological mechanisms of placebo/nocebo effects and/or their related effect sizes.

Condition or domain being studied
Inclusion: Placebo/nocebo effects and placebo/nocebo-related effects, whereby the latter do not require the administration of inert treatments, in pharmacological treatments:
- clinical conditions, i.e. pain, disease of the nervous system, mental and behavioral disorders, immune and endocrine systems, cardiovascular and respiratory systems, gastrointestinal and genitourinary disorders, itch, oncology.
- beyond the healing context, i.e. physical and cognitive performance.

Exclusion: In order to circumscribe the area of investigation and reduce the degree of methodological variability among studies, we excluded the investigation of placebo/nocebo effects and placebo/nocebo- related effects in non-pharmacological treatments, such as psychotherapy, acupuncture, surgery, neuromodulation, physical therapies, hypnosis, mindfulness training, biofeedback, neurofeedback, music.

Participants/population
Studies on the human population are eligible.

Intervention(s), exposure(s)
Placebo and nocebo intervention.

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Comparator(s)/control
No-treatment control group or waiting list.

Context
Over the past 30 years there has been a surge of research on the placebo effect using a neuroscientific approach. The interesting aspects of this effort are related to the identification of several biological mechanisms of both the placebo and nocebo effects. Some important translational implications have emerged both in the setting of clinical trials and in routine medical practice. One of the principal contributions of neuroscience has been to draw the attention of the scientific and medical communities to the important role of psychobiological factors in therapeutic outcomes, be they drug related or not. Indeed, many biological mechanisms triggered by placebos and nocebos resemble those modulated by drugs, suggesting a possible interaction between psychological factors and drug action.

Main outcome(s)
Mapping placebo and nocebo effects across different medical conditions and therapeutic interventions, along with their underlying mechanisms.

Measures of effect
Effects size of placebo and nocebo effects calculated by Cohen's *d* or Hedges' *g*.

Additional outcome(s)
None

Data extraction (selection and coding)
Study selection: One author (EF) will screen the titles and abstracts of all search results (after removing duplicates). After removing ineligible papers, two authors (EF and FP) will independently review the full text of potentially eligible papers against the inclusion and exclusion criteria. Disagreements will be resolved by discussion among all the authors. The study will be developed according to the PRISMA guidelines (Moher D, Liberati A, Tetzlaff J. 2009).
Data extraction: On a spreadsheet previously set up to enter biological mechanisms and effect sizes, this information will be progressively entered for each medical condition and therapeutic intervention of interest.

Risk of bias (quality) assessment
Methodological quality of included systematic reviews and meta-analyses will be appraised using the Assessment of Multiple Systematic Reviews (AMSTAR) 2 tool, which has demonstrated satisfactory reliability and construct validity (Shea et al., 2017).

Strategy for data synthesis
Results from the eligible studies will be clustered and summarized. A table will describe the mechanisms and/or effect sizes obtained by each study. A narrative synthesis will be provided.

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B) Search strategy

PubMed
((“placebo effect” or “placebo effects” or “placebo response” or “placebo responses”) OR (“nocebo effect” or “nocebo effects” or “nocebo response” or “nocebo responses”))
text availability: full text
article type: meta-analysis, review, systematic review
Language: English

Scopus
Search within: article title, abstract, keywords
((“placebo effect” or “placebo effects” or “placebo response” or “placebo responses”) OR (“nocebo effect” or “nocebo effects” or “nocebo response” or “nocebo responses”))
Filters: Limit to
Document type: review
Publication stage: final
Language: English

Web Of Science
search within: abstract
((“placebo effect” or “placebo effects” or “placebo response” or “placebo responses”) OR (“nocebo effect” or “nocebo effects” or “nocebo response” or “nocebo responses”))
Filters: Refine for
document type: review article
Language: English

PsycINFO
search Select a field (optional)
((“placebo effect” or “placebo effects” or “placebo response” or “placebo responses”) OR (“nocebo effect” or “nocebo effects” or “nocebo response” or “nocebo responses”))
AND
Select a field (optional)
((review) OR (systematic review) OR (meta-analysis))
filter:
Language: English

Cochrane Central Register of Controlled Trials (CENTRAL)
advanced search: Title Abstract Keyword
((“placebo effect” or “placebo effects” or “placebo response” or “placebo responses”) OR (“nocebo effect” or “nocebo effects” or “nocebo response” or “nocebo responses”))
Search limits: Cochrane reviews
publication date: all
search word variations: ok

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Supplementary appendix 2 Critical appraisal of the included systematic reviews

Author (year)	Review type	1 - Components of PICO	2 - Protocol	3 – Selection of study design explained	4 – Comprehensive literature search	5 – Study selection	6 – Data extraction	7 – List of excluded studies	8 – Description included studies	9 – Risk of Bias assessment	10 – Funding sources	11 – appropriate statistical methods	13 – Account for RoB in Discussion	14 – Explanation/ Discussion of Heterogeneity	15 – Publication bias assessment	16 – Sources of Conflict of interest	Overall high quality (yes/no)
Placebo effects																	
1. Tang et al. (2022)[20]	SR-MA	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	Yes
2. Charlesworth et al. (2017)[21]	SR-MA	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	Yes
3. Howick et al. (2013)[22]	SR-MA	1	1	1	1	1	1	1	1	1*	1	1	1	1	1	1	Yes
4. Hróbjartsson, Gøtzsche (2010)[23]	SR-MA	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	Yes
5. Meissner et al. (2007)[24]	SR-MA	1	1	1	1	1	1	1	1	1 **	1	1	0	1	1 **	1	Yes
6. Hróbjartsson, Gøtzsche (2004)[25]	SR-MA	1	1	1	1	1	1	0	1	0.5 **	0	1	0.5	1	1	1	Yes
7. Hróbjartsson, Gøtzsche (2001)[26]	SR-MA	1	1	1	1	1	1	1	1	0.5 ***	1	1	0.5	1	1	1	Yes
Nocebo effects																	
8. Bagarić et al. (2022)[27]	SR	1	1	1	1	1	1	0	1	0	1	na	na	na	0	1	No

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Author (year)	Inclusion criteria for study type	Q1 - Components of PICO	Q2 - Protocol	Q3 – Selection of study design explained	Q4 – Comprehensive literature search	Q5 – Study selection	Q6 – Data extraction	Q7 – List of excluded studies	Q8 – Description included studies	Q9 – Risk of Bias assessment	Q10 – Funding sources	Q11 – appropriate statistical methods	Q12 – Assessment of risk of bias in individual studies	Q14 – Explanation/ Discussion of Heterogeneity	Q15 – Publication bias assessment	Q16 – Sources of Conflict of interest	Overall high quality (yes/no)
Predictors																	
9. Vambheim, Flaten (2017)[28]	SR-MA	1	0.5	1	1	1	0.5	1	0	1	1	na	na	0	0	1	Yes
Pain																	
10. Skyt et al. (2020)[29]	SR-MA	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	Yes
11. Daniali, Flaten (2019)[30]	SR	1	0.5	1	1	0.5	1	0.5	1	1	1	na	1	0.5	na	1	Yes
12. Zunhammer et al. (2018)[31]	SR-MA	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	Yes
13. Forsberg et al. (2017)[32]	SR-MA	1	0	1	1	1	1	0	1	0	1	1	na	1	1	1	No
14. Peerdeman et al (2016)[33]	SR-MA	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	Yes
15. Palermo et al. (2015)[34]	SR-MA	1	1	1	1	1	1	0	1	0.5	1	1	na	1	0	1	Yes
16. Atlas, Wager (2014)[35]	SR-MA	1	0	1	1	1	1	0	1	0.5	1	1	na	0	0	1	Yes

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Author (year)	Inclusion criteria for study type	Q1 - Components of PICO	Q2 - Protocol	Q3 – Selection of study design explained	Q4 – Comprehensive literature search	Q5 – Study selection	Q6 – Data extraction	Q7 – List of excluded studies	Q8 – Description included studies	Q9 – Risk of Bias assessment	Q10 – Funding sources	Q11 – appropriate statistical methods	Q13 – Limitations of the evidence, AI training, and similar technologies.	Q14 – Explanation/ Discussion of Heterogeneity	Q15 – Publication bias assessment	Q16 – Sources of Conflict of interest	Overall high quality (yes/no)
17. Petersen et al. (2014)[36]	SR-MA	1	1	1	1	1	1	1	1	0	1	1	na	1	0	1	Yes
18. Amanzio et al. (2013)[37]	SR-MA	1	1	1	1	1	1	1	1	0.5	1	1	na	1	0	1	Yes
19. Vase et al. (2009)[38]	SR-MA	1	1	1	1	1	1	1	1	0.5	1	1	1	1	1	1	Yes
20. Sauro, Greenberg (2005)[39]	SR-MA	1	0	1	0.5	0	1	0	1	0	1	1	na	1	0	0	No
21. Vase et al. (2002)[40]	SR-MA	1	1	1	1	1	1	0	1	0.5 ***	0	1	na	0	0	0	Yes
22. Riet et al. (1998)[41]	SR-MA	1	0	1	1	1	1	0	1	1	1	1	1	0	0	0	No
Disease of Nervous System: Parkinson's disease																	
23. Quattrone et al. (2018)[42]	SR	1	1	1	1	1	1	0	1	0.5	1	na	na	0	na	1	Yes
Disease of Nervous System: Migraine																	
24. Swerts et al. (2022)[43] §	SR-MA	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	Yes

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Author (year)	Inclusion criteria for study type	Q1 - Components of PICO	Q2 - Protocol	Q3 – Selection of study design explained	Q4 – Comprehensive literature search	Q5 – Study selection	Q6 – Data extraction	Q7 – List of excluded studies	Q8 – Description included studies	Q9 – Risk of Bias assessment	Q10 – Funding sources	Q11 – appropriate statistical methods	Q12 – Assessment of Risk of Bias in Discussion	Q13 – Account for RoB	Q14 – Explanation/ Discussion of Heterogeneity	Q15 – Publication bias assessment	Q16 – Sources of Conflict of interest	Overall high quality (yes/no)
25. Amanzio et al. (2009)[44] §	SR-MA	1	0	1	1	1	1	1	1	1	1	1	1	0	1	1	Yes	
26. de Craen et al. (2000)[45] §	SR-MA	1	0	1	1	1	1	0	1	0	1	1	na	1	0	0	No	
Disease of Nervous System: Sleep																		
27. Yeung et al. (2018)[46]	SR-MA	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	Yes	
Disease of Nervous System: Intellectual disability																		
28. Jensen et al. (2017)[47] §	SR-MA	1	1	1	1	1	1	0	1	0	1	1	na	na	1	0	1	No
Mental and behavioral disorders																		
29. Fernández-López et al. (2022)[48]	SR-MA	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	Yes	
Mental and behavioral disorders: Depression and anxiety																		
30. Huneke et al. (2022)[49]	SR	1	1	1	1	1	1	0	1	1	1	na	1	1	1	0	1	Yes
Mental and behavioral disorders: Dementia																		
31. Matthiesen et al. (2021)[50] §	SR-MA	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	Yes

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Author (year)	Inclusion criteria for study type	Q1 - Components of PICO	Q2 - Protocol	Q3 – Selection of study design explained	Q4 – Comprehensive literature search	Q5 – Study selection	Q6 – Data extraction	Q7 – List of excluded studies	Q8 – Description included studies	Q9 – Risk of Bias assessment	Q10 – Funding sources	Q11 – appropriate statistical methods	Q12 – Account for Risk of Bias in Discussion	Q14 – Explanation/ Discussion of Heterogeneity	Q15 – Publication bias assessment	Q16 – Sources of Conflict of interest	Overall high quality (yes/no)
Mental and behavioral disorders: Addiction																	
32. Galindo et al. (2020)[51]	SR	1	1	1	1	1	0	1	0	1	na	na	na	0	0	1	No
33. McKay, Schare (1999)[52]	SR-MA	1	0	1	1	1	0	1	0	0	1	na	na	1	0	0	No
Cardiovascular system																	
34. Daniali, Flaten (2020)[53]	SR	1	1	1	1	1	1	0.5	1	1	1	na	1	1	1	1	Yes
Gastrointestinal disorders																	
35. Quinn, Colagiuri (2015)[54]	SR	1	1	1	1	1	1	0	1	0	1	na	na	1	1	1	Yes
Skin diseases																	
36. Meeuwis et al. (2020)[55]	SR	1	1	1	1	1	1	0	1	1	1	na	1	1	0	1	Yes
Flu and related vaccines																	
37. Amanzio et al. (2022)[56]	SR-MA	1	1	1	1	1	1	0	1	1	1	1	1	1	0	1	Yes

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Author (year)	Inclusion criteria for study type	Q1 - Components of PICO	Q2 - Protocol	Q3 – Selection of study design explained	Q4 – Comprehensive literature search	Q5 – Study selection	Q6 – Data extraction	Q7 – List of excluded studies	Q8 – Description included studies	Q9 – Risk of Bias assessment	Q10 – Funding sources	Q11 – appropriate statistical methods	Q12 – Account for Risk of Bias in discussion	Q14 – Explanation/ Discussion of Heterogeneity	Q15 – Publication bias assessment	Q16 – Sources of Conflict of interest	Overall high quality (yes/no)
Physical performance																	
38. Horváth et al. (2021)[57]	SR-MA	1	1	1	1	0.5	0.5	0	1	1	1	1	1	0	0	1	Yes
39. Marticorena et al. (2021)[58]	SR-MA	1	1	1	1	1	1	0	1	1	1	1	0	0	1	1	Yes
40. Hurst et al. (2020)[59]	SR-MA	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	Yes
41. Bérdi et al. (2011)[60]	SR-MA	1	0	1	1	1	1	1	1	0	0	1	na	1	0	0	No

Abbreviations:

1 = yes, 0.5 = partial yes, 0 = no.

na= not applicable due to qualitative nature of the systematic review or to study limitations, SR=systematic review, SR-MA=systematic review and meta-analysis.

* Information acquired from Hróbjartsson A, Gøtzsche PC. Placebo interventions for all clinical conditions. Cochrane database of systematic reviews 2010:CD003974.

** Information acquired from Hróbjartsson A, Gøtzsche PC. Placebo interventions for all clinical conditions. Cochrane database of systematic reviews 2004:CD003974.

*** Part of the information acquired from Hróbjartsson A, Gøtzsche PC. Placebo treatment versus no treatment. The Cochrane Database of Systematic Reviews 2002, Issue 4. Art. No.: CD003974.

§ Based on placebo controlled RCTs without a no-treatment group, but still informative regarding placebo and nocebo mechanisms.

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Supplementary appendix 3

A) List of narrative reviews included in the meta-review

Identified via databases search (n = 312)

1 Abhishek A, Doherty M. Mechanisms of the placebo response in pain in osteoarthritis. *Osteoarthritis Cartilage* 2013; **21**: 1229–35.

2 Abhishek A, Doherty M. Comprendre l'effet placebo en rhumatologie. *Revue du Rhumatisme* 2015; **82**: 211–3.

3 Ader R. Conditioned immune responses and pharmacotherapy. *Arthritis Care Res* 1989; **2**: A58–64.

4 Amanzio M, Palermo S. Pain Anticipation and Nocebo-Related Responses: A Descriptive Mini-Review of Functional Neuroimaging Studies in Normal Subjects and Precious Hints on Pain Processing in the Context of Neurodegenerative Disorders. *Front Pharmacol* 2019; **10**: 969.

5 Anchisi D, Zanon M. A Bayesian Perspective on Sensory and Cognitive Integration in Pain Perception and Placebo Analgesia. *PLoS ONE* 2015; **10**: e0117270.

6 Anton PA, Shanahan F. Neuroimmunomodulation in inflammatory bowel disease. How far from 'bench' to 'bedside'? *Ann N Y Acad Sci* 1998; **840**: 723–34.

7 Archer T. The role of conditioning in the use of placebo. *Nordic Journal of Psychiatry* 1995; **49**: 43–53.

8 Arnold MH, Finniss DG, Kerridge I. Medicine's inconvenient truth: the placebo and nocebo effect. *Intern Med J* 2014; **44**: 398–405.

9 Arnstein P. The placebo effect. *Seminars in Integrative Medicine* 2003; **1**: 125–35.

10 Arrow K, Burgoyne LL, Cyna AM. Implications of nocebo in anaesthesia care. *Anaesthesia* 2022; **77 Suppl 1**: 11–20.

11 Ashar YK, Chang LJ, Wager TD. Brain Mechanisms of the Placebo Effect: An Affective Appraisal Account. *Annu Rev Clin Psychol* 2017; **13**: 73–98.

12 Atlas LY. A social affective neuroscience lens on placebo analgesia. *Trends Cogn Sci* 2021; **25**: 992–1005.

13 Atlas LY, Wager TD. How expectations shape pain. *Neurosci Lett* 2012; **520**: 140–8.

14 Autret A, Valade D, Debiais S. Placebo and other psychological interactions in headache treatment. *J Headache Pain* 2012; **13**: 191–8.

15 Bąbel P. Classical Conditioning as a Distinct Mechanism of Placebo Effects. *Front Psychiatry* 2019; **10**: 449.

16 Bąbel P. Operant conditioning as a new mechanism of placebo effects. *Eur J Pain* 2020; **24**: 902–8.

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17 Bajcar EA, Bąbel P. How Does Observational Learning Produce Placebo Effects? A Model Integrating Research Findings. *Front Psychol* 2018; **9**: 2041.

18 Barnes K, Faasse K, Geers AL, *et al.* Can Positive Framing Reduce Nocebo Side Effects? Current Evidence and Recommendation for Future Research. *Front Pharmacol* 2019; **10**: 167.

19 Barsky AJ, Saintfort R, Rogers MP, Borus JF. Nonspecific medication side effects and the nocebo phenomenon. *JAMA* 2002; **287**: 622–7.

20 Bartels DJP, van Laarhoven AIM, van de Kerkhof PCM, Evers AWM. Placebo and nocebo effects on itch: effects, mechanisms, and predictors. *Eur J Pain* 2016; **20**: 8–13.

21 Bärtsch P. The Impact of Nocebo and Placebo Effects on Reported Incidence of Acute Mountain Sickness. *High Alt Med Biol* 2022; **23**: 8–17.

22 Beauregard M. Mind does really matter: evidence from neuroimaging studies of emotional self-regulation, psychotherapy, and placebo effect. *Prog Neurobiol* 2007; **81**: 218–36.

23 Beauregard M. Effect of mind on brain activity: evidence from neuroimaging studies of psychotherapy and placebo effect. *Nord J Psychiatry* 2009; **63**: 5–16.

24 Beedie C, Benedetti F, Barbiani D, *et al.* Consensus statement on placebo effects in sports and exercise: The need for conceptual clarity, methodological rigour, and the elucidation of neurobiological mechanisms. *European Journal of Sport Science* 2018; **18**: 1383–9.

25 Beedie C, Benedetti F, Barbiani D, Camerone E, Lindheimer J, Roelands B. Incorporating methods and findings from neuroscience to better understand placebo and nocebo effects in sport. *Eur J Sport Sci* 2020; **20**: 313–25.

26 Beedie CJ. All in the mind? Pain, placebo effect, and ergogenic effect of caffeine in sports performance. *Open Access J Sports Med* 2010; **1**: 87–94.

27 Beedie CJ, Foad AJ. The placebo effect in sports performance: a brief review. *Sports Med* 2009; **39**: 313–29.

28 Belcher AM, Ferré S, Martinez PE, Colloca L. Role of placebo effects in pain and neuropsychiatric disorders. *Prog Neuropsychopharmacol Biol Psychiatry* 2018; **87**: 298–306.

29 Benedetti F. Placebo analgesia. *Neurol Sci* 2006; **27 Suppl 2**: S100-102.

30 Benedetti F, Amanzio M. The neurobiology of placebo analgesia: from endogenous opioids to cholecystokinin. *Prog Neurobiol* 1997; **52**: 109–25.

31 Benedetti F, Lanotte M, Lopiano L, Colloca L. When words are painful: unraveling the mechanisms of the nocebo effect. *Neuroscience* 2007; **147**: 260–71.

32 Benedetti F. How the Doctor's Words Affect the Patient's Brain. *Eval Health Prof* 2002; **25**: 369–86.

33 Benedetti F. Mechanisms of placebo and placebo-related effects across diseases and treatments. *Annu Rev Pharmacol Toxicol* 2008; **48**: 33–60.

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34 Benedetti F. Placebo-induced improvements: how therapeutic rituals affect the patient's brain. *J Acupunct Meridian Stud* 2012; **5**: 97–103.

35 Benedetti F. Placebo and the new physiology of the doctor-patient relationship. *Physiol Rev* 2013; **93**: 1207–46.

36 Benedetti F. Placebo effects: from the neurobiological paradigm to translational implications. *Neuron* 2014; **84**: 623–37.

37 Benedetti F, Amanzio M. The placebo response: how words and rituals change the patient's brain. *Patient Educ Couns* 2011; **84**: 413–9.

38 Benedetti F, Amanzio M. Mechanisms of the placebo response. *Pulm Pharmacol Ther* 2013; **26**: 520–3.

39 Benedetti F, Carlino E, Piedimonte A. Increasing uncertainty in CNS clinical trials: the role of placebo, nocebo, and Hawthorne effects. *Lancet Neurol* 2016; **15**: 736–47.

40 Benedetti F, Carlino E, Pollo A. How placebos change the patient's brain. *Neuropsychopharmacology* 2011; **36**: 339–54.

41 Benedetti F, Frisaldi E, Barbiani D, Camerone E, Shaibani A. Nocebo and the contribution of psychosocial factors to the generation of pain. *J Neural Transm (Vienna)* 2020; **127**: 687–96.

42 Benedetti F, Frisaldi E, Shaibani A. Thirty Years of Neuroscientific Investigation of Placebo and Nocebo: The Interesting, the Good, and the Bad. *Annu Rev Pharmacol Toxicol* 2022; **62**: 323–40.

43 Benedetti F, Mayberg HS, Wager TD, Stohler CS, Zubieta J-K. Neurobiological mechanisms of the placebo effect. *J Neurosci* 2005; **25**: 10390–402.

44 Benedetti F, Piedimonte A. The neurobiological underpinnings of placebo and nocebo effects. *Semin Arthritis Rheum* 2019; **49**: S18–21.

45 Benedetti F, Rainero I, Pollo A. New insights into placebo analgesia. *Curr Opin Anaesthesiol* 2003; **16**: 515–9.

46 Bennett GJ. Does the word 'placebo' evoke a placebo response? *Pain* 2018; **159**: 1928–31.

47 Bensing JM, Verheul W. The silent healer: the role of communication in placebo effects. *Patient Educ Couns* 2010; **80**: 293–9.

48 Benson H, Friedman R. Harnessing the power of the placebo effect and renaming it 'remembered wellness'. *Annu Rev Med* 1996; **47**: 193–9.

49 Benson H, McCallie DP. Angina pectoris and the placebo effect. *N Engl J Med* 1979; **300**: 1424–9.

50 Bienenfeld L, Frishman W, Glasser SP. The placebo effect in cardiovascular disease. *Am Heart J* 1996; **132**: 1207–21.

51 Bingel U, Colloca L, Vase L. Mechanisms and clinical implications of the placebo effect: is there a potential for the elderly? A mini-review. *Gerontology* 2011; **57**: 354–63.

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52 Birch S. A review and analysis of placebo treatments, placebo effects, and placebo controls in trials of medical procedures when sham is not inert. *J Altern Complement Med* 2006; **12**: 303–10.

53 Bittar C, Nascimento OJM. Placebo and nocebo effects in the neurological practice. *Arq Neuropsiquiatr* 2015; **73**: 58–63.

54 Blasini M, Corsi N, Klinger R, Colloca L. Nocebo and pain: an overview of the psychoneurobiological mechanisms. *PR9* 2017; **2**: e585.

55 Blasini M, Peiris N, Wright T, Colloca L. The Role of Patient-Practitioner Relationships in Placebo and Nocebo Phenomena. *Int Rev Neurobiol* 2018; **139**: 211–31.

56 Brand A, Evangelatos N, Özdemir V. Placebogenomics: A New Concept and Tool for Personalized Medicine and Public Health. *OMICS: A Journal of Integrative Biology* 2021; **25**: 76–8.

57 Bräscher A-K, Witthöft M, Becker S. The Underestimated Significance of Conditioning in Placebo Hypoalgesia and Nocebo Hyperalgesia. *Pain Res Manag* 2018; **2018**: 6841985.

58 Brietzke C, Cesario JCS, Hettinga FJ, Pires FO. The reward for placebos: mechanisms underpinning placebo-induced effects on motor performance. *Eur J Appl Physiol* 2022; **122**: 2321–9.

59 Brody H. The placebo response. Recent research and implications for family medicine. *J Fam Pract* 2000; **49**: 649–54.

60 Brody H, Brody D. Three perspectives on the placebo response: Expectancy, conditioning, and meaning. *Advances in Mind-Body Medicine* 2000; **16**: 216–32.

61 Brown C, Watson A, Morton D, Power A, El-Deredy W, Jones A. Role of central neurophysiological systems in placebo analgesia and their relationships with cognitive processes mediating placebo responding. *Future Neurology* 2011; **6**: 389–98.

62 Brown V, Peciña M. Neuroimaging Studies of Antidepressant Placebo Effects: Challenges and Opportunities. *Front Psychiatry* 2019; **10**: 669.

63 Brown WA. Expectation, the placebo effect and the response to treatment. *Rhode Island medical journal (2013)* 2015; **98**: 19–21.

64 Brown WA. How expectation works: psychologic and physiologic pathways. *Rhode Island medical journal (2013)* 2015; **98**: 22–4.

65 Brown WA. Harnessing the Placebo Effect. *Hospital Practice* 1998; **33**: 107–16.

66 Büchel C, Geuter S, Sprenger C, Eippert F. Placebo Analgesia: A Predictive Coding Perspective. *Neuron* 2014; **81**: 1223–39.

67 Buckalew LW, Ross S. Relationship of Perceptual Characteristics to Efficacy of Placebos. *Psychol Rep* 1981; **49**: 955–61.

68 Bystad M, Bystad C, Wynn R. How can placebo effects best be applied in clinical practice? A narrative review. *Psychol Res Behav Manag* 2015; **8**: 41–5.

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69 Cai L, He L. Placebo effects and the molecular biological components involved. *Gen Psychiatr* 2019; **32**: e100089.

70 Carlino E, Benedetti F. Different contexts, different pains, different experiences. *Neuroscience* 2016; **338**: 19–26.

71 Carlino E, Frisaldi E, Benedetti F. Pain and the context. *Nat Rev Rheumatol* 2014; **10**: 348–55.

72 Carlino E, Pollo A, Benedetti F. Placebo analgesia and beyond: a melting pot of concepts and ideas for neuroscience. *Curr Opin Anaesthesiol* 2011; **24**: 540–4.

73 Carlino E, Pollo A, Benedetti F. The placebo in practice: how to use it in clinical routine. *Curr Opin Support Palliat Care* 2012; **6**: 220–5.

74 Cavanna AE, Strigaro G, Monaco F. Brain mechanisms underlying the placebo effect in neurological disorders. *Functional Neurology* 2007; **22**: 89–94.

75 Chae Y, Lee Y-S, Enck P. How Placebo Needles Differ From Placebo Pills? *Front Psychiatry* 2018; **9**: 243.

76 Colagiuri B, Schenk LA, Kessler MD, Dorsey SG, Colloca L. The placebo effect: From concepts to genes. *Neuroscience* 2015; **307**: 171–90.

77 Colloca L. Placebo- and nocebo-induced pain modulation: from bedside to bench and back to bedside. *Douleur analg* 2014; **27**: 203–9.

78 Colloca L. The Placebo Effect in Pain Therapies. *Annu Rev Pharmacol Toxicol* 2019; **59**: 191–211.

79 Colloca L, Barsky AJ. Placebo and Nocebo Effects. *N Engl J Med* 2020; **382**: 554–61.

80 Colloca L, Benedetti F. Placebos and painkillers: is mind as real as matter? *Nat Rev Neurosci* 2005; **6**: 545–52.

81 Colloca L, Benedetti F. Nocebo hyperalgesia: how anxiety is turned into pain. *Curr Opin Anaesthesiol* 2007; **20**: 435–9.

82 Colloca L, Benedetti F, Porro CA. Experimental designs and brain mapping approaches for studying the placebo analgesic effect. *Eur J Appl Physiol* 2008; **102**: 371–80.

83 Colloca L, Grillon C. Understanding placebo and nocebo responses for pain management. *Curr Pain Headache Rep* 2014; **18**: 419.

84 Colloca L, Howick J. Placebos Without Deception: Outcomes, Mechanisms, and Ethics. *Int Rev Neurobiol* 2018; **138**: 219–40.

85 Colloca L, Jonas WB, Killen J, Miller FG, Shurtleff D. Reevaluating the Placebo Effect in Medical Practice. *Zeitschrift für Psychologie* 2014; **222**: 124–7.

86 Colloca L, Klinger R, Flor H, Bingel U. Placebo analgesia: psychological and neurobiological mechanisms. *Pain* 2013; **154**: 511–4.

87 Colloca L, Lopiano L, Benedetti F, Lanotte M. The placebo response in conditions other than pain. *Seminars in Pain Medicine* 2005; **3**: 43–7.

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88 Colloca L, Lopiano L, Lanotte M, Benedetti F. Overt versus covert treatment for pain, anxiety, and Parkinson's disease. *Lancet Neurol* 2004; **3**: 679–84.

89 Colloca L, Miller FG. Role of expectations in health. *Curr Opin Psychiatry* 2011; **24**: 149–55.

90 Colloca L, Miller FG. Harnessing the placebo effect: the need for translational research. *Philos Trans R Soc Lond B Biol Sci* 2011; **366**: 1922–30.

91 Colloca L, Miller FG. How placebo responses are formed: a learning perspective. *Philos Trans R Soc Lond B Biol Sci* 2011; **366**: 1859–69.

92 Colloca L, Miller FG. The nocebo effect and its relevance for clinical practice. *Psychosom Med* 2011; **73**: 598–603.

93 Costanzo C, Verghese A. The Physical Examination as Ritual: Social Sciences and Embodiment in the Context of the Physical Examination. *Med Clin North Am* 2018; **102**: 425–31.

94 Cuyul-Vásquez I, Barría JA, Perez NF, Fuentes J. The influence of verbal suggestions in the management of musculoskeletal pain: a narrative review. *Physical Therapy Reviews* 2019; **24**: 175–81.

95 Czerniak E, Oberlander TF, Weimer K, Kossowsky J, Enck P. 'Placebo by Proxy' and 'Nocebo by Proxy' in Children: A Review of Parents' Role in Treatment Outcomes. *Front Psychiatry* 2020; **11**: 169.

96 Damien J, Colloca L, Bellei-Rodriguez C-É, Marchand S. Pain Modulation: From Conditioned Pain Modulation to Placebo and Nocebo Effects in Experimental and Clinical Pain. *Int Rev Neurobiol* 2018; **139**: 255–96.

97 Dar R, Barrett SP. The effects of beliefs regarding drug assignment in experimental and field studies of nicotine delivery devices: a review. *J Psychopharmacol* 2014; **28**: 1071–9.

98 Darnall BD, Colloca L. Optimizing Placebo and Minimizing Nocebo to Reduce Pain, Catastrophizing, and Opioid Use: A Review of the Science and an Evidence-Informed Clinical Toolkit. *Int Rev Neurobiol* 2018; **139**: 129–57.

99 DaSilva AF, Zubieta J-K, DosSantos MF. Positron emission tomography imaging of endogenous mu-opioid mechanisms during pain and migraine. *Pain Rep* 2019; **4**: e769.

100 Davis AJ, Hettinga F, Beedie C. You don't need to administer a placebo to elicit a placebo effect: Social factors trigger neurobiological pathways to enhance sports performance. *Eur J Sport Sci* 2020; **20**: 302–12.

101 De Felice M, Ossipov MH. Cortical and subcortical modulation of pain. *Pain Manag* 2016; **6**: 111–20.

102 de la Fuente-Fernández R, Schulzer M, Stoessl AJ. The placebo effect in neurological disorders. *Lancet Neurol* 2002; **1**: 85–91.

103 de la Fuente-Fernández R, Schulzer M, Stoessl AJ. Placebo mechanisms and reward circuitry: clues from Parkinson's disease. *Biol Psychiatry* 2004; **56**: 67–71.

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Erasmushogeschool .

104 de la Fuente-Fernández R, Stoessl AJ. The placebo effect in Parkinson's disease. *Trends Neurosci* 2002; **25**: 302–6.

105 de la Fuente-Fernández R, Stoessl AJ. Parkinson's disease: imaging update. *Curr Opin Neurol* 2002; **15**: 477–82.

106 De La Fuentefernández R, Stoessl AJ. The Biochemical Bases for Reward: Implications for the Placebo Effect. *Eval Health Prof* 2002; **25**: 387–98.

107 Di Blasi Z, Kleijnen J. Context effects. Powerful therapies or methodological bias? *Eval Health Prof* 2003; **26**: 166–79.

108 Diederich NJ, Goetz CG. The placebo treatments in neurosciences: New insights from clinical and neuroimaging studies. *Neurology* 2008; **71**: 677–84.

109 Dieppe P, Goldingay S, Greville-Harris M. The power and value of placebo and nocebo in painful osteoarthritis. *Osteoarthritis Cartilage* 2016; **24**: 1850–7.

110 Dobrilla G, Scarpignato C. Placebo and placebo effect: their impact on the evaluation of drug response in patients. *Dig Dis* 1994; **12**: 368–77.

111 Dodd S, Dean OM, Vian J, Berk M. A Review of the Theoretical and Biological Understanding of the Nocebo and Placebo Phenomena. *Clin Ther* 2017; **39**: 469–76.

112 Dumitriu A, Popescu BO. Placebo effects in neurological diseases. *J Med Life* 2010; **3**: 114–21.

113 Dutile S, Kaptchuk TJ, Wechsler ME. The placebo effect in asthma. *Curr Allergy Asthma Rep* 2014; **14**: 456.

114 Eccles R. The powerful placebo in cough studies? *Pulm Pharmacol Ther* 2002; **15**: 303–8.

115 Eccles R. The power of the placebo. *Curr Allergy Asthma Rep* 2007; **7**: 100–4.

116 Eccles R. The Powerful Placebo Effect in Cough: Relevance to Treatment and Clinical Trials. *Lung* 2020; **198**: 13–21.

117 Eccles R. Mechanisms of the placebo effect of sweet cough syrups. *Respir Physiol Neurobiol* 2006; **152**: 340–8.

118 Ellingsen D-M, Leknes S, Løseth G, Wessberg J, Olausson H. The Neurobiology Shaping Affective Touch: Expectation, Motivation, and Meaning in the Multisensory Context. *Front Psychol* 2015; **6**: 1986.

119 Elsenbruch S, Enck P. Placebo effects and their determinants in gastrointestinal disorders. *Nat Rev Gastroenterol Hepatol* 2015; **12**: 472–85.

120 Enck P, Benedetti F, Schedlowski M. New insights into the placebo and nocebo responses. *Neuron* 2008; **59**: 195–206.

121 Enck P, Bingel U, Schedlowski M, Rief W. The placebo response in medicine: minimize, maximize or personalize? *Nat Rev Drug Discov* 2013; **12**: 191–204.

122 Enck P, Horing B, Weimer K, Klosterhalfen S. Placebo responses and placebo effects in functional bowel disorders. *Eur J Gastroenterol Hepatol* 2012; **24**: 1–8.

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Erasmushogeschool .

123 Enck P, Klosterhalfen S. Does Sex/Gender Play a Role in Placebo and Nocebo Effects? Conflicting Evidence From Clinical Trials and Experimental Studies. *Front Neurosci* 2019; **13**: 160.

124 Enck P, Klosterhalfen S. Placebo Responses and Placebo Effects in Functional Gastrointestinal Disorders. *Front Psychiatry* 2020; **11**: 797.

125 Esch T, Stefano GB. The neurobiology of pleasure, reward processes, addiction and their health implications. *Neuroendocrinology Letters* 2004; **25**: 235–51.

126 Faasse K. Nocebo effects in health psychology. *Australian Psychologist* 2019; **54**: 453–65.

127 Faria V, Fredrikson M, Furmark T. Imaging the placebo response: a neurofunctional review. *Eur Neuropsychopharmacol* 2008; **18**: 473–85.

128 Faria V, Linnman C, Lebel A, Borsook D. Harnessing the Placebo Effect in Pediatric Migraine Clinic. *The Journal of Pediatrics* 2014; **165**: 659–65.

129 Fields HL, Levine JD. Placebo analgesia —a role for endorphins? *Trends in Neurosciences* 1984; **7**: 271–3.

130 Finniss DG, Benedetti F. The Neural Matrix of Pain Processing and Placebo Analgesia: Implications for Clinical Practice. *Headache Currents* 2005; **2**: 132–8.

131 Finniss DG, Benedetti F. Mechanisms of the placebo response and their impact on clinical trials and clinical practice. *Pain* 2005; **114**: 3–6.

132 Finniss DG, Kaptchuk TJ, Miller F, Benedetti F. Biological, clinical, and ethical advances of placebo effects. *Lancet* 2010; **375**: 686–95.

133 Fontaine KR, Williams MS, Hoenemeyer TW, Kaptchuk TJ, Dutton GR. Placebo effects in obesity research: Placebo and Obesity. *Obesity* 2016; **24**: 769–71.

134 Frisaldi E, Carlino E, Lanotte M, Lopiano L, Benedetti F. Characterization of the thalamic-subthalamic circuit involved in the placebo response through single-neuron recording in Parkinson patients. *Cortex* 2014; **60**: 3–9.

135 Frisaldi E, Piedimonte A, Benedetti F. Placebo and nocebo effects: a complex interplay between psychological factors and neurochemical networks. *Am J Clin Hypn* 2015; **57**: 267–84.

136 Frisaldi E, Shaibani A, Benedetti F. Understanding the mechanisms of placebo and nocebo effects. *Swiss Med Wkly* 2020; **150**: w20340.

137 Frisaldi E, Shaibani A, Trucco M, Milano E, Benedetti F. What is the role of placebo in neurotherapeutics? *Expert Rev Neurother* 2022; **22**: 15–25.

138 Fu J, Wu S, Liu C, Camilleri JA, Eickhoff SB, Yu R. Distinct neural networks subserve placebo analgesia and nocebo hyperalgesia. *Neuroimage* 2021; **231**: 117833.

139 Geers AL, Briñol P, Petty RE. An analysis of the basic processes of formation and change of placebo expectations. *Review of General Psychology* 2019; **23**: 211–29.

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Erasmushogeschool .

140 Geers AL, Faasse K, Guevarra DA, Clemens KS, Helfer SG, Colagiuri B. Affect and emotions in placebo and nocebo effects: What do we know so far? *Soc Personal Psychol Compass* 2021; **15**. DOI:10.1111/spc3.12575.

141 Geers AL, Miller FG. Understanding and translating the knowledge about placebo effects: the contribution of psychology. *Curr Opin Psychiatry* 2014; **27**: 326–31.

142 Geers AL, Weiland PE, Kosbab K, Landry SJ, Helfer SG. Goal Activation, Expectations, and the Placebo Effect. *Journal of Personality and Social Psychology* 2005; **89**: 143–59.

143 Geers A, Rose J. Treatment Choice and Placebo Expectation Effects: Choice and Placebo Effects. *Social and Personality Psychology Compass* 2011; **5**: 734–50.

144 Gertsch J. The Intricate Influence of the Placebo Effect on Medical Cannabis and Cannabinoids. *Med Cannabis Cannabinoids* 2018; **1**: 60–4.

145 Geuter S, Koban L, Wager TD. The Cognitive Neuroscience of Placebo Effects: Concepts, Predictions, and Physiology. *Annu Rev Neurosci* 2017; **40**: 167–88.

146 Girach A, Aamir A, Zis P. The neurobiology under the placebo effect. *Drugs Today (Barc)* 2019; **55**: 469–76.

147 Gowdey CW. A guide to the pharmacology of placebos. *Can Med Assoc J* 1983; **128**: 921–5.

148 Greville-Harris M, Dieppe P. Bad is more powerful than good: the nocebo response in medical consultations. *Am J Med* 2015; **128**: 126–9.

149 Hadamitzky M, Lückemann L, Pacheco-López G, Schedlowski M. Pavlovian Conditioning of Immunological and Neuroendocrine Functions. *Physiol Rev* 2020; **100**: 357–405.

150 Hadamitzky M, Schedlowski M. Harnessing associative learning paradigms to optimize drug treatment. *Trends in Pharmacological Sciences* 2022; **43**: 464–72.

151 Hagen B, Gunn T. The Placebo Effect and Learning: Implications for Counsellors. *Canadian Journal of Counselling* 2006; **40**: 242–54.

152 Hall KT, Loscalzo J, Kaptchuk T. Pharmacogenomics and the Placebo Response. *ACS Chem Neurosci* 2018; **9**: 633–5.

153 Hall KT, Loscalzo J, Kaptchuk TJ. Genetics and the placebo effect: the placebome. *Trends Mol Med* 2015; **21**: 285–94.

154 Haour F. Mechanisms of the placebo effect and of conditioning. *Neuroimmunomodulation* 2005; **12**: 195–200.

155 Harvey SC, Beedie CJ. Studying placebo effects in model organisms will help us understand them in humans. *Biol Lett* 2017; **13**: 20170585.

156 Häuser W, Hansen E, Enck P. Nocebo phenomena in medicine: their relevance in everyday clinical practice. *Dtsch Arztebl Int* 2012; **109**: 459–65.

157 Hedges D, Burchfield C. The placebo effect and its implications. *Journal of Mind and Behavior* 2005; **26**: 161–79.

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Erasmushogeschool .

158 Heeg MJ, Deutsch KF, Deutsch E. The placebo effect. *Eur J Nucl Med* 1997; **24**: 1433–40.

159 Hoffman GA, Harrington A, Fields HL. Pain and the placebo: what we have learned. *Perspect Biol Med* 2005; **48**: 248–65.

160 Holmes RD, Tiwari AK, Kennedy JL. Mechanisms of the placebo effect in pain and psychiatric disorders. *Pharmacogenomics J* 2016; **16**: 491–500.

161 Horowitz S. New Perspectives on the Placebo Effect: Implications for Research and Clinical Practice. *Alternative and Complementary Therapies* 2012; **18**: 130–5.

162 Howland RH. Understanding the placebo effect. Part 2: underlying psychological & neurobiological processes. *J Psychosoc Nurs Ment Health Serv* 2008; **46**: 15–8.

163 Hróbjartsson A, Gøtzsche PC. Placebo treatment versus no treatment. *Cochrane Database Syst Rev* 2003; : CD003974.

164 Hyland ME. Motivation and placebos: do different mechanisms occur in different contexts? *Philos Trans R Soc Lond B Biol Sci* 2011; **366**: 1828–37.

165 Ingvar M. Learning mechanisms in pain chronification--teachings from placebo research. *Pain* 2015; **156 Suppl 1**: S18–23.

166 Irving G. The Placebo Response: Relationship to Outcomes in Trials of Postherpetic Neuralgia. *Clinical Drug Investigation* 2010; **30**: 739–48.

167 Isawa M, Kajiyama M, Tominaga Y, Nakada H, Aomori T, Mochizuki M. Review of clinical studies on the nocebo effect. *Pharmazie* 2020; **75**: 548–53.

168 Itskovich E, Bowling DL, Garner JP, Parker KJ. Oxytocin and the social facilitation of placebo effects. *Mol Psychiatry* 2022; **27**: 2640–9.

169 Jensen KB. What Is Minimally Required to Elicit Placebo Effects? *Int Rev Neurobiol* 2018; **138**: 181–99.

170 Jensen K, Kelley JM. The therapeutic relationship in psychological and physical treatments, and their placebo controls. *Psychology of Consciousness: Theory, Research, and Practice* 2016; **3**: 132–45.

171 Jubb J, Bensing JM. The sweetest pill to swallow: how patient neurobiology can be harnessed to maximise placebo effects. *Neurosci Biobehav Rev* 2013; **37**: 2709–20.

172 Kaas BM, Humbyrd CJ, Pantelyat A. Functional Movement Disorders and Placebo: A Brief Review of the Placebo Effect in Movement Disorders and Ethical Considerations for Placebo Therapy. *Mov Disord Clin Pract* 2018; **5**: 471–8.

173 Kaptchuk TJ, Hemond CC, Miller FG. Placebos in chronic pain: evidence, theory, ethics, and use in clinical practice. *BMJ* 2020; **370**: m1668.

174 Kaptchuk TJ, Kelley JM, Deykin A, *et al.* Do 'placebo responders' exist? *Contemp Clin Trials* 2008; **29**: 587–95.

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Erasmushogeschool .

175 Keane TM, Lisman SA, Kreutzer J. Alcoholic beverages and their placebos: An empirical evaluation of expectancies. *Addictive Behaviors* 1980; **5**: 313–28.

176 Khullar V, Rahnama'i MS, Veit-Rubin N, Cardozo L, Wein AJ. Can we harness the placebo effect to improve care in lower urinary tract dysfunction? ICI-RS 2019. *Neurourol Urodyn* 2020; **39 Suppl 3**: S80–7.

177 Kihlstrom JF. Placebo: Feeling better, getting better, and the problems of mind and body. *McGill Journal of Medicine* 2008; **11**: 212–4.

178 Kirsch I. Hypnosis and placebos: Response expectancy as a mediator of suggestion effects. *Anales de Psicología* 1999; **15**: 99–110.

179 Kirsch I. Yes, there is a placebo effect, but is there a powerful antidepressant drug effect? *Prevention & Treatment* 2002; **5**. DOI:10.1037/1522-3736.5.1.522i.

180 Klinger R, Blasini M, Schmitz J, Colloca L. Nocebo effects in clinical studies: hints for pain therapy. *PR9* 2017; **2**: e586.

181 Klosterhalfen S, Enck P. The placebo response in gastroenterology and beyond. *Gastroenterologia Polska* 2009; **16**: 7–11.

182 Klosterhalfen S, Enck P. Psychobiology of the placebo response. *Auton Neurosci* 2006; **125**: 94–9.

183 Klosterhalfen S, Enck P. Neurophysiology and psychobiology of the placebo response. *Curr Opin Psychiatry* 2008; **21**: 189–95.

184 Koban L, Jepma M, Geuter S, Wager TD. What's in a word? How instructions, suggestions, and social information change pain and emotion. *Neuroscience & Biobehavioral Reviews* 2017; **81**: 29–42.

185 Koehler PJ, Boes CJ. A history of non-drug treatment in headache, particularly migraine. *Brain* 2010; **133**: 2489–500.

186 Kong J, Kaptchuk TJ, Polich G, Kirsch I, Gollub RL. Placebo analgesia: findings from brain imaging studies and emerging hypotheses. *Rev Neurosci* 2007; **18**: 173–90.

187 Kotzalidis GD, Giugni E, Zangaro S, *et al.* Neuroimaging of the placebo effect Part 2. *Psichiatria e Psicoterapia* 2006; **25**: 287–308.

188 Kradin RL. The Placebo Response: Its Putative Role as a Functional Salutogenic Mechanism of the Central Nervous System. *Perspectives in Biology and Medicine* 2004; **47**: 328–38.

189 Kravvariti E, Kotsani M, Mitsikostas DD, Sfikakis PP. Nocebo phenomena may be enhanced in aging: Implications for clinical practice. *Maturitas* 2021; **143**: 10–6.

190 Kravvariti E, Kitas GD, Mitsikostas DD, Sfikakis PP. Nocebos in rheumatology: emerging concepts and their implications for clinical practice. *Nat Rev Rheumatol* 2018; **14**: 727–40.

191 Krsiak M. Is placebo effective? If yes, what this could mean? *Activitas Nervosa Superior Rediviva* 2009; **51**: 5–8.

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Erasmushogeschool .

192 Langenecker SA, Crane NA, Jenkins LM, Phan KL, Klumpp H. Pathways to Neuroprediction: Opportunities and Challenges to Prediction of Treatment Response in Depression. *Curr Behav Neurosci Rep* 2018; **5**: 48–60.

193 Laverdure-Dupont D, Rainville P, Montplaisir J, Lavigne G. Relief Expectation and Sleep. *Reviews in the Neurosciences* 2010; **21**. DOI:10.1515/REVNEURO.2010.21.5.381.

194 Lidstone SCC, Stoessl AJ. Understanding the placebo effect: contributions from neuroimaging. *Mol Imaging Biol* 2007; **9**: 176–85.

195 Lidstone SC, De La Fuente-Fernandez R, Stoessl AJ. The placebo response as a reward mechanism. *Seminars in Pain Medicine* 2005; **3**: 37–42.

196 Linde K, Fässler M, Meissner K. Placebo interventions, placebo effects and clinical practice. *Philos Trans R Soc Lond B Biol Sci* 2011; **366**: 1905–12.

197 Lindheimer JB, Szabo A, Raglin JS, Beedie C. Advancing the understanding of placebo effects in psychological outcomes of exercise: Lessons learned and future directions. *Eur J Sport Sci* 2020; **20**: 326–37.

198 Liu T. Route of placebo administration: Robust placebo effects in laboratory and clinical settings. *Neurosci Biobehav Rev* 2017; **83**: 451–7.

199 Liu T. Placebo Effects: A New Theory. *Clinical Psychological Science* 2022; **10**: 27–40.

200 Locher C, Gaab J, Blease C, Inderbinen M, Kost L, Koechlin H. Placebos Are Part of the Solution, Not the Problem. An Exemplification of the Case of Antidepressants in Pediatric Chronic Pain Conditions. *Front Psychiatry* 2020; **10**: 998.

201 Lovick TA. Pro-nociceptive action of cholecystokinin in the periaqueductal grey: A role in neuropathic and anxiety-induced hyperalgesic states. *Neuroscience & Biobehavioral Reviews* 2008; **32**: 852–62.

202 Lucassen P, Olesen F. Context as a drug: some consequences of placebo research for primary care. *Scand J Prim Health Care* 2016; **34**: 428–33.

203 Lundh L-G. Placebo, belief, and health. A cognitive–emotion model. *Scand J Psychol* 1987; **28**: 128–43.

204 Manaï M, van Middendorp H, Veldhuijzen DS, Huizinga TWJ, Evers AWM. How to prevent, minimize, or extinguish nocebo effects in pain: a narrative review on mechanisms, predictors, and interventions. *PR9* 2019; **4**: e699.

205 Manchikanti L, Giordano J, Fellows B, Hirsch JA. Placebo and nocebo in interventional pain management: a friend or a foe--or simply foes? *Pain Physician* 2011; **14**: E157-175.

206 Margo CE. The placebo effect. *Surv Ophthalmol* 1999; **44**: 31–44.

207 Matthiesen ST, Lunde SJ, Wohlert Kjær S, Carlino E, Vase L. Placebo analgesia effects across central nervous system diseases: what do we know and where do we need to go? *PR9* 2019; **4**: e717.

208 McQuay HJ, Moore RA. Placebo. *Postgraduate Medical Journal* 2005; **81**: 155–60.

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Erasmushogeschool .

209 Meissner K. The placebo effect and the autonomic nervous system: evidence for an intimate relationship. *Philos Trans R Soc Lond B Biol Sci* 2011; **366**: 1808–17.

210 Meissner K, Bingel U, Colloca L, Wager TD, Watson A, Flaten MA. The placebo effect: advances from different methodological approaches. *J Neurosci* 2011; **31**: 16117–24.

211 Mestre TA, Shamy M, Benedetti F, Lang AE. Harnessing the power of placebos in movement disorders: Insights from Parkinson's disease in clinical research and practice. *Mov Disord* 2018; **33**: 1195–203.

212 Miller FG, Colloca L, Kaptchuk TJ. The placebo effect: illness and interpersonal healing. *Perspect Biol Med* 2009; **52**: 518–39.

213 Miller FG, Rosenstein DL. The nature and power of the placebo effect. *J Clin Epidemiol* 2006; **59**: 331–5.

214 Mitsikostas DD. Nocebo in headache. *Curr Opin Neurol* 2016; **29**: 331–6.

215 Moerman DE, Harrington A. Making space for the placebo effect in pain medicine. *Seminars in Pain Medicine* 2005; **3**: 2–6.

216 Morral A, Urrutia G, Bonfill X. Placebo effect and therapeutic context: A challenge in clinical research. *Med Clin (Barc)* 2017; **149**: 26–31.

217 Murray D, Stoessl AJ. Mechanisms and therapeutic implications of the placebo effect in neurological and psychiatric conditions. *Pharmacol Ther* 2013; **140**: 306–18.

218 Neumann M, Edelhäuser F, Kreps GL, *et al.* Can patient-provider interaction increase the effectiveness of medical treatment or even substitute it?--an exploration on why and how to study the specific effect of the provider. *Patient Educ Couns* 2010; **80**: 307–14.

219 Noon JM. Placebo to credebo: the missing link in the healing process. *Pain reviews* 1999; **6**: 133–42.

220 Oken BS. Placebo effects: clinical aspects and neurobiology. *Brain* 2008; **131**: 2812–23.

221 Okusogu C, Colloca L. Placebo hypoalgesia: above and beyond expectancy and conditioning. *Current Opinion in Behavioral Sciences* 2019; **26**: 75–81.

222 Olshansky B. Placebo and nocebo in cardiovascular health: implications for healthcare, research, and the doctor-patient relationship. *J Am Coll Cardiol* 2007; **49**: 415–21.

223 Ongaro G, Kaptchuk TJ. Symptom perception, placebo effects, and the Bayesian brain. *Pain* 2019; **160**: 1–4.

224 Oronowicz-Jaśkowiak W, Bąbel P. Twenty years after 'Listening to Prozac but hearing placebo'. Do we hear placebo even louder? *Health Psychology Report* 2019; **7**: 1–8.

225 Ortega Á, Salazar J, Galban N, *et al.* Psycho-Neuro-Endocrine-Immunological Basis of the Placebo Effect: Potential Applications beyond Pain Therapy. *Int J Mol Sci* 2022; **23**: 4196.

226 Ossipov MH. The perception and endogenous modulation of pain. *Scientifica (Cairo)* 2012; **2012**: 561761.

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Erasmushogeschool .

227 Pacheco-López G, Engler H, Niemi M-B, Schedlowski M. Expectations and associations that heal: Immunomodulatory placebo effects and its neurobiology. *Brain Behav Immun* 2006; **20**: 430–46.

228 Packer M. The placebo effect in heart failure. *Am Heart J* 1990; **120**: 1579–82.

229 Pardo-Cabello AJ, Manzano-Gamero V, Puche-Cañas E. Placebo: a brief updated review. *Naunyn Schmiedebergs Arch Pharmacol* 2022; **395**: 1343–56.

230 Peciña M, Zubieta J-K. Molecular mechanisms of placebo responses in humans. *Mol Psychiatry* 2015; **20**: 416–23.

231 Pecina M, Zubieta J-K. Expectancy Modulation of Opioid Neurotransmission. *Int Rev Neurobiol* 2018; **138**: 17–37.

232 Peerdeman KJ, van Laarhoven AIM, Peters ML, Evers AWM. An Integrative Review of the Influence of Expectancies on Pain. *Front Psychol* 2016; **7**: 1270.

233 Perfitt JS, Plunkett N, Jones S. Placebo effect in the management of chronic pain. *BJA Educ* 2020; **20**: 382–7.

234 Perkins K, Sayette M, Conklin C, Caggiula A. Placebo effects of tobacco smoking and other nicotine intake. *Nicotine Tob Res* 2003; **5**: 695–709.

235 Perlis ML, McCall WV, Jungquist CR, Pigeon WR, Matteson SE. Placebo effects in primary insomnia. *Sleep Med Rev* 2005; **9**: 381–9.

236 Petrie KJ, Rief W. Psychobiological Mechanisms of Placebo and Nocebo Effects: Pathways to Improve Treatments and Reduce Side Effects. *Annu Rev Psychol* 2019; **70**: 599–625.

237 Petrovic P. Opioid and placebo analgesia share the same network. *Seminars in Pain Medicine* 2005; **3**: 31–6.

238 Polich G, Iaccarino MA, Kaptchuk TJ, Morales-Quezada L, Zafonte R. Nocebo Effects in Concussion: Is All That Is Told Beneficial? *Am J Phys Med Rehabil* 2020; **99**: 71–80.

239 Pollo A, Benedetti F. The placebo response: neurobiological and clinical issues of neurological relevance. *Prog Brain Res* 2009; **175**: 283–94.

240 Pollo A, Carlino E, Benedetti F. Placebo mechanisms across different conditions: from the clinical setting to physical performance. *Philos Trans R Soc Lond B Biol Sci* 2011; **366**: 1790–8.

241 Porto R. The Placebo effect: Its importance in treatment. *Sexologies* 2011; **20**: 15–9.

242 Požgain I, Požgain Z, Degmečić D. Placebo and nocebo effect: a mini-review. *Psychiatr Danub* 2014; **26**: 100–7.

243 Price DD, Fillingim RB, Robinson ME. Placebo analgesia: friend or foe? *Curr Rheumatol Rep* 2006; **8**: 418–24.

244 Price DD, Finniss DG, Benedetti F. A comprehensive review of the placebo effect: recent advances and current thought. *Annu Rev Psychol* 2008; **59**: 565–90.

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Erasmushogeschool .

245 Price DD, Zhou Q, Moshiree B, Robinson ME, Verne GN. Peripheral and central contributions to hyperalgesia in irritable bowel syndrome. *J Pain* 2006; **7**: 529–35.

246 Qiu Y-H, Wu X-Y, Xu H, Sackett D. Neuroimaging study of placebo analgesia in humans. *Neurosci Bull* 2009; **25**: 277–82.

247 Raglin J, Szabo A, Lindheimer JB, Beedie C. Understanding placebo and nocebo effects in the context of sport: A psychological perspective. *Eur J Sport Sci* 2020; **20**: 293–301.

248 Rainville P, Duncan GH. Functional brain imaging of placebo analgesia: methodological challenges and recommendations. *Pain* 2006; **121**: 177–80.

249 Richardson PH. Placebo effects in pain management. *Pain Reviews* 1994; **1**: 15–32.

250 Rief W, Barsky AJ, Bingel U, *et al.* Rethinking psychopharmacotherapy: The role of treatment context and brain plasticity in antidepressant and antipsychotic interventions. *Neurosci Biobehav Rev* 2016; **60**: 51–64.

251 Rief W, Petrie KJ. Can Psychological Expectation Models Be Adapted for Placebo Research? *Front Psychol* 2016; **7**: 1876.

252 Roberts AH, Kewman DG, Mercier L, Hovell M. The power of nonspecific effects in healing: Implications for psychosocial and biological treatments. *Clinical Psychology Review* 1993; **13**: 375–91.

253 Ross M, Olson JM. An expectancy-attribution model of the effects of placebos. *Psychological Review* 1981; **88**: 408–37.

254 Ross S, Buckalew LW. The placebo as an agent in behavioral manipulation: A review of problems, issues and affected measures. *Clinical Psychology Review* 1983; **3**: 457–71.

255 Rossettini G, Carlino E, Testa M. Clinical relevance of contextual factors as triggers of placebo and nocebo effects in musculoskeletal pain. *BMC Musculoskelet Disord* 2018; **19**: 27.

256 Rutherford B, Wager T, Roose S. Expectancy and the Treatment of Depression: A Review of Experimental Methodology and Effects on Patient Outcome. *CPSR* 2010; **6**: 1–10.

257 Sagy I, Abres J, Winnick A, Jotkowitz A. Placebos in the era of open-label trials: An update for clinicians. *Eur J Clin Invest* 2019; **49**: e13038.

258 Salamone JD. A critique of recent studies on placebo effects of antidepressants: importance of research on active placebos. *Psychopharmacology (Berl)* 2000; **152**: 1–6.

259 Sandler A. Placebo effects in developmental disabilities: Implications for research and practice. *Ment Retard Dev Disabil Res Rev* 2005; **11**: 164–70.

260 Schafer SM, Geuter S, Wager TD. Mechanisms of placebo analgesia: A dual-process model informed by insights from cross-species comparisons. *Prog Neurobiol* 2018; **160**: 101–22.

261 Schedlowski M, Enck P, Rief W, Bingel U. Neuro-Bio-Behavioral Mechanisms of Placebo and Nocebo Responses: Implications for Clinical Trials and Clinical Practice. *Pharmacol Rev* 2015; **67**: 697–730.

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262 Schedlowski M, Pacheco-López G. The learned immune response: Pavlov and beyond. *Brain, Behavior, and Immunity* 2010; **24**: 176–85.

263 Schwarz KA, Pfister R, Büchel C. Rethinking Explicit Expectations: Connecting Placebos, Social Cognition, and Contextual Perception. *Trends Cogn Sci* 2016; **20**: 469–80.

264 Shabir A, Hooton A, Tallis J, F. Higgins M. The Influence of Caffeine Expectancies on Sport, Exercise, and Cognitive Performance. *Nutrients* 2018; **10**: 1528.

265 Shafir R, Olson E, Colloca L. The neglect of sex: A call to action for including sex as a biological variable in placebo and nocebo research. *Contemp Clin Trials* 2022; **116**: 106734.

266 Shaibani A, Frisaldi E, Benedetti F. Placebo response in pain, fatigue, and performance: Possible implications for neuromuscular disorders. *Muscle Nerve* 2017; **56**: 358–67.

267 Shapiro AK. FACTORS CONTRIBUTING TO THE PLACEBO EFFECT. THEIR IMPLICATIONS FOR PSYCHOTHERAPY. *Am J Psychother* 1964; **18**: SUPPL 1:73-88.

268 Shapiro AK. A contribution to a history of the placebo effect. *Syst Res* 2007; **5**: 109–35.

269 Sheldon R, Opie-Moran M. The Placebo Effect in Cardiology: Understanding and Using It. *Can J Cardiol* 2017; **33**: 1535–42.

270 Sher L. The Placebo Effect on Mood and Behavior: Possible Role of Opioid and Dopamine Modulation of the Hypothalamic-Pituitary-Adrenal System. *Complement Med Res* 2003; **10**: 61–8.

271 Sher L. The Role of Endogenous Opioids in the Placebo Effect in Post-Traumatic Stress Disorder. *Complement Med Res* 2004; **11**: 354–9.

272 Simmons K, Ortiz R, Kossowsky J, *et al.* Pain and placebo in pediatrics: a comprehensive review of laboratory and clinical findings. *Pain* 2014; **155**: 2229–35.

273 Sliwinski J, Elkins GR. Enhancing placebo effects: insights from social psychology. *Am J Clin Hypn* 2013; **55**: 236–48.

274 Smits RM, Veldhuijzen DS, Wulffraat NM, Evers AWM. The role of placebo effects in immune-related conditions: mechanisms and clinical considerations. *Expert Rev Clin Immunol* 2018; **14**: 761–70.

275 Sölle A, Bartholomäus T, Worm M, Klinger R. How to Psychologically Minimize Scratching Impulses: Benefits of Placebo Effects on Itching Using Classical Conditioning and Expectancy. *Zeitschrift für Psychologie* 2014; **222**: 140–7.

276 Sondermann W, Reinboldt-Jockenhöfer F, Dissemond J, Pfaar O, Bingel U, Schedlowski M. Effects of Patients' Expectation in Dermatology: Evidence from Experimental and Clinical Placebo Studies and Implications for Dermatologic Practice and Research. *Dermatology* 2021; **237**: 857–71.

277 Sonthalia S, Sahaya K, Arora R, *et al.* Nocebo effect in Dermatology. *Indian J Dermatol Venereol Leprol* 2015; **81**: 242–50.

278 Spiegel H. Nocebo: the power of suggestibility. *Prev Med* 1997; **26**: 616–21.

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279 Stewart-Williams S, Podd J. The placebo effect: dissolving the expectancy versus conditioning debate. *Psychol Bull* 2004; **130**: 324–40.

280 Symon A, Williams B, Adelasoye QA, Cheyne H. Nocebo and the potential harm of 'high risk' labelling: a scoping review. *J Adv Nurs* 2015; **71**: 1518–29.

281 Szabo A. Acute psychological benefits of exercise: reconsideration of the placebo effect. *J Ment Health* 2013; **22**: 449–55.

282 Tavel ME. The placebo effect: the good, the bad, and the ugly. *Am J Med* 2014; **127**: 484–8.

283 Testa M, Fillmore MT, Norris J, *et al.* Understanding Alcohol Expectancy Effects: Revisiting the Placebo Condition. *Alcoholism Clin Exp Res* 2006; **30**: 339–48.

284 Theodosis-Nobelos P, Filotheidou A, Triantis C. The placebo phenomenon and the underlying mechanisms. *Hormones (Athens)* 2021; **20**: 61–71.

285 Thomaidou MA, Peerdeman KJ, Koppeschaar MI, Evers AWM, Veldhuijzen DS. How Negative Experience Influences the Brain: A Comprehensive Review of the Neurobiological Underpinnings of Nocebo Hyperalgesia. *Front Neurosci* 2021; **15**: 652552.

286 Tracey I. Imaging pain. *Br J Anaesth* 2008; **101**: 32–9.

287 Tracey I. The Neural Matrix of Pain Processing and Placebo Analgesia: Evidence from Functional Imaging. *Headache Currents* 2005; **2**: 123–6.

288 Tracey I. Getting the pain you expect: mechanisms of placebo, nocebo and reappraisal effects in humans. *Nat Med* 2010; **16**: 1277–83.

289 Trojian TH, Beedie CJ. Placebo Effect and Athletes: *Current Sports Medicine Reports* 2008; **7**: 214–7.

290 Vase L, Baad-Hansen L, Pigg M. How May Placebo Mechanisms Influence Orofacial Neuropathic Pain? *J Dent Res* 2019; **98**: 861–9.

291 Vase L. Can insights from placebo and nocebo mechanisms studies improve the randomized controlled trial? *Scand J Pain* 2020; **20**: 451–67.

292 Vase L, Nørskov KN, Petersen GL, Price DD. Patients' direct experiences as central elements of placebo analgesia. *Philos Trans R Soc Lond B Biol Sci* 2011; **366**: 1913–21.

293 Vase L, Skyt I, Hall KT. Placebo, nocebo, and neuropathic pain. *Pain* 2016; **157 Suppl 1**: S98–105.

294 Vase L, Skyt I, Laue Petersen G, Price DD. Placebo and Nocebo Effects in Chronic Pain Patients: How Expectations and Emotional Feelings Contribute to the Experience of Pain. *Zeitschrift für Psychologie* 2014; **222**: 135–9.

295 Vase L, Wartolowska K. Pain, placebo, and test of treatment efficacy: a narrative review. *Br J Anaesth* 2019; **123**: e254–62.

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296 Vinckier F, Betka S, Nion N, Serresse L, Similowski T. Harnessing the power of anticipation to manage respiratory-related brain suffering and ensuing dyspnoea: insights from the neurobiology of the respiratory nocebo effect. *Eur Respir J* 2021; **58**: 2101876.

297 Vits S, Cesko E, Enck P, Hillen U, Schadendorf D, Schedlowski M. Behavioural conditioning as the mediator of placebo responses in the immune system. *Philos Trans R Soc Lond B Biol Sci* 2011; **366**: 1799–807.

298 Wager TD. The neural bases of placebo effects in anticipation and pain. *Seminars in Pain Medicine* 2005; **3**: 22–30.

299 Wager TD, Atlas LY. The neuroscience of placebo effects: connecting context, learning and health. *Nat Rev Neurosci* 2015; **16**: 403–18.

300 Wager TD, Nitschke JB. Placebo effects in the brain: linking mental and physiological processes. *Brain Behav Immun* 2005; **19**: 281–2.

301 Walach H, Jonas WB. Placebo research: the evidence base for harnessing self-healing capacities. *J Altern Complement Med* 2004; **10 Suppl 1**: S103-112.

302 Waschbusch DA, Pelham WE, Waxmonsky J, Johnston C. Are there placebo effects in the medication treatment of children with attention-deficit hyperactivity disorder? *J Dev Behav Pediatr* 2009; **30**: 158–68.

303 Watanabe T, Sieg M, Lunde SJ, *et al.* What is the nocebo effect and does it apply to dentistry?-A narrative review. *J Oral Rehabil* 2022; **49**: 586–91.

304 Watson A, Power A, Brown C, El-Deredy W, Jones A. Placebo analgesia: cognitive influences on therapeutic outcome. *Arthritis Res Ther* 2012; **14**: 206.

305 Weimer K, Gulewitsch MD, Schlarb AA, Schwille-Kiuntke J, Klosterhalfen S, Enck P. Placebo effects in children: a review. *Pediatr Res* 2013; **74**: 96–102.

306 Wernicke JF, Ossanna MJ. The placebo response in pain and depression: in search of a common pathway. *Front Biosci (Schol Ed)* 2010; **2**: 106–11.

307 Williams KA, Harden N. Managing the placebo effect: enhancing the signal-to-noise ratio. *Curr Pain Headache Rep* 2011; **15**: 35–8.

308 Wojtukiewicz MZ, Politynska B, Skalij P, Tokajuk P, Wojtukiewicz AM, Honn KV. It is not just the drugs that matter: the nocebo effect. *Cancer Metastasis Rev* 2019; **38**: 315–26.

309 Wolf S. The pharmacology of placebos. *Pharmacol Rev* 1959; **11**: 689–704.

310 Wolters F, Peerdeman KJ, Evers AWM. Placebo and Nocebo Effects Across Symptoms: From Pain to Fatigue, Dyspnea, Nausea, and Itch. *Front Psychiatry* 2019; **10**: 470.

311 Zhang W. The powerful placebo effect in osteoarthritis. *Clin Exp Rheumatol* 2019; **37 Suppl 120**: 118–23.

312 Zubieta J-K, Stohler CS. Neurobiological mechanisms of placebo responses. *Ann N Y Acad Sci* 2009; **1156**: 198–210.

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B) List of original research articles included in the meta-review

Identified via databases search (n = 9)

1 Bailey RC, Baillie AJ. The relationship between placebo alcohol and affect: motives for drinking. *Drug Alcohol Rev* 2013; **32**: 162–9.

2 Clifasefi SL, Garry M, Harper DN, Sharman SJ, Sutherland R. Psychotropic placebos create resistance to the misinformation effect. *Psychon Bull Rev* 2007; **14**: 112–7.

3 Fiorio M, Recchia S, Corrà F, Simonetto S, Garcia-Larrea L, Tinazzi M. Enhancing non-noxious perception: behavioural and neurophysiological correlates of a placebo-like manipulation. *Neuroscience* 2012; **217**: 96–104.

4 Haas JW, Rief W, Glombiewski JA, Winkler A, Doering BK. Expectation-induced placebo effect on acute sadness in women with major depression: An experimental investigation. *J Affect Disord* 2020; **274**: 920–8.

5 Malani A, Houser D. Expectations mediate objective physiological placebo effects. *Adv Health Econ Health Serv Res* 2008; **20**: 311–27.

6 Rutherford BR, Wall MM, Brown PJ, *et al.* Patient Expectancy as a Mediator of Placebo Effects in Antidepressant Clinical Trials. *AJP* 2017; **174**: 135–42.

7 Tippens KM, Purnell JQ, Gregory WL, *et al.* Expectancy, Self-Efficacy, and Placebo Effect of a Sham Supplement for Weight Loss in Obese Adults. *J Evid Based Complementary Altern Med* 2014; **19**: 181–8.

8 Wai-lanYeung V, Geers A, Kam SM. Merely Possessing a Placebo Analgesic Reduced Pain Intensity: Preliminary Findings from a Randomized Design. *Curr Psychol* 2019; **38**: 194–203.

9 Wrobel N, Fadai T, Sprenger C, Hebebrand J, Wiech K, Bingel U. Are Children the Better Placebo Analgesia Responders? An Experimental Approach. *The Journal of Pain* 2015; **16**: 1005–11.

Identified via citation search (n = 9)

1 Dar R, Stronguin F, Etter J-F. Assigned versus perceived placebo effects in nicotine replacement therapy for smoking reduction in Swiss smokers. *J Consult Clin Psychol* 2005; **73**: 350–3.

2 McCarney R, Warner J, Iliffe S, van Haselen R, Griffin M, Fisher P. The Hawthorne Effect: a randomised, controlled trial. *BMC Med Res Methodol* 2007; **7**: 30.

3 Olliges E, Schneider S, Schmidt G, *et al.* Placebo and Nocebo Effects in Patients With Takotsubo Cardiomyopathy and Heart-Healthy Controls. *Front Psychiatry* 2019; **10**: 549.

4 Pagnini F, Cavalera C, Volpato E, Banfi P. Illness expectations predict the development of influenza-like symptoms over the winter season. *Complement Ther Med* 2020; **50**: 102396.

5 Park C, Pagnini F, Langer E. Glucose metabolism responds to perceived sugar intake more than actual sugar intake. *Sci Rep* 2020; **10**: 15633.

6 Park C, Pagnini F, Reece A, Phillips D, Langer E. Blood sugar level follows perceived time rather than actual time in people with type 2 diabetes. *Proc Natl Acad Sci U S A* 2016; **113**: 8168–70.

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7 Sandler AD, Glesne CE, Bodfish JW. Conditioned placebo dose reduction: a new treatment in attention-deficit hyperactivity disorder? *J Dev Behav Pediatr* 2010; **31**: 369–75.

8 Sölle A, Worm M, Benedetti F, Sabine Bartholomäus T, Schwender-Groen L, Klinger R. Targeted Use of Placebo Effects Decreases Experimental Itch in Atopic Dermatitis Patients: A Randomized Controlled Trial. *Clin Pharmacol Ther* 2021; **110**: 486–97.

9 Van Ree JM, Schagen Van Leeuwen JH, Koppeschaar HP, Te Velde ER. Unexpected placebo response in premenstrual dysphoric disorder: implication of endogenous opioids. *Psychopharmacology (Berl)* 2005; **182**: 318–9.

Identified via literature search (n = 1)

1 Benedetti F, Shaibani A, Arduino C, Thoen W. Open-label nondeceptive placebo analgesia is blocked by the opioid antagonist naloxone. *Pain* 2022; **Publish Ahead of Print**. DOI:10.1097/j.pain.0000000000002791.

C) List of systematic reviews included in the meta-review but not identified through the database search

Identified via citation search (n = 3)

1 de Craen AJ, Tijssen JG, de Gans J, Kleijnen J. Placebo effect in the acute treatment of migraine: subcutaneous placebos are better than oral placebos. *J Neurol* 2000; **247**: 183–8.

2 Hróbjartsson A, Gøtzsche PC. Placebo interventions for all clinical conditions. *Cochrane Database of Systematic Reviews* 2010; published online Jan 20. DOI:10.1002/14651858.CD003974.pub3.

3 Vase L, Petersen GL, Riley JL, Price DD. Factors contributing to large analgesic effects in placebo mechanism studies conducted between 2002 and 2007. *Pain* 2009; **145**: 36–44.

Identified via literature search (n = 2)

1 Amanzio M, Mitsikostas DD, Giovannelli F, Bartoli M, Cipriani GE, Brown WA. Adverse events of active and placebo groups in SARS-CoV-2 vaccine randomized trials: A systematic review. *Lancet Reg Health Eur* 2022; **12**: 100253.

2 Tang B, Barnes K, Geers A, Livesey E, Colagiuri B. Choice and the Placebo Effect: A Meta-analysis. *Ann Behav Med* 2022; **56**: 977–88.

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Supplementary appendix 4

List of studies excluded from the meta-review after being read in their full length, with reasons for the exclusion

Systematic reviews

- *about non-pharmacological intervention (n = 6)*

1 Hesser H, Weise C, Rief W, Andersson G. The effect of waiting: A meta-analysis of wait-list control groups in trials for tinnitus distress. *Journal of Psychosomatic Research* 2011; **70**: 378–84.

2 Howick J, Webster R, Kirby N, Hood K. Rapid overview of systematic reviews of nocebo effects reported by patients taking placebos in clinical trials. *Trials* 2018; **19**: 674.

3 Kirsch I, Sapirstein G. Listening to Prozac but hearing placebo: A meta-analysis of antidepressant medication. *Prevention & Treatment* 1998; **1**. DOI:10.1037/1522-3736.1.1.12a.

4 Qiu Y, Mao Z, Yun D. Can the add-on placebo effect augment the physical and mental health outcomes of exercise? A meta-analysis. *Appl Psychol Health Well Being* 2022; **14**: 483–98.

5 Sherriff B, Clark C, Killingback C, Newell D. Impact of contextual factors on patient outcomes following conservative low back pain treatment: systematic review. *Chiropr Man Therap* 2022; **30**: 20.

6 Kube T, Glombiewski JA, Rief W. Using Different Expectation Mechanisms to Optimize Treatment of Patients With Medical Conditions: A Systematic Review. *Psychosom Med* 2018; **80**: 535–43.

- *pooled data not specific to either intervention type (pharmacological or non-pharmacological) or three-arm studies (active, placebo, no treatment) (n=1)*

1 Webster RK, Weinman J, Rubin GJ. A systematic review of factors that contribute to nocebo effects. *Health Psychology* 2016; **35**: 1334–55.

- *trials lacking of no-treatment groups (n = 4)*

1 Cao B, Liu YS, Selvitella A, *et al.* Differential power of placebo across major psychiatric disorders: a preliminary meta-analysis and machine learning study. *Sci Rep* 2021; **11**: 21301.

2 Kern A, Kramm C, Witt CM, Barth J. The influence of personality traits on the placebo/nocebo response. *Journal of Psychosomatic Research* 2020; **128**: 109866.

3 Meissner K, Fässler M, Rücker G, *et al.* Differential effectiveness of placebo treatments: a systematic review of migraine prophylaxis. *JAMA Intern Med* 2013; **173**: 1941–51.

4 Weimer K, Colloca L, Enck P. Age and Sex as Moderators of the Placebo Response - An Evaluation of Systematic Reviews and Meta-Analyses across Medicine. *Gerontology* 2015; **61**: 97–108.

- *lack of placebo control group and no-treatment group within the same trial (n = 2)*

1 Bélanger L, Vallières A, Ivers H, Moreau V, Lavigne G, Morin CM. Meta-analysis of sleep changes in control groups of insomnia treatment trials. *J Sleep Res* 2007; **16**: 77–84.

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2 Vallance AK. A systematic review comparing the functional neuroanatomy of patients with depression who respond to placebo to those who recover spontaneously: is there a biological basis for the placebo effect in depression? *J Affect Disord* 2007; **98**: 177–85.

Original research articles

- *Cited in systematic reviews included in the present meta-review (n = 1)*

1 Fratello F, Curcio G, Ferrara M, *et al.* Can an inert sleeping pill affect sleep? Effects on polysomnographic, behavioral and subjective measures. *Psychopharmacology* 2005; **181**: 761–70. *Cited in Yeung et al. (2018)*[45]

- *Cited in narrative reviews included in the present meta-review (n = 1)*

1 Ober K, Benson S, Vogelsang M, *et al.* Plasma Noradrenaline and State Anxiety Levels Predict Placebo Response in Learned Immunosuppression. *Clin Pharmacol Ther* 2012; **91**: 220–6. *Cited in Hadamitzky et al. (2020)*[90]

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PRISMA 2020 for Abstract Checklist

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as a meta-review.	YES
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	YES
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	YES
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	YES
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	YES
Synthesis of results	6	Specify the methods used to present and synthesise results.	YES
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	YES
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	YES
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	NO
Interpretation	10	Provide a general interpretation of the results and important implications.	YES
OTHER			
Funding	11	Specify the primary source of funding for the review.	NO
Registration	12	Provide the register name and registration number.	YES

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PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as a meta-review.	page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	page 4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	pages 7, 8
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	page 8
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	pages 8, 9 and table 1
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	pages 8, 9
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Supplementary appendix 1B
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	page 9
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	page 9
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	page 8 and Table 1
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	page 9 and Table 1
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	pages 9, 10 and Supplementary appendix 2
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	page 8
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	pages 8, 9
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	page 9
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	page 10
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	page 10
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	NA
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	pages 9, 10
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	NA

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Section and Topic	Item #	Checklist item	Location where item is reported
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	NA
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	page 10, figure 1, and Supplementary appendix 3
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	figure 1 and Supplementary appendix 4
Study characteristics	17	Cite each included study and present its characteristics.	pages 10-15 and Table 2
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	page 10 and Supplementary appendix 2
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	page 13 and tables 3 and 4
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	pages 10-15, table 2 and supplementary appendix 2
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	page 10 and tables 3 and 4
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	NA
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	page 10 and Supplementary appendix 2
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	NA
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	pages 16-17
	23b	Discuss any limitations of the evidence included in the review.	page 17
	23c	Discuss any limitations of the review processes used.	page 17
	23d	Discuss implications of the results for practice, policy, and future research.	pages 17
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	page 8
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	page 3 and 8, and Supplementary appendix 1A
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	page 9
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	page 2
Competing interests	26	Declare any competing interests of review authors.	page 2
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	page 3, Tables 3 and 4

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BMJ Open

Placebo and nocebo effects and mechanisms associated with pharmacological interventions: an umbrella review

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Placebo and nocebo effects and mechanisms associated with pharmacological interventions: an umbrella review

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Abstract

Objectives: This review aimed to summarize the existing knowledge about placebo and nocebo effects associated with pharmacological interventions and their mechanisms.

Design: Umbrella review, adopting the Assessment of Multiple Systematic Reviews 2 tool for critical appraisal.

Data sources: MEDLINE/PubMed, Scopus, Web of Science, PsycINFO, Cochrane Central Register of Controlled Trial were searched in September 2022, without any time restriction, for systematic reviews, narrative reviews, original articles. Results were summarized through narrative synthesis, tables, 95% confidence interval (CI).

Outcome measures: Mechanisms underlying placebo/nocebo effects and/or their effect sizes.

Results: The databases search identified 372 studies, for a total of 158,312 participants, comprising 41 systematic reviews, 312 narrative reviews, and 19 original articles. Seventy-three percent of the examined systematic reviews were of high quality.

Our findings revealed that mechanisms underlying placebo and/or nocebo effects have been characterized, at least in part, for: pain, non-noxious somatic sensation, Parkinson's disease, migraine, sleep disorders, intellectual disability, depression, anxiety, dementia, addiction, gynaecological disorders, attention-deficit hyperactivity disorder, immune and endocrine systems, cardiovascular and respiratory systems, gastrointestinal disorders, skin diseases, flu and related vaccines, oncology, obesity, physical and cognitive performance. Their magnitude ranged from 0.08 to 2.01 [95% CI: 0.37, 0.89] for placebo effects and from 0.32 to 0.90 [95% CI: 0.24, 1.00] for nocebo effects.

Conclusions: This study provides a valuable tool for clinicians and researchers, identifying both results ready for clinical practice and gaps to address in the near future.

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Protocol: PROSPERO CRD42023392281

Keywords

placebo effect, placebo response; placebo-related effect; nocebo effect; nocebo response; nocebo-related response; mind-body relationship.

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Strengths and limitations of this study

- The umbrella review was reported according to the PRISMA guidelines.
- By only analysing placebo and nocebo effects associated with pharmacological interventions, it was possible to circumscribe the area of investigation and reduce the degree of methodological variability between studies.
- Systematic reviews were appraised by using the Assessment of Multiple Systematic Reviews 2 tool, which has demonstrated satisfactory reliability and construct validity.
- The database search was conducted by one author, whereas two authors independently reviewed the full text of potentially eligible studies against the inclusion and exclusion criteria.
- While the umbrella review methodology allows for a comprehensive summary of the findings, it does not permit to overcome the single study limitations, which include publication biases, and the lack of information about unpublished data and the grey literature.

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Introduction

Placebo and nocebo effects are the effects of patients' positive and negative expectations, respectively, about their health status and they can occur during treatment with a placebo or an active agent, either in clinical practice or in clinical trials. While placebo effects result in beneficial outcomes, nocebo effects result in patient harms.[1–5]

Over the past 30 years, there has been a surge of research on the placebo and nocebo effects in the fields of neuroscience, medicine, psychology and genetics. What has emerged is that there are many placebo and nocebo effects, not just one. They occur through specific mechanisms in many clinical conditions and in the domain of physical and cognitive performance.[6] Furthermore, it has been shown that many biological mechanisms triggered by placebos and nocebos resemble those modulated by drugs, suggesting a possible interaction between psychological factors and drug action.[6]

In 2018, a consensus of experts emphasized the importance of distinguishing *placebo effects* from *placebo responses*.[7] This need comes from the pharmacological definitions of *drug effect* and *drug response*, whereby the former is the specific pharmaco-dynamic effect of a drug, whereas the latter is the global response to drug administration.[6] Accordingly, while the *placebo* and *nocebo effects* specifically refer to the changes attributable to placebo and nocebo mechanisms, which are the "actual" psychobiological phenomena, the *placebo* and *nocebo responses* include all trial outcome changes resulting from the administration of an inactive treatment, including natural history and regression to the mean.[7]

Besides classical placebo/nocebo effects, today we can also differentiate between placebo/nocebo effects and placebo- and nocebo-related effects. Although the psychosocial context around the treatment plays a key role in both cases, in the former case, an inert treatment is administered, while in the latter case, it is not.[8] These strict definitions remind us that it is not always necessary to administer a placebo to obtain a therapeutic effect, as sometimes doctor's or health care professionals' words, their attitudes, and the therapeutic rituals are enough.[8]

Another important term used in clinical research is the Hawthorne effect, which refers to changes in baseline conditions that occur in response to a participant's awareness of being under study. Improvements that occur after recruitment but before the start of treatment could be attributable to several factors, including increased expectations of health benefits, better observation, better compliance, and treatment adherence.[9]

With the exponential increase in the placebo and nocebo literature,[10] novel interpretative approaches have arisen by both Ongaro and Kaptchuk[11] and Pagnini and colleagues,[12] along

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with the concept of open-label placebos (OLPs), in which patients are informed that they have been prescribed inert treatments.[13]

It is therefore important to incorporate new insights with the existing knowledge. Umbrella reviews provide a unique approach to knowledge integration in circumstances where multiple systematic reviews and meta-analyses have already been published on a specific research topic. In fact, they provide a bird eye's view of the currently available evidence on broad research topics, explore the consistency of findings, and indicate potential priorities for future research.[14,15] This umbrella review aims to present an up-to-date overview of neurobiological basis of both placebo/nocebo effects and placebo/nocebo-related effects associated with pharmacological interventions. Our threefold goal was to present findings regarding: 1) what are the conditions, i.e., clinical or physiological, in which robust placebo/nocebo effects or placebo/nocebo-related effects have been documented to date; 2) what are the contexts/circumstances, i.e. clinical or laboratory setting, in which they occur; 3) what do we know about the biological underpinnings of these effects.

Methods

Review selection

The study was reported according to the PRISMA guidelines,[16] with methods established prior to conducting the umbrella review. The protocol was registered on the international prospective register for systematic reviews PROSPERO (record no. CRD42023392281, see supplementary appendix 1A). The objective was to capture systematic reviews, with or without meta-analyses, and narrative reviews aimed at mapping placebo and nocebo effects, or related effects, associated with pharmacological interventions. These studies were then to be informative in terms of biological mechanisms and/or effect sizes.

The electronic bibliographic databases MEDLINE/PubMed, Scopus, Web of Science, PsycINFO, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched in September 2022, according to the search equation provided in supplementary appendix 1B. The search was conducted applying the Population, Intervention, Comparison, Outcomes, and Study (PICOS) criteria reported in table 1, and no time restrictions were set.

Regarding the interventions, we excluded the investigation of placebo/nocebo effects and placebo/nocebo-related effects in non-pharmacological interventions (e.g., psychotherapy, acupuncture, surgery, neuromodulation, physical therapies, hypnosis, mindfulness training, biofeedback, neurofeedback, music) in order to circumscribe the area of investigation and reduce the degree of methodological variability among studies.

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The randomized clinical trials (RCTs) and OLPs clinical trials included in the present umbrella review were required to have a three-arm design (i.e., genuine treatment, placebo, and no-treatment arms). The latter design allows participants receiving placebo treatment to be compared with those left untreated, and thus to disentangle placebo/nocebo effects from placebo/nocebo responses.[2] To provide additional information on the biological mechanisms of placebo/nocebo effects, a first deviation from the original protocol was made for those meta-analyses based on rigorous placebo-controlled RCTs without a no-treatment group, which examined: i) different routes of placebo administration and reported improvements not attributable to spontaneous remission or regression to the mean; ii) different likelihoods of receiving active treatment or placebo; iii) the type of adverse events (AEs) occurring in both the active and placebo arms. A second deviation was made for original research articles informative about mechanisms and effect sizes that: i) addressed an under-investigated topic in the field of placebo research that missed to be included in systematic or narrative reviews; ii) were too recent to be included in systematic or narrative reviews.

Screening process and data extraction

The database search was conducted by one author (EF), who removed duplicates and screened the titles and abstracts. Two authors (EF and FP) independently reviewed the full text of potentially eligible studies (systematic review, narrative reviews and original research articles) against the inclusion and exclusion criteria. Any disagreements were resolved through discussion among all the authors. The references of the surveyed systematic and narrative reviews, and those of books or book chapters on placebo and nocebo mechanisms, were screened for potentially suitable publications. Narrative review articles were included to verify that database search had been exhaustive. If not, they were used as a valuable source of citations. In addition, they provided useful comparative material regarding the arguments brought by the authors on cutting-edge issues related to placebo and nocebo effects.

Very recent informative studies (systematic reviews and original research articles) were found through literature search. The same two authors (EF and FP) progressively entered the data into a spreadsheet pre-set to record biological mechanisms and effect sizes.

Critical appraisal

EF and FP independently appraised the captured systematic reviews using the Assessment of Multiple Systematic Reviews (AMSTAR) 2 tool, which has demonstrated satisfactory reliability and construct validity.[17] In assessing the overall quality of individual studies, more weight was given to the AMSTAR 2 critical domains (i.e., 7 out 16 items).[17] About the protocol domain, an

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explicit statement was required that the methods had been established prior to conducting the systematic review, and/or that PRISMA guidelines[16] or those for meta-analyses and systematic reviews of observational studies[18] had been adhered to, and/or that any deviations from protocol had been reported.

In the supplementary appendix 2 the full assessment according to AMSTAR 2 tool was provided for each of the examined systematic reviews, including the 7 critical domains marked in yellow and the final positive or negative rating.

Because of the real heterogeneity in the examined conditions and in studies design included in each systematic review, we did not use funnel plots and we choose to summarize the umbrella review results mainly through narrative synthesis and tables.

Statistical analysis

The total number of participants in systematic reviews and original articles was calculated. Since for some systematic reviews only a subset of studies met the inclusion criteria, we took just such studies into account in the overall calculation.

Results of critical appraisal were summarized as: i) the percentage of all surveyed systematic reviews that received a positive final overall assessment; ii) the percentage of systematic reviews, distinguishing between those with and without meta-analysis, that received a positive final overall assessment.

Regarding the effect sizes expressed as Cohen's *d*, Hedges' g, or Standardized Mean Difference they were summarized as a range with the smallest and largest placebo or nocebo effects, along with their respective 95% confidence interval (CI).

Patient and Public Involvement

No patient involved.

Results

Umbrella review outcomes

As shown in figure 1, the main search returned a total of 6,215 records, which were reduced to 3,725 after the exclusion of duplicates. After records were screened for title and abstract, and 3,353 records were excluded, a total of 372 full text papers were retrieved, from which 357 met full inclusion criteria. Fifteen additional studies (5 systematic reviews and 10 original research articles) were identified from citations or literature search, for a total of 372 studies included in the umbrella review and 158,312 participants. In particular, the pool of eligible studies includes 41 systematic

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reviews, 312 narrative reviews, and 19 original articles, with all the examined systematic reviews and original articles published in the last 30 years.

Characteristics of the 41 systematic reviews, 30 with and 11 without meta-analyses, are presented in supplemental appendix 3.[19–59] Furthermore, as documented in supplementary appendix 2, 73% of the eligible systematic reviews were rated as overall high-quality, 77% for those with meta-analysis and 64% for those without.

The supplementary appendix 4 contains the list of both narrative reviews (1, A) and original articles (1, B) included in the umbrella review, together with the list of systematic reviews identified from citation or literature search (1, C). The supplementary appendix 5 contains the list of studies excluded after being read in their full length, with reason for the exclusion.

General concepts and mechanisms

Although placebos are not expected to work uniformly in all clinical conditions, a series of meta-analyses were conducted between 2001 and 2013 on three-arm RCTs across all clinical conditions (comprising mainly pharmacological interventions).[21–25] In particular, Hróbjartsson and Gøtzsche focused on the comparison between placebo and no-treatment groups. They found little evidence in general that placebo interventions had clinically important effects.[24,25] Placebos had no significant effects on continuous objective outcomes and subjective or objective binary outcomes, while they had possible small benefits in studies with continuous subjective outcomes, especially in the settings of pain and nausea.[22] To facilitate quick comprehension for readers, examples of subjective continuous outcomes were the pain intensity measured on 11-point numeric rating scale or the Rhodes Inventory of Nausea and Vomiting for pain and nausea, respectively. An example of objective continuous outcomes for both settings was the dose of rescue medication. Consistently, the incidence of pain or nausea based on specific cutpoints of the adopted clinical scales represented an example of subjective binary outcomes, while the administration or not of rescue medication represented an example of objective binary outcomes. Results obtained from Hróbjartsson and Gøtzsche's meta-analyses were inevitably constrained by the studies selected and the sensitivity of their measures. For example, binary outcomes have less power to detect effects generally than do continuous outcomes. Moreover, the authors used very broad inclusion criteria (i.e., RCTs with a placebo group and a no-treatment group, employing both parallel or crossover designs), and the surveyed studies used 40 different outcome measures, some more reliable than others and some more likely to exhibit a response to placebo than others.[60]

Since the assessment of the clinical utility of placebos requires a comparison with an active treatment, in 2013 Howick and colleagues[21] extracted data about treatment effects from the last

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meta-analysis conducted by Hróbjartsson and Gøtzsche in 2010.[22] They showed that placebos often had a great benefit compared with no-treatment as active treatments had over placebos.[21] In trials with binary outcomes, active treatment effects were usually greater than placebo effects (n = 37, ratio of risk ratios = 0.72 [95% CI: 0.61, 0.86] p < 0.001). In trials with continuous outcomes (n = 115), placebo effects were found to be higher than active treatment effects when the analysis was restricted to studies with a low risk of bias (n = 8, mean difference = 1.59 [95% CI: 0.40, 2.77] p = 0.009).[21]

Starting from the same pool of studies used by Hróbjartsson and Gøtzsche in 2004,[24] and selecting studies that used peripherally measured parameters as outcomes, a subsequent meta-analysis showed that placebo interventions can improve physical disease processes of peripheral organs (n = 20, Hedges' pooled effect size = 0.22 [95% CI: 0.07, 0.36] p = 0.003) more easily and effectively than biochemical processes (n = 6, *g* = -0.17 [95% CI: -0.31, -0.02] p = 0.02).[23]

Regarding nocebo effects, manipulation of expectation, conditioning, or both has been shown to successfully evoke nocebo effects in domains such as those of pain sensation, skin dryness, nausea, and cognitive performance. For example, regarding the manipulation of expectation in pain, it has been shown that pain intensity increases in healthy participants who were informed that during a painful stimulation they would have receive a cream with a hyperalgesic effect. With regard to Pavlovian conditioning of nausea in healthy volunteers (rotation paired with cinnamon breath strips), it has been shown to significantly induce both a decrease in reaction time (stopping the rotation in rotation chair) and an increase in symptom reporting. Conversely, nocebo effects have not been shown to occur in the domains of satiety and dizziness.[26]

Despite their proven effectiveness in many conditions, prescribing placebos is considered unethical because it entails deception.[61] Yet, this idea has been challenged recently by the use of OLPs.[3,62] A positive effect for nondeceptive placebos compared with no-treatment (standardized mean difference 0.88 [95% CI: 0.62, 1.14] p < 0.001) was recently reported in meta-analysis in which the clinical conditions analysed were depression, attention-deficit hyperactivity disorder (ADHD), irritable bowel syndrome (IBS), allergic rhinitis.[20]

The effect size of choice on the placebo effect has also recently been examined in a pool of studies that compared placebo treatment with any form of choice on its administration against placebo treatment without choice.[19] The fifteen eligible studies, which assessed a range of conditions including pain, discomfort, sleep difficulty, and anxiety, showed that choice did significantly enhance the placebo effect, even if with a small effect size (Hedges' *g* = 0.298). Also, the magnitude of the placebo effect without choice (i.e., placebo without choice versus no-treatment) was identified as the only reliable moderator of the choice effect, according to the role that larger

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placebo effect without choice produced smaller choice effects (i.e., placebo with choice vs. placebo without choice). Therefore, treatment choice can effectively facilitate the placebo effect, but this effect appears more pronounced in contexts where the placebo effect without choice is not prominent.[19]

From a psychobiological perspective, most knowledge about the mechanisms of placebo and nocebo effects comes from the field of pain. It shows that expectation and learning are the main mediators. Expectation is a conscious event, whereby the subject expects a future outcome. The link between expectation and clinical outcomes is twofold. First, positive expectations may reduce anxiety. Second, expectation of a positive event (i.e., a therapeutic benefit), may activate reward mechanisms, in which reward is the therapeutic benefit itself. Learning mechanisms, ranging from classical or behavioural conditioning to social learning, are crucial because prior experience toward effective treatments leads to substantial placebo effects. It is important to emphasize that expectation and learning are not mutually exclusive, since learning can lead to the reinforcement of expectations or can even create de novo expectations.[4,6,8]

A central role in placebo effects seems also to be played by the interactions between associative learning systems and appraisals, which are flexible cognitive evaluations of the personal meaning of events and situations. While learning can occur in many neural circuits, appraisal appears to be supported by a specialized system — a collection of midline cortical and temporoparietal regions associated with the so-called "default mode network". This network, involved in emotion generation, social and self-referential cognition, and value-based learning and decision making, allows individuals to simulate potential outcomes and to develop expectations about future events.[63]

In terms of predictive factors, it should be emphasized that many reasons exist why some people respond to placebos (placebo responders) while others do not (placebo non responders). Learning is certainly an important factor, as people who have had prior positive therapeutic experiences show larger placebo effects than those who have not had any.[1–3,6] Other important determinants are: personality traits; genetic variants; gender; individual differences in the efficiency of the neural mechanisms of reward, whereby the ventral striatum — i.e., the nucleus accumbens — is involved in motivation and reward anticipation; prefrontal functioning and connectivity.[4,64,65] Regarding the latter factor, its importance in the placebo component of the analgesic treatments was demonstrated in studies on Alzheimer's disease (AD) patients, while the individual placebo analgesic effect was found to be correlated with the white matter integrity in the descending pain control system in normal subjects. Therefore, the potential disruption of placebo mechanisms should be considered in all those conditions where the prefrontal regions are involved, as occurs in

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vascular and frontotemporal dementia as well as in any lesion of the prefrontal cortex.[4] Regarding sex differences, males have been found to respond more strongly to placebo treatments, while females to nocebo treatments.[27] Furthermore, males respond with larger placebo effects induced by verbal information, whereas females respond with larger nocebo effects induced by conditioning procedures. The observed sex differences in placebo responding are probably due to larger stress reduction in males compared to females. Furthermore, endogenous opioid transmission has been reported to be more effective in males compared to females and may, therefore, explain the observed sex differences in placebo analgesia and nocebo hyperalgesia.[27]

Mechanisms of placebo and nocebo effects across conditions

The retrieved psychobiological mechanisms of placebo/nocebo effects and placebo/nocebo-related effects associated with pharmacological interventions, together with their effect sizes, are reported in supplementary appendix 6. In summary, meaningful results have been found for the following clinical conditions: pain,[2,4,6,8,20],[29–40],[62],[66–75] non-noxious somatic sensation,[76] Parkinson's disease,[2,6,41,77–79] migraine,[42–44] sleep,[45,80] intellectual disability (ID),[46] depression,[2,6,20,47,48,62,69,74,81–83] anxiety,[2,6,8,74] dementia,[2,4,49,84] addiction,[2,4,50,51,63,79,85,86] gynaecological disorders,[87,88] ADHD,[20,89] immune and endocrine systems,[2,4,20,79,90–92] cardiovascular system,[2,52,79,93,94] respiratory system,[2,79,95–97] gastrointestinal disorders,[6,20,53,62,74,98–100] skin diseases,[26,54,62,87,96,101–103] flu and related vaccines,[55,104] oncology,[20,26,53,62,96] and obesity.[9,105,106] Beyond the healing context, meaningful results have also been found for physical[2,56–59,107–109] and cognitive performance.[26,108,110]

Regarding placebo and nocebo effect sizes, they were found to vary from small to large depending on the condition under investigation: from 0.08 to 2.01 [95% CI: 0.37, 0.89] in the case of placebo effects, and from 0.32 to 0.90 [95% CI: 0.24, 1.00] in the case of nocebo effects. Consistently, table 2 lists the clinical and non-clinical conditions according to the effect sizes of the placebo/nocebo effects, and for each of them indicates the outcome measures adopted (subjective and/or objective).

Interpreting the evidence

Some results about the magnitude or mechanisms of placebo and nocebo effects require interpretation and an in-depth analysis. Different settings and mechanisms present peculiarities that should be individually considered.

In the field of pain, the difference in magnitude of placebo analgesia observed between those studies aimed at investigating placebo mechanism compared to those using placebos as control

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condition appears to result from different suggestions given for pain relief.[37] Moreover, magnitudes of placebo and nocebo effects in both nociceptive and idiopathic pain conditions appear to be roughly similar, supporting the hypothesis that similar mechanisms are involved in the opposite effects.[35] Regarding the difference in placebo analgesic effects according to the population type, patients show to benefit from placebo treatment to a greater extent than healthy participants do.[31] Consistently, the analysis of neurotransmitter systems involved in placebo/nocebo effects in healthy participants and chronic pain patients suggests that knowledges obtained in the former population may not necessarily be transferred to the latter.[28]

Major advances in the neuroanatomical viewpoint of placebo analgesia have also been made in the last decade. Placebos administered along with positive verbal suggestions activate and deactivate different brain regions. Many of these regions show anticipatory increases prior to pain, predicting the strength of an individual's placebo analgesic effect, and suggesting that their role in placebo analgesia may not be pain-specific but rather may be tied to broader appraisal and expectation processes.[36,70] Consistently, very small effects are elicited by placebo on the neurologic pain signature, which is a brain-based pattern that can reliably distinguish between responses to painful and nonpainful stimuli, and is sensitive and specific to pain.[30] This finding suggests that placebos might modulate nonspecific affective and cognitive processes rather than affecting nociception.[30,70]

The neuroanatomy of nocebo hyperalgesia has been characterized as well.[33] Cortical systems implicated in the experience of pain have been shown to be involved in pain anticipation. Their involvement suggests that these activations have a preparatory function, whereby potentially threatening stimuli receive more attention and are reliably detected.[33,75]

In anti-migraine clinical trials, adequate controls groups are lacking. Nevertheless, the placebo-controlled RCTs in both chronic migraine prevention and acute migraine treatment trials, which examined the efficacy of different routes of drug and placebo administration, proved to be informative about placebo effects.[42,44] Indeed, as Swerts and co-workers (2022) state,[42] although their meta-analysis evaluated the placebo response deriving from different routes of administration, the methodology of the eligible trials was kept the same (all of which were double-blinded RCTs, with the natural history being kept constant). Therefore, the differences in the placebo response emerged from statistical analysis actually reflect a difference in the placebo effect, and provides a starting point for the investigation of the underlying mechanisms.[42]

The neuroanatomy of placebo effects in depression has also begun to be disclosed. It involves the activity in the ventral striatum, rostral anterior cingulate cortex and other default mode network

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regions, orbitofrontal cortex, and dorsolateral prefrontal cortex, with overlap with some of the areas involved in placebo analgesia.[48]

Dementia deserves special attention because its pathophysiology is complex and varies across the different types of dementia, of which AD is by far the most common. AD patients in moderate and later stages of the disease have shown to not benefit from certainty of receiving genuine treatment (100% certainty) compared to the uncertainty of receiving treatment or placebo (50% certainty).[49] This could be due to the nature/progression of the disease, but it could also be related to an order effect in the practice of running AD trials, where RCTs are conducted prior to open-label trials. These findings have implications for the understanding of non-specific treatment effects in AD patients as well as for the design of clinical trials that test pharmacological treatments in AD.[49]

Regarding respiratory system, expectation-induced dyspnoea in the laboratory setting by using classical conditioning shows important therapeutic perspective.[79,97] Since expectation of dyspnoea can be manipulated by an external intervention, it becomes of major importance not only to interfere with acute brain mechanisms, but also to reverse chronic conditioning to free the patient's mind from negative respiratory anticipation.[97]

In oncology, the experimental tradition in placebo and nocebo effects originated in the study of anticipatory nausea in chemotherapy. The latter refers to the phenomenon whereby patients develop such strong learning between their chemotherapy context and the nausea that they begin to feel nauseous purely when they re-enter this context.[53,96] There is promising preliminary evidence that latent inhibition and overshadowing procedures can be used to prevent or diminish anticipatory nausea.[53] Also, these procedures do not involve deception, so if confirmed as effective in large-scale studies they could be applied and ethically translated into practice.[53]

Placebo and nocebo effects in sport performance involve a variety of factors, such as fatigue endurance, pain tolerance, motivation, and muscle strength. Motor performance is instead a broader term, incorporating not only the execution of sport specific movements, but also including skills that are essential to normal everyday functioning, such as simple reaction time or vigilance.[56] According to the model of central command, motor performance is not limited by a failure of homeostasis in key organs, but rather it is regulated at early stages in order to ensure that exercise is completed before harm develops.[107] Consistently, placebos and nocebos might act in motor performance on the balance between an inhibitory and a facilitatory system, by altering the individual evaluation of the ongoing muscles performance. On one hand, placebos could act to increase fatigue threshold with the consequent increase of motor output and decrease of perceived fatigue; on the other hand, nocebos could act to decrease fatigue threshold.[107,108]

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Discussion

This umbrella review attested the significant progress made in the past 30 years in the investigation of placebo/nocebo effects and placebo/nocebo-related effects, and it offered an up-to-date overview on the topic. The overall high quality of the examined systematic reviews supported the reliability of both the obtained qualitative and quantitative results. Furthermore, even if overlapping meta-analyses on the same topic were found, especially in pain, each of them made specific contributions to the whole picture.

Many biological mechanisms were rigorously characterized in both clinical and non-clinical contexts, as extensively described in supplementary appendix 6. Moreover, the magnitude of placebo effects, ranging from small to large, was calculated for nociceptive, idiopathic and neuropathic pain,[30,66] migraine,[42,44] sleep,[45] depression,[47,81] addiction,[51] respiratory system,[95] and physical performance.[57–59] Moderate placebo-related effect was calculated for ID.[46] The magnitude of nocebo effects, ranging from small to moderate and moderate to large, was calculated for nociceptive and idiopathic pain[35] and for physical performance.[56,58] Cough and asthma showed to undergo powerful placebo effects, measured as cough frequency and airway reactivity, respectively. However, their magnitudes have not yet been quantified in pools of eligible studies.[95,96]

Significant responses to OLP administration were documented for: pain (low back pain and ischemic arm pain),[20,62,72] depression,[20,62] menopausal hot flushes,[87] ADHD,[20,89] allergic rhinitis,[20] irritable bowel syndrome,[20,62] psoriasis,[62] and cancer related fatigue.[20,62] Also, the Hawthorne effect was documented in both dementia[84] and obesity.[9] Indications regarding which outcome measures were assessed for each condition were also provided, including: validated clinical scales of pain relief in the case of pain; reduction in the number of migraine days per month in the case of chronic migraine or headache relief rate in the case of acute migraine treatment; global sleep quality, total sleep time, sleep onset latency in the case of sleep.

With the intention to provide a list of strategies for better future research in clinical practice and clinical trials, table 3 was prepared from our results and from what has been proposed in previous literature.[3,9,79,111,112] Regarding clinical practice, whereby placebo, nocebo and Hawthorne effects are powerful, pervasive, and common, and produce uncertainty in the measurement of therapeutic outcomes,[3,9] the outlined strategies should be considered a priority, also given their numerous benefits at no cost.[113] Our considerations for better future trial design were outlined as well, which do not include the current strategy to artificially reduce placebo responses. Indeed, the double-blind placebo run-in (or lead-in) period for identifying placebo responders and excluding

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them from further random assignment[9] should be interpreted with caution, as should the elimination of placebo responders based on genetic screening.[9] In fact, these procedures create an ideal and strictly controlled conditions (efficacy studies), which do not represent the real world (effectiveness studies). Furthermore, the degree of responsiveness to placebo could vary over time within the same individual, while random assignment of non-responders to both the placebo and active treatment arms could lead to low placebo effects in both groups, with no real benefit.

An additional strength of our study is that it allowed us to identify which research areas presented findings that are ready to be implemented in clinical practice. They are: nociceptive, idiopathic, and neuropathic pain, non-noxious somatic sensation (with implications for conditions characterized by a pathological lack of sensation, e.g., stroke), Parkinson's disease, chronic migraine, ID, depression, AD, addiction, ADHD disorder, allergic diseases, type 2 diabetes, cough, dyspnoea, IBS, itch, Covid-19 vaccination and management of influenza or influenza-like symptoms, physical performance, the latter with important implications for all diseases which have fatigue and/or dyspnoea as cardinal symptoms.

Many other clinical conditions exist that may contribute to the discovery of new placebo and nocebo effects in the near future. These are mainly chronic diseases in which placebos, administered in the context of classic RCTs, have been shown to induce significant improvements. These responses, however, would require the inclusion of an untreated control group in the trial to be accounted for as placebo/nocebo effects. Some of these clinical conditions include myasthenia gravis (MG)[114] and painful diabetic neuropathy (PDN).[115] Placebo and drug responses in MG trials, as assessed by means of the Quantitative Myasthenia Gravis (QMG) scores assigned by neurologists, have been shown to be small and moderate, respectively.[114] In PDN trials, the placebo response, as assessed by patients-perceived pain relief, showed moderate effect size (with the year of study initiation as the only significant moderator), whereas the nocebo response substantially accounted for patients' reported AEs.[115]

Despite the exponential growth of research into placebo and nocebo effects, these phenomena remain complex and far from being fully understood. First of all, meta-analyses rigorously quantifying the magnitude of placebo and nocebo effects are lacking for several of the clinical conditions examined: PD, anxiety, immune, endocrine and cardiovascular systems, gastrointestinal disorders, and oncology. Furthermore, while some studies provided answers to certain questions, they also raised new ones, thus identifying research gaps. For example, the magnitude of placebo and nocebo effects can be modulated through conditioning and instructional strategies? What kind of interaction exists between placebo and nocebo effects, i.e., is it possible for placebos to act, in part or entirely, on a pre-existing nocebo effect under certain conditions? How do placebo and

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nocebo effects modulate subjective/patient-reported and objective (physiological/behavioural) outcomes in different clinical conditions? In addition, further investigations are needed both to study the factors predicting the magnitude of placebo and nocebo responses, e.g., by screening for genetic polymorphisms among individuals, and to pursue the mapping of the conditions under which OLPs work, accompanied by the investigation of the underlying mechanisms.

Focusing instead on the therapist-patient encounter, the biggest challenges for future research include: 1) the identification of those elements, psychological and social, that may lead to a good relationship; 2) in-depth experiments with brain imaging techniques to understand complex functions such as hope, trust, empathy, compassion, and admiration; 3) the development of questionnaires and psychometric measurements able to identify patient's needs.

The present study should be interpreted in the context of its limitations. In fact, while the umbrella review methodology allows for a comprehensive summary of the findings, it does not permit to overcome the single study limitations, which include publication biases, and the lack of information about unpublished data and the grey literature. In addition, as the value of a second reviewer throughout the entire screening process of systematic reviews has been documented,[116] the use of a single reviewer in the database search represent a further potential limitation of the present study.

In conclusion, this umbrella review was intended to raise awareness among clinicians and researchers of the application of clear evidence on the benefits and harms of placebo and nocebo effects. Depending on the contexts, specific tools were provided to best harness, develop, and implement strategies that enhance placebo effects and prevent or minimize potential nocebo effects associated with pharmacological interventions. In addition, the present study identified which findings are ready to be implemented in clinical practice and highlighted research gaps that need to be addressed in the near future.

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Authors' statements

Contributors EF, FP, FB, and AS are guarantors and responsible for the design and protocol design. EF and FP analysed and interpreted the data with the support of FB and AS. All authors drafted the paper and read, commented on, and approved the final draft. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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References

1 Benedetti F. Placebo Effects: From the Neurobiological Paradigm to Translational Implications. *Neuron* 2014;**84**:623–37. doi:10.1016/j.neuron.2014.10.023

2 Finniss DG, Kaptchuk TJ, Miller F, *et al.* Biological, clinical, and ethical advances of placebo effects. *Lancet Lond Engl* 2010;**375**:686–95. doi:10.1016/S0140-6736(09)61706-2

3 Colloca L, Barsky AJ. Placebo and Nocebo Effects. *N Engl J Med* 2020;**382**:554–61. doi:10.1056/NEJMra1907805

4 Benedetti F. Placebo and the New Physiology of the Doctor-Patient Relationship. *Physiol Rev* 2013;**93**:1207–46. doi:10.1152/physrev.00043.2012

5 Benedetti F, Frisaldi E, Piedimonte A. The need to investigate nocebo effects in more detail. *World Psychiatry Off J World Psychiatr Assoc WPA* 2019;**18**:227–8. doi:10.1002/wps.20627

6 Benedetti F, Frisaldi E, Shaibani A. Thirty Years of Neuroscientific Investigation of Placebo and Nocebo: The Interesting, the Good, and the Bad. *Annu Rev Pharmacol Toxicol* 2022;**62**:323–40. doi:10.1146/annurev-pharmtox-052120-104536

7 Evers AWM, Colloca L, Blease C, *et al.* Implications of Placebo and Nocebo Effects for Clinical Practice: Expert Consensus. *Psychother Psychosom* 2018;**87**:204–10. doi:10.1159/000490354

8 Benedetti F. Mechanisms of placebo and placebo-related effects across diseases and treatments. *Annu Rev Pharmacol Toxicol* 2008;**48**:33–60. doi:10.1146/annurev.pharmtox.48.113006.094711

9 Benedetti F, Carlino E, Piedimonte A. Increasing uncertainty in CNS clinical trials: the role of placebo, nocebo, and Hawthorne effects. *Lancet Neurol* 2016;**15**:736–47. doi:10.1016/S1474-4422(16)00066-1

10 Weimer K, Buschhart C, Broelz EK, *et al.* Bibliometric Properties of Placebo Literature From the JIPS Database: A Descriptive Study. *Front Psychiatry* 2022;**13**:853953. doi:10.3389/fpsyt.2022.853953

11 Ongaro G, Kaptchuk TJ. Symptom perception, placebo effects, and the Bayesian brain. *Pain* 2019;**160**:1–4. doi:10.1097/j.pain.0000000000001367

12 Pagnini F, Barbiani D, Cavalera C, *et al.* Placebo and Nocebo Effects as Bayesian-Brain Phenomena: The Overlooked Role of Likelihood and Attention. *Perspect Psychol Sci J Assoc Psychol Sci* 2023;:17456916221141383. doi:10.1177/17456916221141383

13 Kaptchuk TJ, Miller FG. Open label placebo: can honestly prescribed placebos evoke meaningful therapeutic benefits? *BMJ* 2018;**363**:k3889. doi:10.1136/bmj.k3889

14 Belbasis L, Bellou V, Ioannidis JPA. Conducting umbrella reviews. *BMJ Med* 2022;**1**:e000071. doi:10.1136/bmjmed-2021-000071

15 Fusar-Poli P, Radua J. Ten simple rules for conducting umbrella reviews. *Evid Based Ment Health* 2018;**21**:95–100. doi:10.1136/ebmental-2018-300014

16 Page MJ, McKenzie JE, Bossuyt PM, *et al.* The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;**372**:n71. doi:10.1136/bmj.n71

17 Shea BJ, Reeves BC, Wells G, *et al.* AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ* 2017;**358**:j4008. doi:10.1136/bmj.j4008

18 Stroup DF, Berlin JA, Morton SC, *et al.* Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 2000;**283**:2008–12. doi:10.1001/jama.283.15.2008

19 Tang B, Barnes K, Geers A, *et al.* Choice and the Placebo Effect: A Meta-analysis. *Ann Behav Med Publ Soc Behav Med* 2022;**56**:977–88. doi:10.1093/abm/kaab111

20 Charlesworth JEG, Petkovic G, Kelley JM, *et al.* Effects of placebos without deception compared with no treatment: A systematic review and meta-analysis. *J Evid-Based Med*

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Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Erasmushogeschool .

2017;**10**:97–107. doi:10.1111/jebm.12251
21 Howick J, Friedemann C, Tsakok M, *et al.* Are treatments more effective than placebos? A systematic review and meta-analysis. *PloS One* 2013;**8**:e62599. doi:10.1371/journal.pone.0062599
22 Hróbjartsson A, Gøtzsche PC. Placebo interventions for all clinical conditions. *Cochrane Database Syst Rev* 2010;**2010**:CD003974. doi:10.1002/14651858.CD003974.pub3
23 Meissner K, Distel H, Mitzdorf U. Evidence for placebo effects on physical but not on biochemical outcome parameters: a review of clinical trials. *BMC Med* 2007;**5**:3. doi:10.1186/1741-7015-5-3
24 Hróbjartsson A, Gøtzsche PC. Is the placebo powerless? Update of a systematic review with 52 new randomized trials comparing placebo with no treatment. *J Intern Med* 2004;**256**:91–100. doi:10.1111/j.1365-2796.2004.01355.x
25 Hróbjartsson A, Gøtzsche PC. Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. *N Engl J Med* 2001;**344**:1594–602. doi:10.1056/NEJM200105243442106
26 Bagarić B, Jokić-Begić N, Sangster Jokić C. The Nocebo Effect: A Review of Contemporary Experimental Research. *Int J Behav Med* 2022;**29**:255–65. doi:10.1007/s12529-021-10016-y
27 Vambheim SM, Flaten MA. A systematic review of sex differences in the placebo and the nocebo effect. *J Pain Res* 2017;**10**:1831–9. doi:10.2147/JPR.S134745
28 Skyt I, Lunde SJ, Baastrup C, *et al.* Neurotransmitter systems involved in placebo and nocebo effects in healthy participants and patients with chronic pain: a systematic review. *Pain* 2020;**161**:11–23. doi:10.1097/j.pain.0000000000001682
29 Daniali H, Flaten MA. A Qualitative Systematic Review of Effects of Provider Characteristics and Nonverbal Behavior on Pain, and Placebo and Nocebo Effects. *Front Psychiatry* 2019;**10**:242. doi:10.3389/fpsyt.2019.00242
30 Zunhammer M, Bingel U, Wager TD, *et al.* Placebo Effects on the Neurologic Pain Signature: A Meta-analysis of Individual Participant Functional Magnetic Resonance Imaging Data. *JAMA Neurol* 2018;**75**:1321–30. doi:10.1001/jamaneurol.2018.2017
31 Forsberg JT, Martinussen M, Flaten MA. The Placebo Analgesic Effect in Healthy Individuals and Patients: A Meta-Analysis. *Psychosom Med* 2017;**79**:388–94. doi:10.1097/PSY.0000000000000432
32 Peerdeman KJ, van Laarhoven AIM, Keij SM, *et al.* Relieving patients' pain with expectation interventions: A meta-analysis. *Pain* 2016;**157**:1179–91. doi:10.1097/j.pain.0000000000000540
33 Palermo S, Benedetti F, Costa T, *et al.* Pain anticipation: an activation likelihood estimation meta-analysis of brain imaging studies. *Hum Brain Mapp* 2015;**36**:1648–61. doi:10.1002/hbm.22727
34 Atlas LY, Wager TD. A meta-analysis of brain mechanisms of placebo analgesia: consistent findings and unanswered questions. *Handb Exp Pharmacol* 2014;**225**:37–69. doi:10.1007/978-3-662-44519-8_3
35 Petersen GL, Finnerup NB, Colloca L, *et al.* The magnitude of nocebo effects in pain: a meta-analysis. *Pain* 2014;**155**:1426–34. doi:10.1016/j.pain.2014.04.016
36 Amanzio M, Benedetti F, Porro CA, *et al.* Activation likelihood estimation meta-analysis of brain correlates of placebo analgesia in human experimental pain. *Hum Brain Mapp* 2013;**34**:738–52. doi:10.1002/hbm.21471
37 Vase L, Petersen GL, Riley JL, *et al.* Factors contributing to large analgesic effects in placebo mechanism studies conducted between 2002 and 2007. *Pain* 2009;**145**:36–44. doi:10.1016/j.pain.2009.04.008
38 Sauro MD, Greenberg RP. Endogenous opiates and the placebo effect: a meta-analytic review. *J Psychosom Res* 2005;**58**:115–20. doi:10.1016/j.jpsychores.2004.07.001
39 Vase L, Riley JL, Price DD. A comparison of placebo effects in clinical analgesic trials

For peer review only - http://bmjopen.bmj.com/site/about/guidelines.xhtml

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
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versus studies of placebo analgesia. *Pain* 2002;**99**:443–52. doi:10.1016/S0304-3959(02)00205-1
40 Ter Riet G, de Craen AJM, de Boer A, *et al.* Is placebo analgesia mediated by endogenous opioids? A systematic review. *Pain* 1998;**76**:273–5. doi:10.1016/S0304-3959(98)00057-8
41 Quattrone A, Barbagallo G, Cerasa A, *et al.* Neurobiology of placebo effect in Parkinson's disease: What we have learned and where we are going. *Mov Disord Off J Mov Disord Soc* 2018;**33**:1213–27. doi:10.1002/mds.27438
42 Swerts DB, Benedetti F, Peres MFP. Different routes of administration in chronic migraine prevention lead to different placebo responses: a meta-analysis. *Pain* 2022;**163**:415–24. doi:10.1097/j.pain.0000000000002365
43 Amanzio M, Corazzini LL, Vase L, *et al.* A systematic review of adverse events in placebo groups of anti-migraine clinical trials. *Pain* 2009;**146**:261–9. doi:10.1016/j.pain.2009.07.010
44 de Craen AJ, Tijssen JG, de Gans J, *et al.* Placebo effect in the acute treatment of migraine: subcutaneous placebos are better than oral placebos. *J Neurol* 2000;**247**:183–8.
45 Yeung V, Sharpe L, Glozier N, *et al.* A systematic review and meta-analysis of placebo versus no treatment for insomnia symptoms. *Sleep Med Rev* 2018;**38**:17–27. doi:10.1016/j.smrv.2017.03.006
46 Jensen KB, Kirsch I, Pontén M, *et al.* Certainty of genuine treatment increases drug responses among intellectually disabled patients. *Neurology* 2017;**88**:1912–8. doi:10.1212/WNL.0000000000003934
47 Fernández-López R, Riquelme-Gallego B, Bueno-Cavanillas A, *et al.* Influence of placebo effect in mental disorders research: A systematic review and meta-analysis. *Eur J Clin Invest* 2022;**52**:e13762. doi:10.1111/eci.13762
48 Huneke NTM, Aslan IH, Fagan H, *et al.* Functional neuroimaging correlates of placebo response in patients with depressive or anxiety disorders: A systematic review. *Int J Neuropsychopharmacol* 2022;**25**:433–47. doi:10.1093/ijnp/pyac009
49 Matthiesen ST, Rosenkjær S, Pontén M, *et al.* Does Certainty of Genuine Treatment Increase the Drug Response in Alzheimer's Disease Patients: A Meta-Analysis and Critical Discussion. *J Alzheimers Dis JAD* 2021;**84**:1821–32. doi:10.3233/JAD-210108
50 Galindo MN, Navarro JF, Cavas M. The Influence of Placebo Effect on Craving and Cognitive Performance in Alcohol, Caffeine, or Nicotine Consumers: A Systematic Review. *Front Psychiatry* 2020;**11**:849. doi:10.3389/fpsyt.2020.00849
51 McKay D, Schare ML. The effects of alcohol and alcohol expectancies on subjective reports and physiological reactivity: a meta-analysis. *Addict Behav* 1999;**24**:633–47. doi:10.1016/s0306-4603(99)00021-0
52 Daniali H, Flaten MA. Placebo Analgesia, Nocebo Hyperalgesia, and the Cardiovascular System: A Qualitative Systematic Review. *Front Physiol* 2020;**11**:549807. doi:10.3389/fphys.2020.549807
53 Quinn VF, Colagiuri B. Placebo interventions for nausea: a systematic review. *Ann Behav Med Publ Soc Behav Med* 2015;**49**:449–62. doi:10.1007/s12160-014-9670-3
54 Meeuwis SH, van Middendorp H, van Laarhoven AIM, *et al.* Placebo and nocebo effects for itch and itch-related immune outcomes: A systematic review of animal and human studies. *Neurosci Biobehav Rev* 2020;**113**:325–37. doi:10.1016/j.neubiorev.2020.03.025
55 Amanzio M, Mitsikostas DD, Giovannelli F, *et al.* Adverse events of active and placebo groups in SARS-CoV-2 vaccine randomized trials: A systematic review. *Lancet Reg Health - Eur* 2022;**12**:100253. doi:10.1016/j.lanepe.2021.100253
56 Horváth Á, Köteles F, Szabo A. Nocebo effects on motor performance: A systematic literature review. *Scand J Psychol* 2021;**62**:665–74. doi:10.1111/sjop.12753
57 Marticorena FM, Carvalho A, Oliveira LFD, *et al.* Nonplacebo Controls to Determine the Magnitude of Ergogenic Interventions: A Systematic Review and Meta-analysis. *Med Sci Sports Exerc* 2021;**53**:1766–77. doi:10.1249/MSS.0000000000002635
58 Hurst P, Schipof-Godart L, Szabo A, *et al.* The Placebo and Nocebo effect on sports

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performance: A systematic review. *Eur J Sport Sci* 2020;**20**:279–92. doi:10.1080/17461391.2019.1655098
59 Bérdi M, Köteles F, Szabó A, *et al.* Placebo Effects in Sport and Exercise: A Meta-Analysis. *Eur J Ment Health* 2011;**6**:196–212. doi:10.5708/EJMH.6.2011.2.5
60 Spiegel D, Kraemer H, Carlson RW. Is the Placebo Powerless? *N Engl J Med* 2001;**345**:1276–9. doi:10.1056/NEJM200110253451712
61 Blease C, Colloca L, Kaptchuk TJ. Are open-Label Placebos Ethical? Informed Consent and Ethical Equivocations. *Bioethics* 2016;**30**:407–14. doi:10.1111/bioe.12245
62 Colloca L, Howick J. Placebos Without Deception: Outcomes, Mechanisms, and Ethics. *Int Rev Neurobiol* 2018;**138**:219–40. doi:10.1016/bs.irn.2018.01.005
63 Ashar YK, Chang LJ, Wager TD. Brain Mechanisms of the Placebo Effect: An Affective Appraisal Account. *Annu Rev Clin Psychol* 2017;**13**:73–98. doi:10.1146/annurev-clinpsy-021815-093015
64 Benedetti F, Frisaldi E. Creating placebo responders and nonresponders in the laboratory: boons and banes. *Pain Manag* 2014;**4**:165–7. doi:10.2217/pmt.14.11
65 Frisaldi E, Shaibani A, Benedetti F. Placebo responders and nonresponders: what's new? *Pain Manag* 2018;**8**:405–8. doi:10.2217/pmt-2018-0054
66 Vase L, Skyt I, Hall KT. Placebo, nocebo, and neuropathic pain. *Pain* 2016;**157 Suppl 1**:S98–105. doi:10.1097/j.pain.0000000000000445
67 Carlino E, Frisaldi E, Benedetti F. Pain and the context. *Nat Rev Rheumatol* 2014;**10**:348–55. doi:10.1038/nrrheum.2014.17
68 Peciña M, Zubieta J-K. Molecular mechanisms of placebo responses in humans. *Mol Psychiatry* 2015;**20**:416–23. doi:10.1038/mp.2014.164
69 Pecina M, Zubieta J-K. Expectancy Modulation of Opioid Neurotransmission. *Int Rev Neurobiol* 2018;**138**:17–37. doi:10.1016/bs.irn.2018.02.003
70 Atlas LY. A social affective neuroscience lens on placebo analgesia. *Trends Cogn Sci* 2021;**25**:992–1005. doi:10.1016/j.tics.2021.07.016
71 Wai-lanYeung V, Geers A, Kam SM. Merely Possessing a Placebo Analgesic Reduced Pain Intensity: Preliminary Findings from a Randomized Design. *Curr Psychol* 2019;**38**:194–203. doi:10.1007/s12144-017-9601-0
72 Benedetti F, Shaibani A, Arduino C, *et al.* Open-label nondeceptive placebo analgesia is blocked by the opioid antagonist naloxone. *Pain* 2022;**Publish Ahead of Print**. doi:10.1097/j.pain.0000000000002791
73 Wrobel N, Fadai T, Sprenger C, *et al.* Are Children the Better Placebo Analgesia Responders? An Experimental Approach. *J Pain* 2015;**16**:1005–11. doi:10.1016/j.jpain.2015.06.013
74 Hall KT, Loscalzo J, Kaptchuk TJ. Genetics and the placebo effect: the placebome. *Trends Mol Med* 2015;**21**:285–94. doi:10.1016/j.molmed.2015.02.009
75 Amanzio M, Palermo S. Pain Anticipation and Nocebo-Related Responses: A Descriptive Mini-Review of Functional Neuroimaging Studies in Normal Subjects and Precious Hints on Pain Processing in the Context of Neurodegenerative Disorders. *Front Pharmacol* 2019;**10**:969. doi:10.3389/fphar.2019.00969
76 Fiorio M, Recchia S, Corrà F, *et al.* Enhancing non-noxious perception: behavioural and neurophysiological correlates of a placebo-like manipulation. *Neuroscience* 2012;**217**:96–104. doi:10.1016/j.neuroscience.2012.04.066
77 Murray D, Stoessl AJ. Mechanisms and therapeutic implications of the placebo effect in neurological and psychiatric conditions. *Pharmacol Ther* 2013;**140**:306–18. doi:10.1016/j.pharmthera.2013.07.009
78 Frisaldi E, Carlino E, Lanotte M, *et al.* Characterization of the thalamic-subthalamic circuit involved in the placebo response through single-neuron recording in Parkinson patients. *Cortex J Devoted Study Nerv Syst Behav* 2014;**60**:3–9. doi:10.1016/j.cortex.2013.12.003

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Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Erasmushogeschool .

79 Enck P, Bingel U, Schedlowski M, *et al.* The placebo response in medicine: minimize, maximize or personalize? *Nat Rev Drug Discov* 2013;**12**:191–204. doi:10.1038/nrd3923
80 Laverdure-Dupont D, Rainville P, Montplaisir J, *et al.* Relief expectation and sleep. *Rev Neurosci* 2010;**21**:381–95. doi:10.1515/revneuro.2010.21.5.381
81 Haas JW, Rief W, Glombiewski JA, *et al.* Expectation-induced placebo effect on acute sadness in women with major depression: An experimental investigation. *J Affect Disord* 2020;**274**:920–8. doi:10.1016/j.jad.2020.05.056
82 Colagiuri B, Schenk LA, Kessler MD, *et al.* The placebo effect: From concepts to genes. *Neuroscience* 2015;**307**:171–90. doi:10.1016/j.neuroscience.2015.08.017
83 Rutherford BR, Wall MM, Brown PJ, *et al.* Patient Expectancy as a Mediator of Placebo Effects in Antidepressant Clinical Trials. *Am J Psychiatry* 2017;**174**:135–42. doi:10.1176/appi.ajp.2016.16020225
84 McCarney R, Warner J, Iliffe S, *et al.* The Hawthorne Effect: a randomised, controlled trial. *BMC Med Res Methodol* 2007;**7**:30. doi:10.1186/1471-2288-7-30
85 Bailey RC, Baillie AJ. The relationship between placebo alcohol and affect: motives for drinking. *Drug Alcohol Rev* 2013;**32**:162–9. doi:10.1111/j.1465-3362.2012.00500.x
86 Dar R, Stronguin F, Etter J-F. Assigned versus perceived placebo effects in nicotine replacement therapy for smoking reduction in Swiss smokers. *J Consult Clin Psychol* 2005;**73**:350–3. doi:10.1037/0022-006X.73.2.350
87 Pardo-Cabello AJ, Manzano-Gamero V, Puche-Cañas E. Placebo: a brief updated review. *Naunyn Schmiedebergs Arch Pharmacol* 2022;**395**:1343–56. doi:10.1007/s00210-022-02280-w
88 Van Ree JM, Schagen Van Leeuwen JH, Koppeschaar HP, *et al.* Unexpected placebo response in premenstrual dysphoric disorder: implication of endogenous opioids. *Psychopharmacology (Berl)* 2005;**182**:318–9. doi:10.1007/s00213-005-0090-8
89 Sandler AD, Glesne CE, Bodfish JW. Conditioned placebo dose reduction: a new treatment in attention-deficit hyperactivity disorder? *J Dev Behav Pediatr JDBP* 2010;**31**:369–75. doi:10.1097/DBP.0b013e3181e121ed
90 Hadamitzky M, Lückemann L, Pacheco-López G, *et al.* Pavlovian Conditioning of Immunological and Neuroendocrine Functions. *Physiol Rev* 2020;**100**:357–405. doi:10.1152/physrev.00033.2018
91 Park C, Pagnini F, Langer E. Glucose metabolism responds to perceived sugar intake more than actual sugar intake. *Sci Rep* 2020;**10**:15633. doi:10.1038/s41598-020-72501-w
92 Park C, Pagnini F, Reece A, *et al.* Blood sugar level follows perceived time rather than actual time in people with type 2 diabetes. *Proc Natl Acad Sci* 2016;**113**:8168–70. doi:10.1073/pnas.1603444113
93 Malani A, Houser D. Expectations mediate objective physiological placebo effects. *Adv Health Econ Health Serv Res* 2008;**20**:311–27.
94 Olliges E, Schneider S, Schmidt G, *et al.* Placebo and Nocebo Effects in Patients With Takotsubo Cardiomyopathy and Heart-Healthy Controls. *Front Psychiatry* 2019;**10**:549. doi:10.3389/fpsyt.2019.00549
95 Eccles R. The Powerful Placebo Effect in Cough: Relevance to Treatment and Clinical Trials. *Lung* 2020;**198**:13–21. doi:10.1007/s00408-019-00305-5
96 Wolters F, Peerdeman KJ, Evers AWM. Placebo and Nocebo Effects Across Symptoms: From Pain to Fatigue, Dyspnea, Nausea, and Itch. *Front Psychiatry* 2019;**10**:470. doi:10.3389/fpsyt.2019.00470
97 Vinckier F, Betka S, Nion N, *et al.* Harnessing the power of anticipation to manage respiratory-related brain suffering and ensuing dyspnoea: insights from the neurobiology of the respiratory nocebo effect. *Eur Respir J* 2021;**58**:2101876. doi:10.1183/13993003.01876-2021
98 Elsenbruch S, Enck P. Placebo effects and their determinants in gastrointestinal disorders. *Nat Rev Gastroenterol Hepatol* 2015;**12**:472–85. doi:10.1038/nrgastro.2015.117
99 Enck P, Horing B, Weimer K, *et al.* Placebo responses and placebo effects in functional

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bowel disorders. *Eur J Gastroenterol Hepatol* 2012;**24**:1–8. doi:10.1097/MEG.0b013e32834bb951
100 Price DD, Finniss DG, Benedetti F. A comprehensive review of the placebo effect: recent advances and current thought. *Annu Rev Psychol* 2008;**59**:565–90. doi:10.1146/annurev.psych.59.113006.095941
101 Sondermann W, Reinboldt-Jockenhöfer F, Dissemond J, *et al.* Effects of Patients' Expectation in Dermatology: Evidence from Experimental and Clinical Placebo Studies and Implications for Dermatologic Practice and Research. *Dermatol Basel Switz* 2021;**237**:857–71. doi:10.1159/000513445
102 Bartels DJP, van Laarhoven AIM, van de Kerkhof PCM, *et al.* Placebo and nocebo effects on itch: effects, mechanisms, and predictors. *Eur J Pain Lond Engl* 2016;**20**:8–13. doi:10.1002/ejp.750
103 Sölle A, Worm M, Benedetti F, *et al.* Targeted Use of Placebo Effects Decreases Experimental Itch in Atopic Dermatitis Patients: A Randomized Controlled Trial. *Clin Pharmacol Ther* 2021;**110**:486–97. doi:10.1002/cpt.2276
104 Pagnini F, Cavalera C, Volpato E, *et al.* Illness expectations predict the development of influenza-like symptoms over the winter season. *Complement Ther Med* 2020;**50**:102396. doi:10.1016/j.ctim.2020.102396
105 Tippens KM, Purnell JQ, Gregory WL, *et al.* Expectancy, Self-Efficacy, and Placebo Effect of a Sham Supplement for Weight Loss in Obese Adults. *J Evid-Based Complement Altern Med* 2014;**19**:181–8. doi:10.1177/2156587214528513
106 Fontaine KR, Williams MS, Hoenemeyer TW, *et al.* Placebo effects in obesity research. *Obes Silver Spring Md* 2016;**24**:769–71. doi:10.1002/oby.21456
107 Shaibani A, Frisaldi E, Benedetti F. Placebo response in pain, fatigue, and performance: Possible implications for neuromuscular disorders: Placebo Response. *Muscle Nerve* 2017;**56**:358–67. doi:10.1002/mus.25635
108 Beedie C, Benedetti F, Barbiani D, *et al.* Incorporating methods and findings from neuroscience to better understand placebo and nocebo effects in sport. *Eur J Sport Sci* 2020;**20**:313–25. doi:10.1080/17461391.2019.1675765
109 Davis AJ, Hettinga F, Beedie C. You don't need to administer a placebo to elicit a placebo effect: Social factors trigger neurobiological pathways to enhance sports performance. *Eur J Sport Sci* 2020;**20**:302–12. doi:10.1080/17461391.2019.1635212
110 Clifasefi SL, Garry M, Harper DN, *et al.* Psychotropic placebos create resistance to the misinformation effect. *Psychon Bull Rev* 2007;**14**:112–7. doi:10.3758/bf03194037
111 Bingel U. Placebo 2.0: the impact of expectations on analgesic treatment outcome. *Pain* 2020;**161 Suppl 1**:S48–56. doi:10.1097/j.pain.0000000000001981
112 Frisaldi E, Shaibani A, Benedetti F. Why We should Assess Patients' Expectations in Clinical Trials. *Pain Ther* 2017;**6**:107–10. doi:10.1007/s40122-017-0071-8
113 Evers AWM, Colloca L, Blease C, *et al.* What Should Clinicians Tell Patients about Placebo and Nocebo Effects? Practical Considerations Based on Expert Consensus. *Psychother Psychosom* 2021;**90**:49–56. doi:10.1159/000510738
114 Frisaldi E, Shaibani A, Vollert J, *et al.* The placebo response in myasthenia gravis assessed by quantitative myasthenia gravis score: A meta-analysis. *Muscle Nerve* 2019;**59**:671–8. doi:10.1002/mus.26469
115 Frisaldi E, Vollert J, Al Sultani H, *et al.* Placebo and nocebo responses in painful diabetic neuropathy: systematic review and meta-analysis. *Pain* Published Online First: 2 August 2023. doi:10.1097/j.pain.0000000000003000
116 Stoll CRT, Izadi S, Fowler S, *et al.* The value of a second reviewer for study selection in systematic reviews. *Res Synth Methods* 2019;**10**:539–45. doi:10.1002/jrsm.1369

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Figure Legends

Fig 1. PRISMA flowchart. Trial flow of the selection process, showing both the number of events and reasons for the exclusion of most of the 6215 initially selected records.

Table 1: Description of PICOS components of umbrella review

P	Human population, across different clinical conditions and beyond the healing context.
I	Placebo and nocebo effects: inert treatments undistinguishable from the matched active pharmacological interventions, administered with suggestions of improvement/worsening or according to conditioning procedures. Placebo-related and nocebo-related effects: suggestions of improvement/worsening without administration of inert treatments, or difference between expected (open) and unexpected (hidden) active pharmacological interventions.
C	No-treatment condition or control group, waiting list, pharmacological placebo not associated with expectation for symptoms improvement/worsening, baseline condition (told placebo, get placebo) according to the balanced-placebo design.
O	Biological mechanisms of placebo/nocebo effects and of placebo/nocebo-related effects, along with their effect sizes.
S	Peer-reviewed studies, published in English, informative in terms of biological mechanisms and/or effect sizes. Specifically: - Systematic-reviews and narrative reviews providing data obtained from: RCTs with a no-treatment control group, OLPs trials with a no-treatment control group, placebo/nocebo mechanism studies conducted in the laboratory settings on healthy subjects and/or patients; - Rigorous placebo-controlled RCTs without a no-treatment group investigating: i) different routes of placebo administration and reported improvements not attributable to spontaneous remission or regression to the mean; ii) different likelihoods of receiving active treatment or placebo; iii) the type of AEs occurring in both the active and placebo arms; - Original research articles that: i) addressed an under-investigated topic in the field of placebo research that missed to be included in systematic or narrative reviews; ii) were too recent to be included in systematic or narrative reviews.

AEs, adverse events; OLPs, open label placebos; RCTs, randomized clinical trials.

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Table 2: Magnitude of placebo and nocebo effects across conditions

Magnitude of the effect size	Type of effect	Condition	Values	Outcome measures
Large	Placebo	Nociceptive, idiopathic, and neuropathic pain in placebo mechanism studies	Nociceptive pain Cohen's *d* = 1.01[66] Idiopathic pain Cohen's *d* = 1.63[66] Neuropathic pain Cohen's *d* = 2.01[66]	Validated clinical scales of pain relief, filled in by patients (subjective self-reported measure)
	Placebo	Chronic migraine prevention trials: strictly dependent by route of placebo administration (application to the head being superior to the other routes)	Seventy-five percent of the therapeutic gain[42]	Reduction in the number of days with migraine in the month (subjective self-reported measure)
	Placebo	Acute sadness in female depressed patients	Hedge's *g* = 0.92[81]	Validated clinical scale for major depression, filled in by patients (subjective measure)
	Placebo	Respiratory system: cough	Fifty percent reduction in cough frequency[95]	Reduction in cough frequency, recorded by means of a microphone (objective measure)
	Placebo	Sport performance assuming purported anabolic steroids or an erythropoietin like substance	Purported anabolic steroids Cohen's *d* = 1.44[58] Erythropoietin like substance Cohen's *d* = 0.81[58]	Direct measure of performance, e.g. power output, speed, or time to completion (objective measures)
Moderate to large	Nocebo	Nociceptive and idiopathic pain, where nocebo effects were induced by verbal suggestions	Cohen's *d* around 0.66 to 0.90[35]	Validated clinical scales of pain relief, filled in by patients (subjective self-reported measure)
Moderate	Placebo	Addiction: alcohol-challenge studies whereby the experimental setting consists of a natural environment (both less tension and experimental reactivity than in experimental lab situations)	Cohen's *d* = 0.658[51]	Self-reported measures (subjective measures); physiological or behavioural measures (objective measures)
	Placebo-related	Intellectual disability: effect associated to the certainty of receiving the active treatment	Hedges' g = 0.65[46]	Validated clinical scales filled in by patients (subjective measure)
	Nocebo	Motor performance	Cohen's *d* = 0.60[56]	Rotor task performance, sprint time, alertness reaction time, biceps curl total repetitions (objective measures)
Small to moderate	Placebo	Sleep	Sleep onset latency Hedges' *g* = 0.272[45]	Global sleep quality, total sleep time, sleep onset latency (patients' subjective self-reported measures)

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			Total sleep time Hedges' g = 0.322[45] Perceived global sleep quality Hedges' g = 0.58[45]	
	Placebo	Addition: alcohol-challenge studies conducted according to the balanced-placebo design	Behavioural Cohen's d = 0.221[51] Self-report Cohen's d = 0.348[51] Physiological Cohen's d = 0.394[51]	Self-report variables (subjective); behavioural and physiological variables (objective)
	Placebo	Sport performance assuming placebo described as amino acids or caffeine	Amino acids Cohen's d = 0.36 [58] Caffeine Cohen's d = 0.40[58]	Direct measure of performance, e.g. power output, speed, or time to completion (objective measures)
	Placebo	Acute migraine treatment (small for oral placebo administration, moderate for subcutaneous placebo administration)	Oral placebo administration, 25.7% of patients[44] Subcutaneous placebo administration, 32.4% of patients[44]	Headache relief rate (patients' subjective self-reported measure)
	Nocebo	Sport performance assuming a fictitious sport supplement thought to be detrimental to performance	Cohen's d = 0.32[58]	Sprint time (objective measure)
Small	Placebo	Pain	Hedges' g = 0.08[30]	Activation of neurologic pain signature (NPS, objective measure)
	Placebo	Depression	Standardized Mean Difference 0.22, 95%[47]	Validated clinical scale for major depression, filled in by patients (subjective measure); number of relapses (objective measure)
	Placebo	Sport performance assuming a fictitious sport supplement	Cohen's d = 0.21[58]	Direct measure of performance, e.g. power output, speed, or time to completion (objective measures)
	Placebo	Sport performance assuming the active nutritional supplements caffeine and extracellular buffers	Hedges' g = 0.09[57]	Total work done, means: power output, mean velocity, mean height, and time to completion (i.e., performance test)/time to exhaustion (i.e., capacity test).

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Table 3: Strategies for better future research in clinical practice and clinical trials

Clinical practice	Clinical trials
Communication style and verbal information	
Enhance the physician-patient relationship by adopting an authentic and empathetic communication style. Provide adequate information regarding disease, diagnoses, and treatments. Present patients with realistic possible effects of the intervention, balancing the presentation of desired treatment effects, adverse effects, and frame information about side effects. Provide patients with an introduction to the mechanisms of placebo and nocebo effects as a basis for promoting healing processes. Ask patients to summarize the treatment information they were provided with, to prevent negative biases and misunderstandings. Favour positive associations and minimize negative associations between the therapeutic intervention and contextual factors. Refer to sources that provide evidence-based information about the ongoing treatment, instead of unproven and/or anxiogenic comments. Use communication strategies to reduce the likelihood of nonadherence to the treatment regimen or discontinuation of the drug. Teach and train strategies to cope with adverse effects.	Standardize the language used to present the benefit-risk profile of the intervention under investigation. Standardize framing strategies used to present information about side effects. Standardize questions and use structured checklists to collect data on side effects. Standardize the duration and number of therapeutic visits across study sites.
Expectations	
Encourage patients to recount their previous positive or negative experiences with interventions. Regularly assess and address patients' treatment expectations. Optimize treatment expectations and adverse effects expectations, but avoid violations of expectations. Regularly assess and address possible factors that may influence patients' treatment expectations, especially anxiety. Provide "open-medication" (i.e., administer the pharmacological agent in full view of the patient) together with positive instructions about its potential benefits.	Ask patients at baseline how much improvement they would expect from the active treatment. All trials should assess patients' perceived assignment by asking participants which group they believe they belong to. Adverse events in placebo arms, namely nocebo effects, might depend on the adverse events of the active medication against which the placebo is compared; such comparisons could provide important information on the role of patients' expectations.
Conditioning	
Provide multisensory treatment cues (e.g., sight, smell, and taste stimulations) associated with the active medication to promote conditioning. Use placebo-controlled drug tapering, if applicable; it consists of starting treatment with repeated full doses to establish associative learning processes and replacing drugs with placebo at a later time. When pre-treatments are allowed or required, they should be designed to be highly effective and the patient should receive feedback on their positive effects.	Different placebos use different mechanisms, which in turn might lead to different outcomes; thus, the careful selection of placebos (pills, injections, delivery systems, etc) and outcome measures is crucial. Longer and larger trials can produce large placebo responses; thus, shorter and smaller trials are sometimes preferable to longer, larger, multicentre trials.
Social learning	
Promote social learning of the positive effects of drugs: patients starting a new treatment could talk to other patients who have received the same treatment successfully or observe their response through video clips.	Social interactions among trial participants should be avoided to prevent possible effects on baseline clinical and biological variables.
Hawthorne effect	
The effect of being under study should be considered and investigated in detail.	The effect of being under study should be considered in any clinical trial and investigated in detail.

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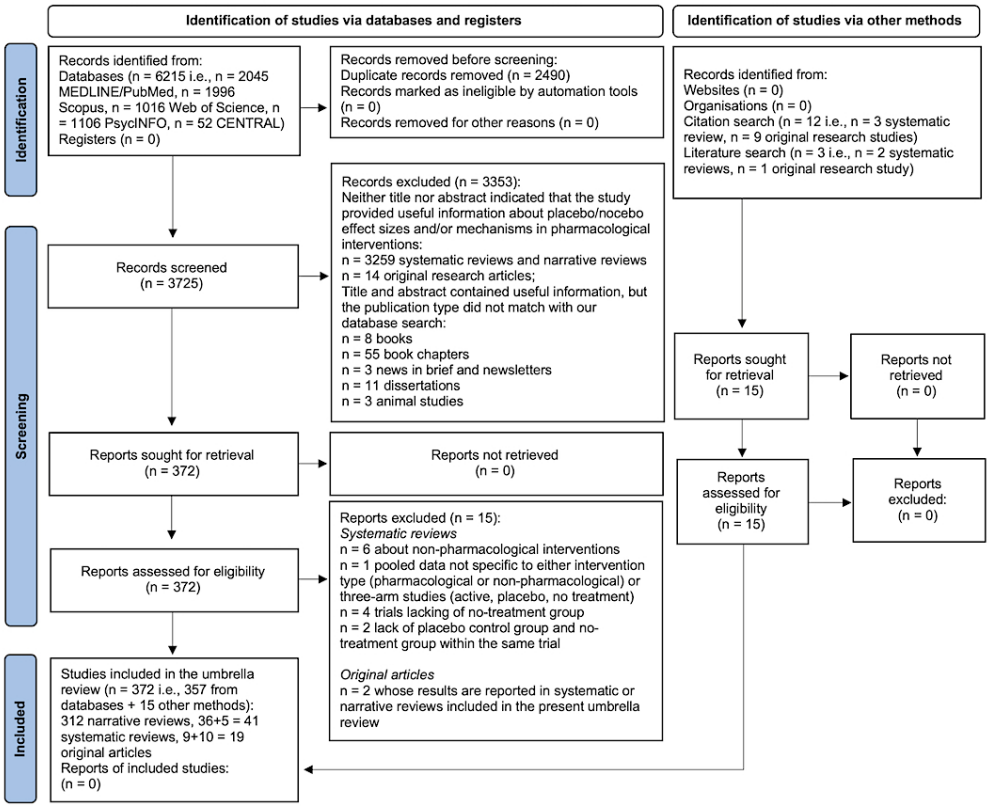

PRISMA flowchart. Trial flow of the selection process, showing both the number of events and reasons for the exclusion of most of the 6215 initially selected records.

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Supplementary appendix 1

A) Protocol registration: **PROSPERO 2023 CRD42023392281**
Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42023392281 and submitted as a supplementary file.

Review question
- Where (in which medical conditions) have robust placebo and nocebo effects been documented so far?
- When do they occur (any particular circumstances, such as experimental vs clinical setting)?
- How do they work (what do we know about the biological underpinnings)?

Searches
1. No time restrictions will be posed.
2. Language: English.
3. Publication stage: final.
4. Only peer-reviewed literature will be searched.
5. Databases will be used: PubMed, Scopus, Web of Science, PsycINFO, and Cochrane Central Register of Controlled Trials (CENTRAL). Search terms will be used accordingly based on different databases.
6. Relevant references cited in included reviews will also be hand-searched.
7. The search terms will have the following concepts: placebo, nocebo, placebo effect, placebo response, nocebo effect, nocebo response.

Types of study to be included
Systematic reviews, meta-analyses and reviews that:
- refer to randomized clinical trials (RCTs) with no-treatment control group, open label RCTs with no- treatment control group, experimental studies;
- are informative about biological mechanisms of placebo/nocebo effects and/or their related effect sizes.

Condition or domain being studied
Inclusion: Placebo/nocebo effects and placebo/nocebo-related effects, whereby the latter do not require the administration of inert treatments, in pharmacological treatments:
- clinical conditions, i.e. pain, disease of the nervous system, mental and behavioral disorders, immune and endocrine systems, cardiovascular and respiratory systems, gastrointestinal and genitourinary disorders, itch, oncology.
- beyond the healing context, i.e. physical and cognitive performance.

Exclusion: In order to circumscribe the area of investigation and reduce the degree of methodological variability among studies, we excluded the investigation of placebo/nocebo effects and placebo/nocebo- related effects in non-pharmacological treatments, such as psychotherapy, acupuncture, surgery, neuromodulation, physical therapies, hypnosis, mindfulness training, biofeedback, neurofeedback, music.

Participants/population
Studies on the human population are eligible.

Intervention(s), exposure(s)
Placebo and nocebo intervention.

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Comparator(s)/control
No-treatment control group or waiting list.

Context
Over the past 30 years there has been a surge of research on the placebo effect using a neuroscientific approach. The interesting aspects of this effort are related to the identification of several biological mechanisms of both the placebo and nocebo effects. Some important translational implications have emerged both in the setting of clinical trials and in routine medical practice. One of the principal contributions of neuroscience has been to draw the attention of the scientific and medical communities to the important role of psychobiological factors in therapeutic outcomes, be they drug related or not. Indeed, many biological mechanisms triggered by placebos and nocebos resemble those modulated by drugs, suggesting a possible interaction between psychological factors and drug action.

Main outcome(s)
Mapping placebo and nocebo effects across different medical conditions and therapeutic interventions, along with their underlying mechanisms.

Measures of effect
Effects size of placebo and nocebo effects calculated by Cohen's *d* or Hedges' *g*.

Additional outcome(s)
None

Data extraction (selection and coding)
Study selection: One author (EF) will screen the titles and abstracts of all search results (after removing duplicates). After removing ineligible papers, two authors (EF and FP) will independently review the full text of potentially eligible papers against the inclusion and exclusion criteria. Disagreements will be resolved by discussion among all the authors. The study will be developed according to the PRISMA guidelines (Moher D, Liberati A, Tetzlaff J. 2009).
Data extraction: On a spreadsheet previously set up to enter biological mechanisms and effect sizes, this information will be progressively entered for each medical condition and therapeutic intervention of interest.

Risk of bias (quality) assessment
Methodological quality of included systematic reviews and meta-analyses will be appraised using the Assessment of Multiple Systematic Reviews (AMSTAR) 2 tool, which has demonstrated satisfactory reliability and construct validity (Shea et al., 2017).

Strategy for data synthesis
Results from the eligible studies will be clustered and summarized. A table will describe the mechanisms and/or effect sizes obtained by each study. A narrative synthesis will be provided.

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B) Search strategy

PubMed
((“placebo effect” or “placebo effects” or “placebo response” or “placebo responses”) OR (“nocebo effect” or “nocebo effects” or “nocebo response” or “nocebo responses”))
text availability: full text
article type: meta-analysis, review, systematic review
Language: English

Scopus
Search within: article title, abstract, keywords
((“placebo effect” or “placebo effects” or “placebo response” or “placebo responses”) OR (“nocebo effect” or “nocebo effects” or “nocebo response” or “nocebo responses”))
Filters: Limit to
Document type: review
Publication stage: final
Language: English

Web Of Science
search within: abstract
((“placebo effect” or “placebo effects” or “placebo response” or “placebo responses”) OR (“nocebo effect” or “nocebo effects” or “nocebo response” or “nocebo responses”))
Filters: Refine for
document type: review article
Language: English

PsycINFO
search Select a field (optional)
((“placebo effect” or “placebo effects” or “placebo response” or “placebo responses”) OR (“nocebo effect” or “nocebo effects” or “nocebo response” or “nocebo responses”))
AND
Select a field (optional)
((review) OR (systematic review) OR (meta-analysis))
filter:
Language: English

Cochrane Central Register of Controlled Trials (CENTRAL)
advanced search: Title Abstract Keyword
((“placebo effect” or “placebo effects” or “placebo response” or “placebo responses”) OR (“nocebo effect” or “nocebo effects” or “nocebo response” or “nocebo responses”))
Search limits: Cochrane reviews
publication date: all
search word variations: ok

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Supplementary appendix 2

Assessment of Multiple Systematic Reviews (AMSTAR) 2 tool: critical appraisal of the included systematic reviews, with critical domains marked in yellow

Author (year)	Review type	1 - Components of PICO	2 - Protocol	3 – Selection of study design explained	4 – Comprehensive literature search	5 – Study selection	6 – Data extraction	7 – List of excluded studies	8 – Description included studies	9 – Risk of Bias assessment	10 – Funding sources	11 – appropriate statistical methods	12 – [illegible]	13 – Account for Risk of Bias in Discussion	14 – Explanation/ Discussion of Heterogeneity	15 – Publication bias assessment	16 – Sources of Conflict of interest	Overall high quality (yes/no)
Placebo effects																		
1. Tang et al. (2022)[19]	SR-MA	1	1	1	1	1	1	1	1	1	1	1	[illegible]	0	1	1	1	Yes
2. Charlesworth et al. (2017)[20]	SR-MA	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	Yes
3. Howick et al. (2013)[21]	SR-MA	1	1	1	1	1	1	1	1	1*	1	1	1	1	1	1	1	Yes
4. Hróbjartsson, Gøtzsche (2010)[22]	SR-MA	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	Yes
5. Meissner et al. (2007)[23]	SR-MA	1	1	1	1	1	1	1	1	1 **	1	1	0	0	1	1 **	1	Yes

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Author (year)	Inclusion criteria for study type	Q1 - Components of PICO	Q2 - Protocol	Q3 – Selection of study design explained	Q4 – Comprehensive literature search	Q5 – Study selection	Q6 – Data extraction	Q7 – List of excluded studies	Q8 – Description included studies	Q9 – Risk of Bias assessment	Q10 – Funding sources	Q11 – appropriate statistical methods	Q12 – Appropriate use of AI tools for text and data mining, AI training, and similar technologies.	Q13 – Account for risk of Bias in discussion	Q14 – Explanation/ Discussion of Heterogeneity	Q15 – Publication bias assessment	Q16 – Sources of Conflict of interest	Overall high quality (yes/no)
6. Hróbjartsson, Gøtzsche (2004)[24]	SR-MA	1	1	1	1	1	1	0	1	0.5 **	0	1	0.5	1	1	1	1	Yes
7. Hróbjartsson, Gøtzsche (2001)[25]	SR-MA	1	1	1	1	1	1	1	1	0.5 ***	1	1	0.5	1	1	1	1	Yes
Nocebo effects																		
8. Bagarić et al. (2022)[26]	SR	1	1	1	1	1	1	0	1	0	1	na	na	na	0	0	1	No
Predictors																		
9. Vambheim, Flaten (2017)[27]	SR	1	0.5	1	1	1	1	0.5	1	0	1	na	na	na	0	0	1	No
Pain																		
10. Skyt et al. (2020)[28]	SR	1	1	1	1	1	1	1	1	1	1	na	1	0	1	1	1	Yes
11. Daniali, Flaten (2019)[29]	SR	1	0.5	1	1	0.5	1	0.5	1	1	1	na	1	1	0.5	na	1	Yes
12. Zunhammer et al. (2018)[30]	SR-MA	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	Yes
13. Forsberg et al. (2017)[31]	SR-MA	1	0	1	1	1	1	0	1	0	1	1	na	na	1	1	1	No
14. Peerdeman et al (2016)[32]	SR-MA	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	Yes

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Author (year)	Inclusion criteria for study type	Q1 - Components of PICO	Q2 - Protocol	Q3 – Selection of study design explained	Q4 – Comprehensive literature search	Q5 – Study selection	Q6 – Data extraction	Q7 – List of excluded studies	Q8 – Description included studies	Q9 – Risk of Bias assessment	Q10 – Funding sources	Q11 – appropriate statistical methods	Q12 – Publication bias assessment	Q13 – Account for Risk of Bias in Discussion	Q14 – Explanation/ Discussion of Heterogeneity	Q15 – Publication bias assessment	Q16 – Sources of Conflict of interest	Overall high quality (yes/no)
15. Palermo et al. (2015)[33]	SR-MA	1	1	1	1	1	1	0	1	0.5	1	1	na	na	1	0	1	Yes
16. Atlas, Wager (2014)[34]	SR-MA	1	0	1	1	1	1	0	1	0.5	1	1	na	na	0	0	1	No
17. Petersen et al. (2014)[35]	SR-MA	1	1	1	1	1	1	1	1	0	1	1	na	na	1	0	1	Yes
18. Amanzio et al. (2013)[36]	SR-MA	1	1	1	1	1	1	1	1	0.5	1	1	na	na	1	0	1	Yes
19. Vase et al. (2009)[37]	SR-MA	1	1	1	1	1	1	1	1	0.5	1	1	1	1	1	1	1	Yes
20. Sauro, Greenberg (2005)[38]	SR-MA	1	0	1	0.5	0	1	0	1	0	1	1	na	na	1	0	0	No
21. Vase et al. (2002)[39]	SR-MA	1	1	1	1	1	1	0	1	0.5 ***	0	1	na	na	0	0	0	Yes
22. Ter Riet et al. (1998)[40]	SR	1	0	1	1	1	1	0	1	1	1	na	1	1	0	0	0	No
Disease of Nervous System: Parkinson's disease																		
23. Quattrone et al. (2018)[41]	SR	1	1	1	1	1	1	0	1	0.5	1	na	na	na	0	na	1	Yes
Disease of Nervous System: Migraine																		
24. Swerts et al. (2022)[42]§	SR-MA	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	Yes

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Author (year)	Inclusion criteria for study type	Q1 - Components of PICO	Q2 - Protocol	Q3 – Selection of study design explained	Q4 – Comprehensive literature search	Q5 – Study selection	Q6 – Data extraction	Q7 – List of excluded studies	Q8 – Description included studies	Q9 – Risk of Bias assessment	Q10 – Funding sources	Q11 – appropriate statistical methods	Q12 – Risk of Bias assessment or discussion	Q13 – Account for RoB in analysis or discussion	Q14 – Explanation/ Discussion of Heterogeneity	Q15 – Publication bias assessment	Q16 – Sources of Conflict of interest	Overall high quality (yes/no)
25. Amanzio et al. (2009)[43]§	SR-MA	1	0	1	1	1	1	1	1	1	1	1	1	0	1	1	Yes	
26. de Craen et al. (2000)[44]§	SR-MA	1	0	1	1	1	1	0	1	0	1	1	na	na	1	0	0	No
Disease of Nervous System: Sleep																		
27. Yeung et al. (2018)[45]	SR-MA	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	Yes
Disease of Nervous System: Intellectual disability																		
28. Jensen et al. (2017)[46]§	SR-MA	1	1	1	1	1	1	0	1	0	1	1	na	na	1	0	1	No
Mental and behavioral disorders																		
29. Fernández-López et al. (2022)[47]	SR-MA	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	Yes
Mental and behavioral disorders: Depression and anxiety																		
30. Huneke et al. (2022)[48]	SR	1	1	1	1	1	1	0	1	1	1	na	1	1	1	0	1	Yes
Mental and behavioral disorders: Dementia																		
31. Matthiesen et al. (2021)[49]§	SR-MA	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	Yes

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Author (year)	Inclusion criteria for study type	Q1 - Components of PICO	Q2 - Protocol	Q3 – Selection of study design explained	Q4 – Comprehensive literature search	Q5 – Study selection	Q6 – Data extraction	Q7 – List of excluded studies	Q8 – Description included studies	Q9 – Risk of Bias assessment	Q10 – Funding sources	Q11 – appropriate statistical methods	Q12 – Account for Risk of Bias in discussion	Q14 – Explanation/ Discussion of Heterogeneity	Q15 – Publication bias assessment	Q16 – Sources of Conflict of interest	Overall high quality (yes/no)
Mental and behavioral disorders: Addiction																	
32. Galindo et al. (2020)[50]	SR	1	1	1	1	1	0	1	0	1	na	na	na	0	0	1	No
33. McKay, Schare (1999)[51]	SR-MA	1	0	1	1	1	1	0	1	0	0	1	na	1	0	0	No
Cardiovascular system																	
34. Daniali, Flaten (2020)[52]	SR	1	1	1	1	1	1	0.5	1	1	1	na	1	1	1	1	Yes
Gastrointestinal disorders																	
35. Quinn, Colagiuri (2015)[53]	SR	1	1	1	1	1	1	0	1	0	1	na	na	1	1	1	Yes
Skin diseases																	
36. Meeuwis et al. (2020)[54]	SR	1	1	1	1	1	1	0	1	1	1	na	1	1	0	1	Yes
Flu and related vaccines																	
37. Amanzio et al. (2022)[55]	SR-MA	1	1	1	1	1	1	0	1	1	1	1	1	1	0	1	Yes

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Author (year)	Inclusion criteria for study type	Q1 - Components of PICO	Q2 - Protocol	Q3 – Selection of study design explained	Q4 – Comprehensive literature search	Q5 – Study selection	Q6 – Data extraction	Q7 – List of excluded studies	Q8 – Description included studies	Q9 – Risk of Bias assessment	Q10 – Funding sources	Q11 – appropriate statistical methods	Q12 – Account for Risk of Bias in discussion	Q13 – Account for heterogeneity	Q14 – Explanation/ Discussion of Heterogeneity	Q15 – Publication bias assessment	Q16 – Sources of Conflict of interest	Overall high quality (yes/no)
Physical performance																		
38. Horváth et al. (2021)[56]	SR-MA	1	1	1	1	0.5	0.5	0	1	1	1	1	1	0	0	1	Yes	
39. Marticorena et al. (2021)[57]	SR-MA	1	1	1	1	1	1	0	1	1	1	1	0	0	1	1	Yes	
40. Hurst et al. (2020)[58]	SR-MA	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	Yes	
41. Bérdi et al. (2011)[59]	SR-MA	1	0	1	1	1	1	1	1	0	0	1	na	na	1	0	0	No

Abbreviations:

1 = yes, 0.5 = partial yes, 0 = no.

na= not applicable due to qualitative nature of the systematic review or to study limitations, SR=systematic review, SR-MA=systematic review and meta-analysis.

* Information acquired from Hróbjartsson A, Gøtzsche PC. Placebo interventions for all clinical conditions. Cochrane database of systematic reviews 2010:CD003974.

** Information acquired from Hróbjartsson A, Gøtzsche PC. Placebo interventions for all clinical conditions. Cochrane database of systematic reviews 2004:CD003974.

*** Part of the information acquired from Hróbjartsson A, Gøtzsche PC. Placebo treatment versus no treatment. The Cochrane Database of Systematic Reviews 2002, Issue 4. Art. No.: CD003974.

§ Based on placebo controlled RCTs without a no-treatment group, but still informative regarding placebo and nocebo mechanisms.

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Supplementary appendix 3

Summary of captured systematic reviews

	Review type	Topic	Population	Inclusion criteria for study type	Specific domain(s) of interest
1. Tang et al. (2022)[19]	SR-MA	Placebo effects	Adult individuals, both healthy volunteers and clinical patients	Randomized design comparing having choice over placebo treatment with a placebo treatment without choice.	The impact of choice over placebo treatment on the placebo effect.
2. Charlesworth et al. (2017)[20]	SR-MA	Placebo effects	Participants with any diagnosed medical condition	Studies that included a comparison of an open-label placebo intervention with a "no treatment" condition.	Effects of placebos without deception.
3. Howick et al. (2013)[21]	SR-MA	Placebo effects	Across clinical conditions	Three-arm RCTs (no treatment, placebo, and active treatment).	Comparison of benefits due to placebos versus no treatments, and benefits due to active treatments versus placebos.
4. Hróbjartsson, Gøtzsche (2010)[22]	SR-MA	Placebo effects	Across clinical conditions	Three-arm RCTs (no treatment, placebo, and active treatment).	Benefit of placebos compared to no-treatments.
5. Meissner et al. (2007)[23]	SR-MA	Placebo effects	Across clinical conditions	We focused on the second dataset, consisting of three-arm RCTs with untreated groups (N = 26).	The impact of placebo treatment on peripheral disease processes.
6. Hróbjartsson, Gøtzsche (2004)[24]	SR-MA	Placebo effects	Across clinical conditions	Three-arm RCTs (no treatment, placebo, and active treatment).	Magnitude and characteristics of placebos compared to no-treatments.
7. Hróbjartsson, Gøtzsche (2001)[25]	SR-MA	Placebo effects	Across clinical conditions	Three-arm RCTs (no treatment, placebo, and active treatment).	Magnitude and characteristics of placebos compared to no-treatments.
8. Bagarić et al. (2022)[26]	SR	Nocebo effects	Predominantly young healthy adults, with one study on women suffering from breast cancer	Studies conducted in the laboratory setting, aimed at examining the mechanisms underlying the nocebo effect. We focused on those studies including pharmacological placebos (N = 7).	State of the art of contemporary laboratory research.
9. Vambheim, Flaten (2017)[27]	SR	Predictors of placebo and nocebo effects	Any condition	Studies conducted in the laboratory setting, with a natural history control group or condition.	Sex differences in the placebo and the nocebo effect.
10. Skyt et al. (2020)[28]	SR	Pain	Healthy volunteers, patients with acute or chronic pain	Placebo/nocebo mechanism studies with no-treatment group.	Neurotransmitter systems involved in placebo/nocebo effects in pain.

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11. Daniali, Flaten (2019)[29]	SR	Pain	Healthy participants, patients, or animals	Studies conducted in the laboratory setting, including no-treatment group. We focused on studies on human beings (N = 33).	Effects of experimenter/clinician characteristics and nonverbal behaviour on pain, placebo, and nocebo effects.
12. Zunhammer et al. (2018)[30]	SR-MA	Pain	Healthy participants	Studies with an experimental placebo intervention to induce placebo analgesia, plus a functional imaging measurement, plus at least one control condition (no placebo-intervention).	Placebo effects on the neurologic pain signature.
13. Forsberg et al. (2017)[31]	SR-MA	Pain	Healthy individuals and patients	Studies conducted in the laboratory setting, including a group or a condition where a placebo treatment was administrated with information that it was a painkiller, together with a natural history/no-treatment group. Studies adopting the open/hidden design were included as well.	Investigates whether the magnitude of placebo analgesia is different in patients compared with healthy individuals, and whether placebo analgesia is different in experimentally induced pain compared with clinical pain in patients.
14. Peerdeman et al (2016)[32]	SR-MA	Pain	Adult patients with a somatic condition and/or undergoing medical treatment	Studies that assessed the effect of expectation inductions on pain relief in a clinical sample. We focused on those studies that used verbal suggestions of pain relief referred to placebo (N = 11) or active treatment (N = 5), in both cases compared to no treatment or a control treatment that was believed to not induce expectations of pain relief.	The effect of brief expectation interventions referred to a placebo or an active treatment on patients' pain relief.
15. Palermo et al. (2015)[33]	SR-MA	Pain	Healthy participants	Brain imaging studies conducted in the laboratory setting. Each study used one of the typical experimental paradigms for pain induction. We focused on the only experimental studies where pain anticipation was induced as a result of verbal suggestions associated with a pharmacological	Neuroanatomy of pain anticipation.

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				placebo (N = 2; we excluded cue-based expectancy studies).	
16. Atlas, Wager (2014)[34]	SR-MA	Pain	Any human population	Neuroimaging studies conducted in the laboratory setting. We focused on studies of placebo-based treatment expectancy (N = 17), and excluded stimulus expectancies studies.	Brain mechanisms of placebo analgesia.
17. Petersen et al. (2014)[35]	SR-MA	Pain	Mainly healthy participants, and two studies with patients (thoracoscopy or IBS)	Studies conducted in the laboratory setting, including a nocebo-treated group/condition and a no-treatment. We focused on those studies in which nocebo treatment was induced by verbal suggestions alone, as most of the nocebo treatments were conceptualized as administration of inert agent (N = 6).	Magnitude of nocebo effects in pain.
18. Amanzio et al. (2013)[36]	SR-MA	Pain	Mainly healthy participants, and two studies with patients (IBS, FGID)	Brain imaging studies conducted in the laboratory setting and mainly using pharmacological placebo treatments.	Brain correlates of placebo analgesia.
19. Vase et al. (2009)[37]	SR-MA	Pain	Healthy participants and patients (IBS, AD)	Studies conducted in the laboratory setting, including a placebo-treated group/condition (mainly pharmacological placebos) and a no-treatment group/condition.	Factors contributing to large analgesic effects in placebo mechanism studies conducted between 2002 and 2007.
20. Sauro, Greenberg (2005)[38]	SR-MA	Pain	Healthy participants and post-surgical/clinical patients	Studies conducted in the laboratory setting, measuring both placebo analgesia and its reversal by naloxone administered via hidden injection or through a blinded procedure.	Investigate the ability of placebo administration to reduce self-report of pain, and examine the related mechanisms.
21. Vase et al. (2002)[39]	SR-MA	Pain	Patients affected by a variety of pain conditions	Studies had to include a natural history condition without treatment and were divided into those in which placebo was used as a control condition (23 studies) and those in which the aim was to investigate	Comparing the magnitude of placebo effects in studies of placebo analgesia mechanisms versus clinical analgesic trials.

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				the analgesia mechanisms of placebo (14 studies).	
22. Ter Riet et al. (1998)[40]	SR	Pain	Healthy volunteers, postsurgical patients (removal of 3rd molars and posterolateral thoracotomy)	Studies employing placebo administration for clinical or experimental pain in addition to the hidden infusions with an endorphin antagonist or an endorphin synergistic drug.	Assessment of an antagonistic effect of naloxone and a synergistic effect of proglumide on placebo-induced analgesia.
23. Quattrone et al. (2018)[41]	SR	PD	PD patients	Studies conducted in the laboratory setting, using different neuroimaging procedures and validated experimental protocols to evaluate the placebo effect.	Neurobiology of placebo effect in PD.
24. Swerts et al. (2022)[42]*	SR-MA	Migraine	Adults patients with chronic migraine and no associated comorbidities	Placebo-controlled RCTs.	Investigate the relationship between route of placebo administration and headache relief in chronic migraine preventive treatment.
25. Amanzio et al. (2009)[43]*	SR-MA	Migraine	Migraine patients with or without aura	Anti-migraine placebo-controlled RCTs.	AEs profiles of anti-migraine drugs: NSAIDs, triptans and anticonvulsants.
26. de Craen et al. (2000)[44]*	SR-MA	Migraine	Patients with acute migraine	Placebo-controlled RCTs with at least one group treated with sumatriptan and one group with placebo.	Investigate the relationship between route of placebo administration and headache relief in the acute treatment of migraine.
27. Yeung et al. (2017)[45]	SR-MA	Sleep	Adult with insomnia symptoms	Three-arm placebo-controlled RCTs and experimental studies whose sole purpose was to compare placebo treatment with no treatment. All participants were blind to the possibility of receiving a placebo. Even if not all three-arm RCTs were pharmacological, the "study type" factor was shown not to moderate the placebo effect size.	Placebo effect size for insomnia symptoms.
28. Jensen et al. (2017)[46]*	SR-MA	Intellectual disability	Fragile X, Down, Prader-Willi, or Williams syndrome patients	OLT and placebo-controlled RCTs including placebo group.	To determine the placebo component (different probabilities of receiving the active treatment) of treatment responses

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					in patients with intellectual disability.
29. Fernández-López et al. (2022)[47]	SR-MA	Mental and behavioural disorders	Mental Disorders classified by DSM-5	Three-arm placebo-controlled RCTs. We focused on placebo effect in depression (N = 9, i.e., the only investigated mental disorder which comprised mainly pharmacological interventions).	Placebo effects in depression.
30. Huneke et al. (2022)[48]	SR	Depression and anxiety	Adults with unipolar depression or anxiety disorders	We focused on studies presenting neuroimaging data associated with placebo mechanisms such as learning or expectancy (N = 5).	Functional neuroanatomy of the placebo effect in patients with anxiety or depressive disorders.
31. Matthiesen et al. (2021)[49]*	SR-MA	Dementia	AD patients	OLT and placebo-controlled RCTs including placebo group.	Role of expectations (different probabilities of receiving genuine treatment) in AD clinical trials.
32. Galindo et al. (2020)[50]	SR	Addiction	Alcohol, caffeine, or nicotine consumers	Studies conducted in the laboratory setting whose topic was placebo effect.	The influence of placebo effect on craving and cognitive performance.
33. McKay, Schare (1999)[51]	SR-MA	Addiction	Any human population	Studies conducted in the laboratory setting, where the BPD was adopted.	Expectancy effects and their moderators in the BPD literature.
34. Daniali, Flaten (2020)[52]	SR	Cardiovascular system	Healthy subjects and patients experiencing pain	Laboratory or clinical randomized studies including at least two comparison groups/conditions or a control group/condition (natural history).	The effects of placebo analgesia and nocebo hyperalgesia on cardiac activity.
35. Quinn, Colagiuri (2015)[53]	SR	Gastrointestinal disorders	Healthy and clinical populations (chemotherapy patients)	Instructional and conditioning interventions aimed at altering nausea via the placebo effect (most of them used nutritional or pharmacological placebos).	Determine if placebo interventions can affect nausea and which features of these interventions are effective.
36. Meeuwis et al. (2020)[54]	SR	Skin diseases	Patients with acute or chronic itching, and healthy volunteers	Original observational/experimental studies in which placebo or nocebo effects were experimentally induced. We focused on studies on human beings (N = 55).	Placebo and nocebo effects in dermatological conditions and itch.
37.	SR-MA	Flu and related vaccines	Safety population (adult, at least 1 dose	Placebo-controlled RCTs, phase-III, for	AEs in the placebo control groups

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Amanzio et al. (2022)[55]*			of vaccine, safety data available), mainly Caucasian	SARS-CoV-2 vaccines (BNT162b2, mRNA-1273, Ad26.COV2.S) approved by EMA or FDA. The placebo control group was treated with a saline solution.	associated with COVID-19 vaccines.
38. Horváth et al. (2021)[56]	SR-MA	Physical performance	Any human population (mainly studies on healthy individuals and some studies on Parkinson's patients)	Studies conducted in the laboratory setting. We focused on studies where the control was a no-intervention condition, i.e., no agent, information, or conditioning was delivered (N = 6). They were conducted on healthy individuals.	Nocebo effects induced by inert substances on motor performance.
39. Marticorena et al. (2021)[57]	SR-MA	Physical performance	Healthy human males and females of any age	Any randomized and blinded, crossover, or parallel-group design requiring a supplementation protocol and including both a placebo and a no treatment group.	Estimate the size of the placebo effects associated with caffeine and buffering supplements.
40. Hurst et al. (2020)[58]	SR-MA	Physical performance	Participants described as "apparently healthy" or "athletes"	Studies conducted in the laboratory setting, assessing the effect of placebo/nocebo ergogenic aids. We focused on nutritional and pharmacological ergogenic aids (N = 20). Each study included no-treatment control or a baseline in which participants' own performance acted as a no-treatment control.	Placebo and nocebo effect on sports performance.
41. Bérdi et al. (2011)[59]	SR-MA	Physical performance	Healthy subjects at all levels of fitness	Studies conducted in the laboratory setting, assessing the effect of placebo nutritional supplements in any sporting performance at all level of fitness. Each study included no-treatment group or baseline measurement.	Placebo effects in sport and exercise.

AD = Alzheimer's disease, AEs = Adverse events, BPD = balanced-placebo-design, EMA, European Medicine Agency, DSM-5 = The Diagnostic and Statistical Manual of Mental Disorders Fifth Edition, FDA, Food and Drug Administration, FGID = functional gastrointestinal disorder, IBS = irritable bowel syndrome, OLT = open label trial, PD = Parkinson's disease, RCTs = randomized controlled trials, NSAIDs = non-steroid anti-inflammatory drugs, SR = systematic review, SR-MA = systematic review and meta-analysis.

* Based on placebo-controlled RCTs without a no-treatment group, but still informative regarding placebo and nocebo mechanisms.

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Supplementary appendix 4

A) List of narrative reviews included in the umbrella review

Identified via databases search (n = 312)

1 Abhishek A, Doherty M. Mechanisms of the placebo response in pain in osteoarthritis. *Osteoarthritis Cartilage* 2013; **21**: 1229–35.

2 Abhishek A, Doherty M. Understanding placebo effects in rheumatology. *Joint Bone Spine* 2015; **82**: 222-4.

3 Ader R. Conditioned immune responses and pharmacotherapy. *Arthritis Care Res* 1989; **2**: A58–64.

4 Amanzio M, Palermo S. Pain Anticipation and Nocebo-Related Responses: A Descriptive Mini-Review of Functional Neuroimaging Studies in Normal Subjects and Precious Hints on Pain Processing in the Context of Neurodegenerative Disorders. *Front Pharmacol* 2019; **10**: 969.

5 Anchisi D, Zanon M. A Bayesian Perspective on Sensory and Cognitive Integration in Pain Perception and Placebo Analgesia. *PLoS ONE* 2015; **10**: e0117270.

6 Anton PA, Shanahan F. Neuroimmunomodulation in inflammatory bowel disease. How far from 'bench' to 'bedside'? *Ann N Y Acad Sci* 1998; **840**: 723–34.

7 Archer T. The role of conditioning in the use of placebo. *Nordic Journal of Psychiatry* 1995; **49**: 43–53.

8 Arnold MH, Finniss DG, Kerridge I. Medicine's inconvenient truth: the placebo and nocebo effect. *Intern Med J* 2014; **44**: 398–405.

9 Arnstein P. The placebo effect. *Seminars in Integrative Medicine* 2003; **1**: 125–35.

10 Arrow K, Burgoyne LL, Cyna AM. Implications of nocebo in anaesthesia care. *Anaesthesia* 2022; **77 Suppl 1**: 11–20.

11 Ashar YK, Chang LJ, Wager TD. Brain Mechanisms of the Placebo Effect: An Affective Appraisal Account. *Annu Rev Clin Psychol* 2017; **13**: 73–98.

12 Atlas LY. A social affective neuroscience lens on placebo analgesia. *Trends Cogn Sci* 2021; **25**: 992–1005.

13 Atlas LY, Wager TD. How expectations shape pain. *Neurosci Lett* 2012; **520**: 140–8.

14 Autret A, Valade D, Debiais S. Placebo and other psychological interactions in headache treatment. *J Headache Pain* 2012; **13**: 191–8.

15 Bąbel P. Classical Conditioning as a Distinct Mechanism of Placebo Effects. *Front Psychiatry* 2019; **10**: 449.

16 Bąbel P. Operant conditioning as a new mechanism of placebo effects. *Eur J Pain* 2020; **24**: 902–8.

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17 Bajcar EA, Bąbel P. How Does Observational Learning Produce Placebo Effects? A Model Integrating Research Findings. *Front Psychol* 2018; **9**: 2041.

18 Barnes K, Faasse K, Geers AL, *et al.* Can Positive Framing Reduce Nocebo Side Effects? Current Evidence and Recommendation for Future Research. *Front Pharmacol* 2019; **10**: 167.

19 Barsky AJ, Saintfort R, Rogers MP, Borus JF. Nonspecific medication side effects and the nocebo phenomenon. *JAMA* 2002; **287**: 622–7.

20 Bartels DJP, van Laarhoven AIM, van de Kerkhof PCM, Evers AWM. Placebo and nocebo effects on itch: effects, mechanisms, and predictors. *Eur J Pain* 2016; **20**: 8–13.

21 Bärtsch P. The Impact of Nocebo and Placebo Effects on Reported Incidence of Acute Mountain Sickness. *High Alt Med Biol* 2022; **23**: 8–17.

22 Beauregard M. Mind does really matter: evidence from neuroimaging studies of emotional self-regulation, psychotherapy, and placebo effect. *Prog Neurobiol* 2007; **81**: 218–36.

23 Beauregard M. Effect of mind on brain activity: evidence from neuroimaging studies of psychotherapy and placebo effect. *Nord J Psychiatry* 2009; **63**: 5–16.

24 Beedie C, Benedetti F, Barbiani D, *et al.* Consensus statement on placebo effects in sports and exercise: The need for conceptual clarity, methodological rigour, and the elucidation of neurobiological mechanisms. *European Journal of Sport Science* 2018; **18**: 1383–9.

25 Beedie C, Benedetti F, Barbiani D, Camerone E, Lindheimer J, Roelands B. Incorporating methods and findings from neuroscience to better understand placebo and nocebo effects in sport. *Eur J Sport Sci* 2020; **20**: 313–25.

26 Beedie CJ. All in the mind? Pain, placebo effect, and ergogenic effect of caffeine in sports performance. *Open Access J Sports Med* 2010; **1**: 87–94.

27 Beedie CJ, Foad AJ. The placebo effect in sports performance: a brief review. *Sports Med* 2009; **39**: 313–29.

28 Belcher AM, Ferré S, Martinez PE, Colloca L. Role of placebo effects in pain and neuropsychiatric disorders. *Prog Neuropsychopharmacol Biol Psychiatry* 2018; **87**: 298–306.

29 Benedetti F. Placebo analgesia. *Neurol Sci* 2006; **27 Suppl 2**: S100-102.

30 Benedetti F, Amanzio M. The neurobiology of placebo analgesia: from endogenous opioids to cholecystokinin. *Prog Neurobiol* 1997; **52**: 109–25.

31 Benedetti F, Lanotte M, Lopiano L, Colloca L. When words are painful: unraveling the mechanisms of the nocebo effect. *Neuroscience* 2007; **147**: 260–71.

32 Benedetti F. How the Doctor's Words Affect the Patient's Brain. *Eval Health Prof* 2002; **25**: 369–86.

33 Benedetti F. Mechanisms of placebo and placebo-related effects across diseases and treatments. *Annu Rev Pharmacol Toxicol* 2008; **48**: 33–60.

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34 Benedetti F. Placebo-induced improvements: how therapeutic rituals affect the patient's brain. *J Acupunct Meridian Stud* 2012; **5**: 97–103.

35 Benedetti F. Placebo and the new physiology of the doctor-patient relationship. *Physiol Rev* 2013; **93**: 1207–46.

36 Benedetti F. Placebo effects: from the neurobiological paradigm to translational implications. *Neuron* 2014; **84**: 623–37.

37 Benedetti F, Amanzio M. The placebo response: how words and rituals change the patient's brain. *Patient Educ Couns* 2011; **84**: 413–9.

38 Benedetti F, Amanzio M. Mechanisms of the placebo response. *Pulm Pharmacol Ther* 2013; **26**: 520–3.

39 Benedetti F, Carlino E, Piedimonte A. Increasing uncertainty in CNS clinical trials: the role of placebo, nocebo, and Hawthorne effects. *Lancet Neurol* 2016; **15**: 736–47.

40 Benedetti F, Carlino E, Pollo A. How placebos change the patient's brain. *Neuropsychopharmacology* 2011; **36**: 339–54.

41 Benedetti F, Frisaldi E, Barbiani D, Camerone E, Shaibani A. Nocebo and the contribution of psychosocial factors to the generation of pain. *J Neural Transm (Vienna)* 2020; **127**: 687–96.

42 Benedetti F, Frisaldi E, Shaibani A. Thirty Years of Neuroscientific Investigation of Placebo and Nocebo: The Interesting, the Good, and the Bad. *Annu Rev Pharmacol Toxicol* 2022; **62**: 323–40.

43 Benedetti F, Mayberg HS, Wager TD, Stohler CS, Zubieta J-K. Neurobiological mechanisms of the placebo effect. *J Neurosci* 2005; **25**: 10390–402.

44 Benedetti F, Piedimonte A. The neurobiological underpinnings of placebo and nocebo effects. *Semin Arthritis Rheum* 2019; **49**: S18–21.

45 Benedetti F, Rainero I, Pollo A. New insights into placebo analgesia. *Curr Opin Anaesthesiol* 2003; **16**: 515–9.

46 Bennett GJ. Does the word 'placebo' evoke a placebo response? *Pain* 2018; **159**: 1928–31.

47 Bensing JM, Verheul W. The silent healer: the role of communication in placebo effects. *Patient Educ Couns* 2010; **80**: 293–9.

48 Benson H, Friedman R. Harnessing the power of the placebo effect and renaming it 'remembered wellness'. *Annu Rev Med* 1996; **47**: 193–9.

49 Benson H, McCallie DP. Angina pectoris and the placebo effect. *N Engl J Med* 1979; **300**: 1424–9.

50 Bienenfeld L, Frishman W, Glasser SP. The placebo effect in cardiovascular disease. *Am Heart J* 1996; **132**: 1207–21.

51 Bingel U, Colloca L, Vase L. Mechanisms and clinical implications of the placebo effect: is there a potential for the elderly? A mini-review. *Gerontology* 2011; **57**: 354–63.

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Erasmushogeschool .

52 Birch S. A review and analysis of placebo treatments, placebo effects, and placebo controls in trials of medical procedures when sham is not inert. *J Altern Complement Med* 2006; **12**: 303–10.

53 Bittar C, Nascimento OJM. Placebo and nocebo effects in the neurological practice. *Arq Neuropsiquiatr* 2015; **73**: 58–63.

54 Blasini M, Corsi N, Klinger R, Colloca L. Nocebo and pain: an overview of the psychoneurobiological mechanisms. *PR9* 2017; **2**: e585.

55 Blasini M, Peiris N, Wright T, Colloca L. The Role of Patient-Practitioner Relationships in Placebo and Nocebo Phenomena. *Int Rev Neurobiol* 2018; **139**: 211–31.

56 Brand A, Evangelatos N, Özdemir V. Placebogenomics: A New Concept and Tool for Personalized Medicine and Public Health. *OMICS: A Journal of Integrative Biology* 2021; **25**: 76–8.

57 Bräscher A-K, Witthöft M, Becker S. The Underestimated Significance of Conditioning in Placebo Hypoalgesia and Nocebo Hyperalgesia. *Pain Res Manag* 2018; **2018**: 6841985.

58 Brietzke C, Cesario JCS, Hettinga FJ, Pires FO. The reward for placebos: mechanisms underpinning placebo-induced effects on motor performance. *Eur J Appl Physiol* 2022; **122**: 2321–9.

59 Brody H. The placebo response. Recent research and implications for family medicine. *J Fam Pract* 2000; **49**: 649–54.

60 Brody H, Brody D. Three perspectives on the placebo response: Expectancy, conditioning, and meaning. *Advances in Mind-Body Medicine* 2000; **16**: 216–32.

61 Brown C, Watson A, Morton D, Power A, El-Deredy W, Jones A. Role of central neurophysiological systems in placebo analgesia and their relationships with cognitive processes mediating placebo responding. *Future Neurology* 2011; **6**: 389–98.

62 Brown V, Peciña M. Neuroimaging Studies of Antidepressant Placebo Effects: Challenges and Opportunities. *Front Psychiatry* 2019; **10**: 669.

63 Brown WA. Expectation, the placebo effect and the response to treatment. *Rhode Island medical journal (2013)* 2015; **98**: 19–21.

64 Brown WA. How expectation works: psychologic and physiologic pathways. *Rhode Island medical journal (2013)* 2015; **98**: 22–4.

65 Brown WA. Harnessing the Placebo Effect. *Hospital Practice* 1998; **33**: 107–16.

66 Büchel C, Geuter S, Sprenger C, Eippert F. Placebo Analgesia: A Predictive Coding Perspective. *Neuron* 2014; **81**: 1223–39.

67 Buckalew LW, Ross S. Relationship of Perceptual Characteristics to Efficacy of Placebos. *Psychol Rep* 1981; **49**: 955–61.

68 Bystad M, Bystad C, Wynn R. How can placebo effects best be applied in clinical practice? A narrative review. *Psychol Res Behav Manag* 2015; **8**: 41–5.

For peer review only

Erasmushogeschool . Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.

69 Cai L, He L. Placebo effects and the molecular biological components involved. *Gen Psychiatr* 2019; **32**: e100089.

70 Carlino E, Benedetti F. Different contexts, different pains, different experiences. *Neuroscience* 2016; **338**: 19–26.

71 Carlino E, Frisaldi E, Benedetti F. Pain and the context. *Nat Rev Rheumatol* 2014; **10**: 348–55.

72 Carlino E, Pollo A, Benedetti F. Placebo analgesia and beyond: a melting pot of concepts and ideas for neuroscience. *Curr Opin Anaesthesiol* 2011; **24**: 540–4.

73 Carlino E, Pollo A, Benedetti F. The placebo in practice: how to use it in clinical routine. *Curr Opin Support Palliat Care* 2012; **6**: 220–5.

74 Cavanna AE, Strigaro G, Monaco F. Brain mechanisms underlying the placebo effect in neurological disorders. *Functional Neurology* 2007; **22**: 89–94.

75 Chae Y, Lee Y-S, Enck P. How Placebo Needles Differ From Placebo Pills? *Front Psychiatry* 2018; **9**: 243.

76 Colagiuri B, Schenk LA, Kessler MD, Dorsey SG, Colloca L. The placebo effect: From concepts to genes. *Neuroscience* 2015; **307**: 171–90.

77 Colloca L. Placebo- and nocebo-induced pain modulation: from bedside to bench and back to bedside. *Douleur analg* 2014; **27**: 203–9.

78 Colloca L. The Placebo Effect in Pain Therapies. *Annu Rev Pharmacol Toxicol* 2019; **59**: 191–211.

79 Colloca L, Barsky AJ. Placebo and Nocebo Effects. *N Engl J Med* 2020; **382**: 554–61.

80 Colloca L, Benedetti F. Placebos and painkillers: is mind as real as matter? *Nat Rev Neurosci* 2005; **6**: 545–52.

81 Colloca L, Benedetti F. Nocebo hyperalgesia: how anxiety is turned into pain. *Curr Opin Anaesthesiol* 2007; **20**: 435–9.

82 Colloca L, Benedetti F, Porro CA. Experimental designs and brain mapping approaches for studying the placebo analgesic effect. *Eur J Appl Physiol* 2008; **102**: 371–80.

83 Colloca L, Grillon C. Understanding placebo and nocebo responses for pain management. *Curr Pain Headache Rep* 2014; **18**: 419.

84 Colloca L, Howick J. Placebos Without Deception: Outcomes, Mechanisms, and Ethics. *Int Rev Neurobiol* 2018; **138**: 219–40.

85 Colloca L, Jonas WB, Killen J, Miller FG, Shurtleff D. Reevaluating the Placebo Effect in Medical Practice. *Zeitschrift für Psychologie* 2014; **222**: 124–7.

86 Colloca L, Klinger R, Flor H, Bingel U. Placebo analgesia: psychological and neurobiological mechanisms. *Pain* 2013; **154**: 511–4.

87 Colloca L, Lopiano L, Benedetti F, Lanotte M. The placebo response in conditions other than pain. *Seminars in Pain Medicine* 2005; **3**: 43–7.

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Erasmushogeschool .

88 Colloca L, Lopiano L, Lanotte M, Benedetti F. Overt versus covert treatment for pain, anxiety, and Parkinson's disease. *Lancet Neurol* 2004; **3**: 679–84.

89 Colloca L, Miller FG. Role of expectations in health. *Curr Opin Psychiatry* 2011; **24**: 149–55.

90 Colloca L, Miller FG. Harnessing the placebo effect: the need for translational research. *Philos Trans R Soc Lond B Biol Sci* 2011; **366**: 1922–30.

91 Colloca L, Miller FG. How placebo responses are formed: a learning perspective. *Philos Trans R Soc Lond B Biol Sci* 2011; **366**: 1859–69.

92 Colloca L, Miller FG. The nocebo effect and its relevance for clinical practice. *Psychosom Med* 2011; **73**: 598–603.

93 Costanzo C, Verghese A. The Physical Examination as Ritual: Social Sciences and Embodiment in the Context of the Physical Examination. *Med Clin North Am* 2018; **102**: 425–31.

94 Cuyul-Vásquez I, Barría JA, Perez NF, Fuentes J. The influence of verbal suggestions in the management of musculoskeletal pain: a narrative review. *Physical Therapy Reviews* 2019; **24**: 175–81.

95 Czerniak E, Oberlander TF, Weimer K, Kossowsky J, Enck P. 'Placebo by Proxy' and 'Nocebo by Proxy' in Children: A Review of Parents' Role in Treatment Outcomes. *Front Psychiatry* 2020; **11**: 169.

96 Damien J, Colloca L, Bellei-Rodriguez C-É, Marchand S. Pain Modulation: From Conditioned Pain Modulation to Placebo and Nocebo Effects in Experimental and Clinical Pain. *Int Rev Neurobiol* 2018; **139**: 255–96.

97 Dar R, Barrett SP. The effects of beliefs regarding drug assignment in experimental and field studies of nicotine delivery devices: a review. *J Psychopharmacol* 2014; **28**: 1071–9.

98 Darnall BD, Colloca L. Optimizing Placebo and Minimizing Nocebo to Reduce Pain, Catastrophizing, and Opioid Use: A Review of the Science and an Evidence-Informed Clinical Toolkit. *Int Rev Neurobiol* 2018; **139**: 129–57.

99 DaSilva AF, Zubieta J-K, DosSantos MF. Positron emission tomography imaging of endogenous mu-opioid mechanisms during pain and migraine. *Pain Rep* 2019; **4**: e769.

100 Davis AJ, Hettinga F, Beedie C. You don't need to administer a placebo to elicit a placebo effect: Social factors trigger neurobiological pathways to enhance sports performance. *Eur J Sport Sci* 2020; **20**: 302–12.

101 De Felice M, Ossipov MH. Cortical and subcortical modulation of pain. *Pain Manag* 2016; **6**: 111–20.

102 de la Fuente-Fernández R, Schulzer M, Stoessl AJ. The placebo effect in neurological disorders. *Lancet Neurol* 2002; **1**: 85–91.

103 de la Fuente-Fernández R, Schulzer M, Stoessl AJ. Placebo mechanisms and reward circuitry: clues from Parkinson's disease. *Biol Psychiatry* 2004; **56**: 67–71.

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Erasmushogeschool .

104 de la Fuente-Fernández R, Stoessl AJ. The placebo effect in Parkinson's disease. *Trends Neurosci* 2002; **25**: 302–6.

105 de la Fuente-Fernández R, Stoessl AJ. Parkinson's disease: imaging update. *Curr Opin Neurol* 2002; **15**: 477–82.

106 De La Fuentefernández R, Stoessl AJ. The Biochemical Bases for Reward: Implications for the Placebo Effect. *Eval Health Prof* 2002; **25**: 387–98.

107 Di Blasi Z, Kleijnen J. Context effects. Powerful therapies or methodological bias? *Eval Health Prof* 2003; **26**: 166–79.

108 Diederich NJ, Goetz CG. The placebo treatments in neurosciences: New insights from clinical and neuroimaging studies. *Neurology* 2008; **71**: 677–84.

109 Dieppe P, Goldingay S, Greville-Harris M. The power and value of placebo and nocebo in painful osteoarthritis. *Osteoarthritis Cartilage* 2016; **24**: 1850–7.

110 Dobrilla G, Scarpignato C. Placebo and placebo effect: their impact on the evaluation of drug response in patients. *Dig Dis* 1994; **12**: 368–77.

111 Dodd S, Dean OM, Vian J, Berk M. A Review of the Theoretical and Biological Understanding of the Nocebo and Placebo Phenomena. *Clin Ther* 2017; **39**: 469–76.

112 Dumitriu A, Popescu BO. Placebo effects in neurological diseases. *J Med Life* 2010; **3**: 114–21.

113 Dutile S, Kaptchuk TJ, Wechsler ME. The placebo effect in asthma. *Curr Allergy Asthma Rep* 2014; **14**: 456.

114 Eccles R. The powerful placebo in cough studies? *Pulm Pharmacol Ther* 2002; **15**: 303–8.

115 Eccles R. The power of the placebo. *Curr Allergy Asthma Rep* 2007; **7**: 100–4.

116 Eccles R. The Powerful Placebo Effect in Cough: Relevance to Treatment and Clinical Trials. *Lung* 2020; **198**: 13–21.

117 Eccles R. Mechanisms of the placebo effect of sweet cough syrups. *Respir Physiol Neurobiol* 2006; **152**: 340–8.

118 Ellingsen D-M, Leknes S, Løseth G, Wessberg J, Olausson H. The Neurobiology Shaping Affective Touch: Expectation, Motivation, and Meaning in the Multisensory Context. *Front Psychol* 2015; **6**: 1986.

119 Elsenbruch S, Enck P. Placebo effects and their determinants in gastrointestinal disorders. *Nat Rev Gastroenterol Hepatol* 2015; **12**: 472–85.

120 Enck P, Benedetti F, Schedlowski M. New insights into the placebo and nocebo responses. *Neuron* 2008; **59**: 195–206.

121 Enck P, Bingel U, Schedlowski M, Rief W. The placebo response in medicine: minimize, maximize or personalize? *Nat Rev Drug Discov* 2013; **12**: 191–204.

122 Enck P, Horing B, Weimer K, Klosterhalfen S. Placebo responses and placebo effects in functional bowel disorders. *Eur J Gastroenterol Hepatol* 2012; **24**: 1–8.

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Erasmushogeschool .

123 Enck P, Klosterhalfen S. Does Sex/Gender Play a Role in Placebo and Nocebo Effects? Conflicting Evidence From Clinical Trials and Experimental Studies. *Front Neurosci* 2019; **13**: 160.

124 Enck P, Klosterhalfen S. Placebo Responses and Placebo Effects in Functional Gastrointestinal Disorders. *Front Psychiatry* 2020; **11**: 797.

125 Esch T, Stefano GB. The neurobiology of pleasure, reward processes, addiction and their health implications. *Neuroendocrinology Letters* 2004; **25**: 235–51.

126 Faasse K. Nocebo effects in health psychology. *Australian Psychologist* 2019; **54**: 453–65.

127 Faria V, Fredrikson M, Furmark T. Imaging the placebo response: a neurofunctional review. *Eur Neuropsychopharmacol* 2008; **18**: 473–85.

128 Faria V, Linnman C, Lebel A, Borsook D. Harnessing the Placebo Effect in Pediatric Migraine Clinic. *The Journal of Pediatrics* 2014; **165**: 659–65.

129 Fields HL, Levine JD. Placebo analgesia —a role for endorphins? *Trends in Neurosciences* 1984; **7**: 271–3.

130 Finniss DG, Benedetti F. The Neural Matrix of Pain Processing and Placebo Analgesia: Implications for Clinical Practice. *Headache Currents* 2005; **2**: 132–8.

131 Finniss DG, Benedetti F. Mechanisms of the placebo response and their impact on clinical trials and clinical practice. *Pain* 2005; **114**: 3–6.

132 Finniss DG, Kaptchuk TJ, Miller F, Benedetti F. Biological, clinical, and ethical advances of placebo effects. *Lancet* 2010; **375**: 686–95.

133 Fontaine KR, Williams MS, Hoenemeyer TW, Kaptchuk TJ, Dutton GR. Placebo effects in obesity research: Placebo and Obesity. *Obesity* 2016; **24**: 769–71.

134 Frisaldi E, Carlino E, Lanotte M, Lopiano L, Benedetti F. Characterization of the thalamic-subthalamic circuit involved in the placebo response through single-neuron recording in Parkinson patients. *Cortex* 2014; **60**: 3–9.

135 Frisaldi E, Piedimonte A, Benedetti F. Placebo and nocebo effects: a complex interplay between psychological factors and neurochemical networks. *Am J Clin Hypn* 2015; **57**: 267–84.

136 Frisaldi E, Shaibani A, Benedetti F. Understanding the mechanisms of placebo and nocebo effects. *Swiss Med Wkly* 2020; **150**: w20340.

137 Frisaldi E, Shaibani A, Trucco M, Milano E, Benedetti F. What is the role of placebo in neurotherapeutics? *Expert Rev Neurother* 2022; **22**: 15–25.

138 Fu J, Wu S, Liu C, Camilleri JA, Eickhoff SB, Yu R. Distinct neural networks subserve placebo analgesia and nocebo hyperalgesia. *Neuroimage* 2021; **231**: 117833.

139 Geers AL, Briñol P, Petty RE. An analysis of the basic processes of formation and change of placebo expectations. *Review of General Psychology* 2019; **23**: 211–29.

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Erasmushogeschool .

140 Geers AL, Faasse K, Guevarra DA, Clemens KS, Helfer SG, Colagiuri B. Affect and emotions in placebo and nocebo effects: What do we know so far? *Soc Personal Psychol Compass* 2021; **15**. DOI:10.1111/spc3.12575.

141 Geers AL, Miller FG. Understanding and translating the knowledge about placebo effects: the contribution of psychology. *Curr Opin Psychiatry* 2014; **27**: 326–31.

142 Geers AL, Weiland PE, Kosbab K, Landry SJ, Helfer SG. Goal Activation, Expectations, and the Placebo Effect. *Journal of Personality and Social Psychology* 2005; **89**: 143–59.

143 Geers A, Rose J. Treatment Choice and Placebo Expectation Effects: Choice and Placebo Effects. *Social and Personality Psychology Compass* 2011; **5**: 734–50.

144 Gertsch J. The Intricate Influence of the Placebo Effect on Medical Cannabis and Cannabinoids. *Med Cannabis Cannabinoids* 2018; **1**: 60–4.

145 Geuter S, Koban L, Wager TD. The Cognitive Neuroscience of Placebo Effects: Concepts, Predictions, and Physiology. *Annu Rev Neurosci* 2017; **40**: 167–88.

146 Girach A, Aamir A, Zis P. The neurobiology under the placebo effect. *Drugs Today (Barc)* 2019; **55**: 469–76.

147 Gowdey CW. A guide to the pharmacology of placebos. *Can Med Assoc J* 1983; **128**: 921–5.

148 Greville-Harris M, Dieppe P. Bad is more powerful than good: the nocebo response in medical consultations. *Am J Med* 2015; **128**: 126–9.

149 Hadamitzky M, Lückemann L, Pacheco-López G, Schedlowski M. Pavlovian Conditioning of Immunological and Neuroendocrine Functions. *Physiol Rev* 2020; **100**: 357–405.

150 Hadamitzky M, Schedlowski M. Harnessing associative learning paradigms to optimize drug treatment. *Trends in Pharmacological Sciences* 2022; **43**: 464–72.

151 Hagen B, Gunn T. The Placebo Effect and Learning: Implications for Counsellors. *Canadian Journal of Counselling* 2006; **40**: 242–54.

152 Hall KT, Loscalzo J, Kaptchuk T. Pharmacogenomics and the Placebo Response. *ACS Chem Neurosci* 2018; **9**: 633–5.

153 Hall KT, Loscalzo J, Kaptchuk TJ. Genetics and the placebo effect: the placebome. *Trends Mol Med* 2015; **21**: 285–94.

154 Haour F. Mechanisms of the placebo effect and of conditioning. *Neuroimmunomodulation* 2005; **12**: 195–200.

155 Harvey SC, Beedie CJ. Studying placebo effects in model organisms will help us understand them in humans. *Biol Lett* 2017; **13**: 20170585.

156 Häuser W, Hansen E, Enck P. Nocebo phenomena in medicine: their relevance in everyday clinical practice. *Dtsch Arztebl Int* 2012; **109**: 459–65.

157 Hedges D, Burchfield C. The placebo effect and its implications. *Journal of Mind and Behavior* 2005; **26**: 161–79.

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Erasmushogeschool .

158 Heeg MJ, Deutsch KF, Deutsch E. The placebo effect. *Eur J Nucl Med* 1997; **24**: 1433–40.

159 Hoffman GA, Harrington A, Fields HL. Pain and the placebo: what we have learned. *Perspect Biol Med* 2005; **48**: 248–65.

160 Holmes RD, Tiwari AK, Kennedy JL. Mechanisms of the placebo effect in pain and psychiatric disorders. *Pharmacogenomics J* 2016; **16**: 491–500.

161 Horowitz S. New Perspectives on the Placebo Effect: Implications for Research and Clinical Practice. *Alternative and Complementary Therapies* 2012; **18**: 130–5.

162 Howland RH. Understanding the placebo effect. Part 2: underlying psychological & neurobiological processes. *J Psychosoc Nurs Ment Health Serv* 2008; **46**: 15–8.

163 Hróbjartsson A, Gøtzsche PC. Placebo treatment versus no treatment. *Cochrane Database Syst Rev* 2003; : CD003974.

164 Hyland ME. Motivation and placebos: do different mechanisms occur in different contexts? *Philos Trans R Soc Lond B Biol Sci* 2011; **366**: 1828–37.

165 Ingvar M. Learning mechanisms in pain chronification--teachings from placebo research. *Pain* 2015; **156 Suppl 1**: S18–23.

166 Irving G. The Placebo Response: Relationship to Outcomes in Trials of Postherpetic Neuralgia. *Clinical Drug Investigation* 2010; **30**: 739–48.

167 Isawa M, Kajiyama M, Tominaga Y, Nakada H, Aomori T, Mochizuki M. Review of clinical studies on the nocebo effect. *Pharmazie* 2020; **75**: 548–53.

168 Itskovich E, Bowling DL, Garner JP, Parker KJ. Oxytocin and the social facilitation of placebo effects. *Mol Psychiatry* 2022; **27**: 2640–9.

169 Jensen KB. What Is Minimally Required to Elicit Placebo Effects? *Int Rev Neurobiol* 2018; **138**: 181–99.

170 Jensen K, Kelley JM. The therapeutic relationship in psychological and physical treatments, and their placebo controls. *Psychology of Consciousness: Theory, Research, and Practice* 2016; **3**: 132–45.

171 Jubb J, Bensing JM. The sweetest pill to swallow: how patient neurobiology can be harnessed to maximise placebo effects. *Neurosci Biobehav Rev* 2013; **37**: 2709–20.

172 Kaas BM, Humbyrd CJ, Pantelyat A. Functional Movement Disorders and Placebo: A Brief Review of the Placebo Effect in Movement Disorders and Ethical Considerations for Placebo Therapy. *Mov Disord Clin Pract* 2018; **5**: 471–8.

173 Kaptchuk TJ, Hemond CC, Miller FG. Placebos in chronic pain: evidence, theory, ethics, and use in clinical practice. *BMJ* 2020; **370**: m1668.

174 Kaptchuk TJ, Kelley JM, Deykin A, *et al.* Do 'placebo responders' exist? *Contemp Clin Trials* 2008; **29**: 587–95.

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Erasmushogeschool .

175 Keane TM, Lisman SA, Kreutzer J. Alcoholic beverages and their placebos: An empirical evaluation of expectancies. *Addictive Behaviors* 1980; **5**: 313–28.

176 Khullar V, Rahnama'i MS, Veit-Rubin N, Cardozo L, Wein AJ. Can we harness the placebo effect to improve care in lower urinary tract dysfunction? ICI-RS 2019. *Neurourol Urodyn* 2020; **39 Suppl 3**: S80–7.

177 Kihlstrom JF. Placebo: Feeling better, getting better, and the problems of mind and body. *McGill Journal of Medicine* 2008; **11**: 212–4.

178 Kirsch I. Hypnosis and placebos: Response expectancy as a mediator of suggestion effects. *Anales de Psicología* 1999; **15**: 99–110.

179 Kirsch I. Yes, there is a placebo effect, but is there a powerful antidepressant drug effect? *Prevention & Treatment* 2002; **5**. DOI:10.1037/1522-3736.5.1.522i.

180 Klinger R, Blasini M, Schmitz J, Colloca L. Nocebo effects in clinical studies: hints for pain therapy. *PR9* 2017; **2**: e586.

181 Klosterhalfen S, Enck P. The placebo response in gastroenterology and beyond. *Gastroenterologia Polska* 2009; **16**: 7–11.

182 Klosterhalfen S, Enck P. Psychobiology of the placebo response. *Auton Neurosci* 2006; **125**: 94–9.

183 Klosterhalfen S, Enck P. Neurophysiology and psychobiology of the placebo response. *Curr Opin Psychiatry* 2008; **21**: 189–95.

184 Koban L, Jepma M, Geuter S, Wager TD. What's in a word? How instructions, suggestions, and social information change pain and emotion. *Neuroscience & Biobehavioral Reviews* 2017; **81**: 29–42.

185 Koehler PJ, Boes CJ. A history of non-drug treatment in headache, particularly migraine. *Brain* 2010; **133**: 2489–500.

186 Kong J, Kaptchuk TJ, Polich G, Kirsch I, Gollub RL. Placebo analgesia: findings from brain imaging studies and emerging hypotheses. *Rev Neurosci* 2007; **18**: 173–90.

187 Kotzalidis GD, Giugni E, Zangaro S, *et al.* Neuroimaging of the placebo effect Part 2. *Psichiatria e Psicoterapia* 2006; **25**: 287–308.

188 Kradin RL. The Placebo Response: Its Putative Role as a Functional Salutogenic Mechanism of the Central Nervous System. *Perspectives in Biology and Medicine* 2004; **47**: 328–38.

189 Kravvariti E, Kotsani M, Mitsikostas DD, Sfikakis PP. Nocebo phenomena may be enhanced in aging: Implications for clinical practice. *Maturitas* 2021; **143**: 10–6.

190 Kravvariti E, Kitas GD, Mitsikostas DD, Sfikakis PP. Nocebos in rheumatology: emerging concepts and their implications for clinical practice. *Nat Rev Rheumatol* 2018; **14**: 727–40.

191 Krsiak M. Is placebo effective? If yes, what this could mean? *Activitas Nervosa Superior Rediviva* 2009; **51**: 5–8.

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Erasmushogeschool .

192 Langenecker SA, Crane NA, Jenkins LM, Phan KL, Klumpp H. Pathways to Neuroprediction: Opportunities and Challenges to Prediction of Treatment Response in Depression. *Curr Behav Neurosci Rep* 2018; **5**: 48–60.

193 Laverdure-Dupont D, Rainville P, Montplaisir J, Lavigne G. Relief Expectation and Sleep. *Reviews in the Neurosciences* 2010; **21**. DOI:10.1515/REVNEURO.2010.21.5.381.

194 Lidstone SCC, Stoessl AJ. Understanding the placebo effect: contributions from neuroimaging. *Mol Imaging Biol* 2007; **9**: 176–85.

195 Lidstone SC, De La Fuente-Fernandez R, Stoessl AJ. The placebo response as a reward mechanism. *Seminars in Pain Medicine* 2005; **3**: 37–42.

196 Linde K, Fässler M, Meissner K. Placebo interventions, placebo effects and clinical practice. *Philos Trans R Soc Lond B Biol Sci* 2011; **366**: 1905–12.

197 Lindheimer JB, Szabo A, Raglin JS, Beedie C. Advancing the understanding of placebo effects in psychological outcomes of exercise: Lessons learned and future directions. *Eur J Sport Sci* 2020; **20**: 326–37.

198 Liu T. Route of placebo administration: Robust placebo effects in laboratory and clinical settings. *Neurosci Biobehav Rev* 2017; **83**: 451–7.

199 Liu T. Placebo Effects: A New Theory. *Clinical Psychological Science* 2022; **10**: 27–40.

200 Locher C, Gaab J, Blease C, Inderbinen M, Kost L, Koechlin H. Placebos Are Part of the Solution, Not the Problem. An Exemplification of the Case of Antidepressants in Pediatric Chronic Pain Conditions. *Front Psychiatry* 2020; **10**: 998.

201 Lovick TA. Pro-nociceptive action of cholecystokinin in the periaqueductal grey: A role in neuropathic and anxiety-induced hyperalgesic states. *Neuroscience & Biobehavioral Reviews* 2008; **32**: 852–62.

202 Lucassen P, Olesen F. Context as a drug: some consequences of placebo research for primary care. *Scand J Prim Health Care* 2016; **34**: 428–33.

203 Lundh L-G. Placebo, belief, and health. A cognitive–emotion model. *Scand J Psychol* 1987; **28**: 128–43.

204 Manaï M, van Middendorp H, Veldhuijzen DS, Huizinga TWJ, Evers AWM. How to prevent, minimize, or extinguish nocebo effects in pain: a narrative review on mechanisms, predictors, and interventions. *PR9* 2019; **4**: e699.

205 Manchikanti L, Giordano J, Fellows B, Hirsch JA. Placebo and nocebo in interventional pain management: a friend or a foe--or simply foes? *Pain Physician* 2011; **14**: E157-175.

206 Margo CE. The placebo effect. *Surv Ophthalmol* 1999; **44**: 31–44.

207 Matthiesen ST, Lunde SJ, Wohlert Kjær S, Carlino E, Vase L. Placebo analgesia effects across central nervous system diseases: what do we know and where do we need to go? *PR9* 2019; **4**: e717.

208 McQuay HJ, Moore RA. Placebo. *Postgraduate Medical Journal* 2005; **81**: 155–60.

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Erasmushogeschool .

209 Meissner K. The placebo effect and the autonomic nervous system: evidence for an intimate relationship. *Philos Trans R Soc Lond B Biol Sci* 2011; **366**: 1808–17.

210 Meissner K, Bingel U, Colloca L, Wager TD, Watson A, Flaten MA. The placebo effect: advances from different methodological approaches. *J Neurosci* 2011; **31**: 16117–24.

211 Mestre TA, Shamy M, Benedetti F, Lang AE. Harnessing the power of placebos in movement disorders: Insights from Parkinson's disease in clinical research and practice. *Mov Disord* 2018; **33**: 1195–203.

212 Miller FG, Colloca L, Kaptchuk TJ. The placebo effect: illness and interpersonal healing. *Perspect Biol Med* 2009; **52**: 518–39.

213 Miller FG, Rosenstein DL. The nature and power of the placebo effect. *J Clin Epidemiol* 2006; **59**: 331–5.

214 Mitsikostas DD. Nocebo in headache. *Curr Opin Neurol* 2016; **29**: 331–6.

215 Moerman DE, Harrington A. Making space for the placebo effect in pain medicine. *Seminars in Pain Medicine* 2005; **3**: 2–6.

216 Morral A, Urrutia G, Bonfill X. Placebo effect and therapeutic context: A challenge in clinical research. *Med Clin (Barc)* 2017; **149**: 26–31.

217 Murray D, Stoessl AJ. Mechanisms and therapeutic implications of the placebo effect in neurological and psychiatric conditions. *Pharmacol Ther* 2013; **140**: 306–18.

218 Neumann M, Edelhäuser F, Kreps GL, *et al.* Can patient-provider interaction increase the effectiveness of medical treatment or even substitute it?--an exploration on why and how to study the specific effect of the provider. *Patient Educ Couns* 2010; **80**: 307–14.

219 Noon JM. Placebo to credebo: the missing link in the healing process. *Pain reviews* 1999; **6**: 133–42.

220 Oken BS. Placebo effects: clinical aspects and neurobiology. *Brain* 2008; **131**: 2812–23.

221 Okusogu C, Colloca L. Placebo hypoalgesia: above and beyond expectancy and conditioning. *Current Opinion in Behavioral Sciences* 2019; **26**: 75–81.

222 Olshansky B. Placebo and nocebo in cardiovascular health: implications for healthcare, research, and the doctor-patient relationship. *J Am Coll Cardiol* 2007; **49**: 415–21.

223 Ongaro G, Kaptchuk TJ. Symptom perception, placebo effects, and the Bayesian brain. *Pain* 2019; **160**: 1–4.

224 Oronowicz-Jaśkowiak W, Bąbel P. Twenty years after 'Listening to Prozac but hearing placebo'. Do we hear placebo even louder? *Health Psychology Report* 2019; **7**: 1–8.

225 Ortega Á, Salazar J, Galban N, *et al.* Psycho-Neuro-Endocrine-Immunological Basis of the Placebo Effect: Potential Applications beyond Pain Therapy. *Int J Mol Sci* 2022; **23**: 4196.

226 Ossipov MH. The perception and endogenous modulation of pain. *Scientifica (Cairo)* 2012; **2012**: 561761.

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227 Pacheco-López G, Engler H, Niemi M-B, Schedlowski M. Expectations and associations that heal: Immunomodulatory placebo effects and its neurobiology. *Brain Behav Immun* 2006; **20**: 430–46.

228 Packer M. The placebo effect in heart failure. *Am Heart J* 1990; **120**: 1579–82.

229 Pardo-Cabello AJ, Manzano-Gamero V, Puche-Cañas E. Placebo: a brief updated review. *Naunyn Schmiedebergs Arch Pharmacol* 2022; **395**: 1343–56.

230 Peciña M, Zubieta J-K. Molecular mechanisms of placebo responses in humans. *Mol Psychiatry* 2015; **20**: 416–23.

231 Pecina M, Zubieta J-K. Expectancy Modulation of Opioid Neurotransmission. *Int Rev Neurobiol* 2018; **138**: 17–37.

232 Peerdeman KJ, van Laarhoven AIM, Peters ML, Evers AWM. An Integrative Review of the Influence of Expectancies on Pain. *Front Psychol* 2016; **7**: 1270.

233 Perfitt JS, Plunkett N, Jones S. Placebo effect in the management of chronic pain. *BJA Educ* 2020; **20**: 382–7.

234 Perkins K, Sayette M, Conklin C, Caggiula A. Placebo effects of tobacco smoking and other nicotine intake. *Nicotine Tob Res* 2003; **5**: 695–709.

235 Perlis ML, McCall WV, Jungquist CR, Pigeon WR, Matteson SE. Placebo effects in primary insomnia. *Sleep Med Rev* 2005; **9**: 381–9.

236 Petrie KJ, Rief W. Psychobiological Mechanisms of Placebo and Nocebo Effects: Pathways to Improve Treatments and Reduce Side Effects. *Annu Rev Psychol* 2019; **70**: 599–625.

237 Petrovic P. Opioid and placebo analgesia share the same network. *Seminars in Pain Medicine* 2005; **3**: 31–6.

238 Polich G, Iaccarino MA, Kaptchuk TJ, Morales-Quezada L, Zafonte R. Nocebo Effects in Concussion: Is All That Is Told Beneficial? *Am J Phys Med Rehabil* 2020; **99**: 71–80.

239 Pollo A, Benedetti F. The placebo response: neurobiological and clinical issues of neurological relevance. *Prog Brain Res* 2009; **175**: 283–94.

240 Pollo A, Carlino E, Benedetti F. Placebo mechanisms across different conditions: from the clinical setting to physical performance. *Philos Trans R Soc Lond B Biol Sci* 2011; **366**: 1790–8.

241 Porto R. The Placebo effect: Its importance in treatment. *Sexologies* 2011; **20**: 15–9.

242 Požgain I, Požgain Z, Degmečić D. Placebo and nocebo effect: a mini-review. *Psychiatr Danub* 2014; **26**: 100–7.

243 Price DD, Fillingim RB, Robinson ME. Placebo analgesia: friend or foe? *Curr Rheumatol Rep* 2006; **8**: 418–24.

244 Price DD, Finniss DG, Benedetti F. A comprehensive review of the placebo effect: recent advances and current thought. *Annu Rev Psychol* 2008; **59**: 565–90.

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Erasmushogeschool .

245 Price DD, Zhou Q, Moshiree B, Robinson ME, Verne GN. Peripheral and central contributions to hyperalgesia in irritable bowel syndrome. *J Pain* 2006; **7**: 529–35.

246 Qiu Y-H, Wu X-Y, Xu H, Sackett D. Neuroimaging study of placebo analgesia in humans. *Neurosci Bull* 2009; **25**: 277–82.

247 Raglin J, Szabo A, Lindheimer JB, Beedie C. Understanding placebo and nocebo effects in the context of sport: A psychological perspective. *Eur J Sport Sci* 2020; **20**: 293–301.

248 Rainville P, Duncan GH. Functional brain imaging of placebo analgesia: methodological challenges and recommendations. *Pain* 2006; **121**: 177–80.

249 Richardson PH. Placebo effects in pain management. *Pain Reviews* 1994; **1**: 15–32.

250 Rief W, Barsky AJ, Bingel U, *et al.* Rethinking psychopharmacotherapy: The role of treatment context and brain plasticity in antidepressant and antipsychotic interventions. *Neurosci Biobehav Rev* 2016; **60**: 51–64.

251 Rief W, Petrie KJ. Can Psychological Expectation Models Be Adapted for Placebo Research? *Front Psychol* 2016; **7**: 1876.

252 Roberts AH, Kewman DG, Mercier L, Hovell M. The power of nonspecific effects in healing: Implications for psychosocial and biological treatments. *Clinical Psychology Review* 1993; **13**: 375–91.

253 Ross M, Olson JM. An expectancy-attribution model of the effects of placebos. *Psychological Review* 1981; **88**: 408–37.

254 Ross S, Buckalew LW. The placebo as an agent in behavioral manipulation: A review of problems, issues and affected measures. *Clinical Psychology Review* 1983; **3**: 457–71.

255 Rossettini G, Carlino E, Testa M. Clinical relevance of contextual factors as triggers of placebo and nocebo effects in musculoskeletal pain. *BMC Musculoskelet Disord* 2018; **19**: 27.

256 Rutherford B, Wager T, Roose S. Expectancy and the Treatment of Depression: A Review of Experimental Methodology and Effects on Patient Outcome. *CPSR* 2010; **6**: 1–10.

257 Sagy I, Abres J, Winnick A, Jotkowitz A. Placebos in the era of open-label trials: An update for clinicians. *Eur J Clin Invest* 2019; **49**: e13038.

258 Salamone JD. A critique of recent studies on placebo effects of antidepressants: importance of research on active placebos. *Psychopharmacology (Berl)* 2000; **152**: 1–6.

259 Sandler A. Placebo effects in developmental disabilities: Implications for research and practice. *Ment Retard Dev Disabil Res Rev* 2005; **11**: 164–70.

260 Schafer SM, Geuter S, Wager TD. Mechanisms of placebo analgesia: A dual-process model informed by insights from cross-species comparisons. *Prog Neurobiol* 2018; **160**: 101–22.

261 Schedlowski M, Enck P, Rief W, Bingel U. Neuro-Bio-Behavioral Mechanisms of Placebo and Nocebo Responses: Implications for Clinical Trials and Clinical Practice. *Pharmacol Rev* 2015; **67**: 697–730.

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies. Erasmushogeschool .

262 Schedlowski M, Pacheco-López G. The learned immune response: Pavlov and beyond. *Brain, Behavior, and Immunity* 2010; **24**: 176–85.

263 Schwarz KA, Pfister R, Büchel C. Rethinking Explicit Expectations: Connecting Placebos, Social Cognition, and Contextual Perception. *Trends Cogn Sci* 2016; **20**: 469–80.

264 Shabir A, Hooton A, Tallis J, F. Higgins M. The Influence of Caffeine Expectancies on Sport, Exercise, and Cognitive Performance. *Nutrients* 2018; **10**: 1528.

265 Shafir R, Olson E, Colloca L. The neglect of sex: A call to action for including sex as a biological variable in placebo and nocebo research. *Contemp Clin Trials* 2022; **116**: 106734.

266 Shaibani A, Frisaldi E, Benedetti F. Placebo response in pain, fatigue, and performance: Possible implications for neuromuscular disorders. *Muscle Nerve* 2017; **56**: 358–67.

267 Shapiro AK. FACTORS CONTRIBUTING TO THE PLACEBO EFFECT. THEIR IMPLICATIONS FOR PSYCHOTHERAPY. *Am J Psychother* 1964; **18**: SUPPL 1:73-88.

268 Shapiro AK. A contribution to a history of the placebo effect. *Syst Res* 2007; **5**: 109–35.

269 Sheldon R, Opie-Moran M. The Placebo Effect in Cardiology: Understanding and Using It. *Can J Cardiol* 2017; **33**: 1535–42.

270 Sher L. The Placebo Effect on Mood and Behavior: Possible Role of Opioid and Dopamine Modulation of the Hypothalamic-Pituitary-Adrenal System. *Complement Med Res* 2003; **10**: 61–8.

271 Sher L. The Role of Endogenous Opioids in the Placebo Effect in Post-Traumatic Stress Disorder. *Complement Med Res* 2004; **11**: 354–9.

272 Simmons K, Ortiz R, Kossowsky J, *et al.* Pain and placebo in pediatrics: a comprehensive review of laboratory and clinical findings. *Pain* 2014; **155**: 2229–35.

273 Sliwinski J, Elkins GR. Enhancing placebo effects: insights from social psychology. *Am J Clin Hypn* 2013; **55**: 236–48.

274 Smits RM, Veldhuijzen DS, Wulffraat NM, Evers AWM. The role of placebo effects in immune-related conditions: mechanisms and clinical considerations. *Expert Rev Clin Immunol* 2018; **14**: 761–70.

275 Sölle A, Bartholomäus T, Worm M, Klinger R. How to Psychologically Minimize Scratching Impulses: Benefits of Placebo Effects on Itching Using Classical Conditioning and Expectancy. *Zeitschrift für Psychologie* 2014; **222**: 140–7.

276 Sondermann W, Reinboldt-Jockenhöfer F, Dissemond J, Pfaar O, Bingel U, Schedlowski M. Effects of Patients' Expectation in Dermatology: Evidence from Experimental and Clinical Placebo Studies and Implications for Dermatologic Practice and Research. *Dermatology* 2021; **237**: 857–71.

277 Sonthalia S, Sahaya K, Arora R, *et al.* Nocebo effect in Dermatology. *Indian J Dermatol Venereol Leprol* 2015; **81**: 242–50.

278 Spiegel H. Nocebo: the power of suggestibility. *Prev Med* 1997; **26**: 616–21.

For peer review only

Protected by copyright, including for uses related to text and data mining, AI training, and similar technologies.
Erasmushogeschool .

279 Stewart-Williams S, Podd J. The placebo effect: dissolving the expectancy versus conditioning debate. *Psychol Bull* 2004; **130**: 324–40.

280 Symon A, Williams B, Adelasoye QA, Cheyne H. Nocebo and the potential harm of 'high risk' labelling: a scoping review. *J Adv Nurs* 2015; **71**: 1518–29.

281 Szabo A. Acute psychological benefits of exercise: reconsideration of the placebo effect. *J Ment Health* 2013; **22**: 449–55.

282 Tavel ME. The placebo effect: the good, the bad, and the ugly. *Am J Med* 2014; **127**: 484–8.

283 Testa M, Fillmore MT, Norris J, *et al.* Understanding Alcohol Expectancy Effects: Revisiting the Placebo Condition. *Alcoholism Clin Exp Res* 2006; **30**: 339–48.

284 Theodosis-Nobelos P, Filotheidou A, Triantis C. The placebo phenomenon and the underlying mechanisms. *Hormones (Athens)* 2021; **20**: 61–71.

285 Thomaidou MA, Peerdeman KJ, Koppeschaar MI, Evers AWM, Veldhuijzen DS. How Negative Experience Influences the Brain: A Comprehensive Review of the Neurobiological Underpinnings of Nocebo Hyperalgesia. *Front Neurosci* 2021; **15**: 652552.

286 Tracey I. Imaging pain. *Br J Anaesth* 2008; **101**: 32–9.

287 Tracey I. The Neural Matrix of Pain Processing and Placebo Analgesia: Evidence from Functional Imaging. *Headache Currents* 2005; **2**: 123–6.

288 Tracey I. Getting the pain you expect: mechanisms of placebo, nocebo and reappraisal effects in humans. *Nat Med* 2010; **16**: 1277–83.

289 Trojian TH, Beedie CJ. Placebo Effect and Athletes: *Current Sports Medicine Reports* 2008; **7**: 214–7.

290 Vase L, Baad-Hansen L, Pigg M. How May Placebo Mechanisms Influence Orofacial Neuropathic Pain? *J Dent Res* 2019; **98**: 861–9.

291 Vase L. Can insights from placebo and nocebo mechanisms studies improve the randomized controlled trial? *Scand J Pain* 2020; **20**: 451–67.

292 Vase L, Nørskov KN, Petersen GL, Price DD. Patients' direct experiences as central elements of placebo analgesia. *Philos Trans R Soc Lond B Biol Sci* 2011; **366**: 1913–21.

293 Vase L, Skyt I, Hall KT. Placebo, nocebo, and neuropathic pain. *Pain* 2016; **157 Suppl 1**: S98–105.

294 Vase L, Skyt I, Laue Petersen G, Price DD. Placebo and Nocebo Effects in Chronic Pain Patients: How Expectations and Emotional Feelings Contribute to the Experience of Pain. *Zeitschrift für Psychologie* 2014; **222**: 135–9.

295 Vase L, Wartolowska K. Pain, placebo, and test of treatment efficacy: a narrative review. *Br J Anaesth* 2019; **123**: e254–62.

For peer review only

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296 Vinckier F, Betka S, Nion N, Serresse L, Similowski T. Harnessing the power of anticipation to manage respiratory-related brain suffering and ensuing dyspnoea: insights from the neurobiology of the respiratory nocebo effect. *Eur Respir J* 2021; **58**: 2101876.

297 Vits S, Cesko E, Enck P, Hillen U, Schadendorf D, Schedlowski M. Behavioural conditioning as the mediator of placebo responses in the immune system. *Philos Trans R Soc Lond B Biol Sci* 2011; **366**: 1799–807.

298 Wager TD. The neural bases of placebo effects in anticipation and pain. *Seminars in Pain Medicine* 2005; **3**: 22–30.

299 Wager TD, Atlas LY. The neuroscience of placebo effects: connecting context, learning and health. *Nat Rev Neurosci* 2015; **16**: 403–18.

300 Wager TD, Nitschke JB. Placebo effects in the brain: linking mental and physiological processes. *Brain Behav Immun* 2005; **19**: 281–2.

301 Walach H, Jonas WB. Placebo research: the evidence base for harnessing self-healing capacities. *J Altern Complement Med* 2004; **10 Suppl 1**: S103-112.

302 Waschbusch DA, Pelham WE, Waxmonsky J, Johnston C. Are there placebo effects in the medication treatment of children with attention-deficit hyperactivity disorder? *J Dev Behav Pediatr* 2009; **30**: 158–68.

303 Watanabe T, Sieg M, Lunde SJ, *et al.* What is the nocebo effect and does it apply to dentistry?-A narrative review. *J Oral Rehabil* 2022; **49**: 586–91.

304 Watson A, Power A, Brown C, El-Deredy W, Jones A. Placebo analgesia: cognitive influences on therapeutic outcome. *Arthritis Res Ther* 2012; **14**: 206.

305 Weimer K, Gulewitsch MD, Schlarb AA, Schwille-Kiuntke J, Klosterhalfen S, Enck P. Placebo effects in children: a review. *Pediatr Res* 2013; **74**: 96–102.

306 Wernicke JF, Ossanna MJ. The placebo response in pain and depression: in search of a common pathway. *Front Biosci (Schol Ed)* 2010; **2**: 106–11.

307 Williams KA, Harden N. Managing the placebo effect: enhancing the signal-to-noise ratio. *Curr Pain Headache Rep* 2011; **15**: 35–8.

308 Wojtukiewicz MZ, Polityńska B, Skalij P, Tokajuk P, Wojtukiewicz AM, Honn KV. It is not just the drugs that matter: the nocebo effect. *Cancer Metastasis Rev* 2019; **38**: 315–26.

309 Wolf S. The pharmacology of placebos. *Pharmacol Rev* 1959; **11**: 689–704.

310 Wolters F, Peerdeman KJ, Evers AWM. Placebo and Nocebo Effects Across Symptoms: From Pain to Fatigue, Dyspnea, Nausea, and Itch. *Front Psychiatry* 2019; **10**: 470.

311 Zhang W. The powerful placebo effect in osteoarthritis. *Clin Exp Rheumatol* 2019; **37 Suppl 120**: 118–23.

312 Zubieta J-K, Stohler CS. Neurobiological mechanisms of placebo responses. *Ann N Y Acad Sci* 2009; **1156**: 198–210.

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B) List of original research articles included in the umbrella review

Identified via databases search (n = 9)

1 Bailey RC, Baillie AJ. The relationship between placebo alcohol and affect: motives for drinking. *Drug Alcohol Rev* 2013; **32**: 162–9.

2 Clifasefi SL, Garry M, Harper DN, Sharman SJ, Sutherland R. Psychotropic placebos create resistance to the misinformation effect. *Psychon Bull Rev* 2007; **14**: 112–7.

3 Fiorio M, Recchia S, Corrà F, Simonetto S, Garcia-Larrea L, Tinazzi M. Enhancing non-noxious perception: behavioural and neurophysiological correlates of a placebo-like manipulation. *Neuroscience* 2012; **217**: 96–104.

4 Haas JW, Rief W, Glombiewski JA, Winkler A, Doering BK. Expectation-induced placebo effect on acute sadness in women with major depression: An experimental investigation. *J Affect Disord* 2020; **274**: 920–8.

5 Malani A, Houser D. Expectations mediate objective physiological placebo effects. *Adv Health Econ Health Serv Res* 2008; **20**: 311–27.

6 Rutherford BR, Wall MM, Brown PJ, *et al.* Patient Expectancy as a Mediator of Placebo Effects in Antidepressant Clinical Trials. *AJP* 2017; **174**: 135–42.

7 Tippens KM, Purnell JQ, Gregory WL, *et al.* Expectancy, Self-Efficacy, and Placebo Effect of a Sham Supplement for Weight Loss in Obese Adults. *J Evid Based Complementary Altern Med* 2014; **19**: 181–8.

8 Wai-lanYeung V, Geers A, Kam SM. Merely Possessing a Placebo Analgesic Reduced Pain Intensity: Preliminary Findings from a Randomized Design. *Curr Psychol* 2019; **38**: 194–203.

9 Wrobel N, Fadai T, Sprenger C, Hebebrand J, Wiech K, Bingel U. Are Children the Better Placebo Analgesia Responders? An Experimental Approach. *The Journal of Pain* 2015; **16**: 1005–11.

Identified via citation search (n = 9)

1 Dar R, Stronguin F, Etter J-F. Assigned versus perceived placebo effects in nicotine replacement therapy for smoking reduction in Swiss smokers. *J Consult Clin Psychol* 2005; **73**: 350–3.

2 McCarney R, Warner J, Iliffe S, van Haselen R, Griffin M, Fisher P. The Hawthorne Effect: a randomised, controlled trial. *BMC Med Res Methodol* 2007; **7**: 30.

3 Olliges E, Schneider S, Schmidt G, *et al.* Placebo and Nocebo Effects in Patients With Takotsubo Cardiomyopathy and Heart-Healthy Controls. *Front Psychiatry* 2019; **10**: 549.

4 Pagnini F, Cavalera C, Volpato E, Banfi P. Illness expectations predict the development of influenza-like symptoms over the winter season. *Complement Ther Med* 2020; **50**: 102396.

5 Park C, Pagnini F, Langer E. Glucose metabolism responds to perceived sugar intake more than actual sugar intake. *Sci Rep* 2020; **10**: 15633.

6 Park C, Pagnini F, Reece A, Phillips D, Langer E. Blood sugar level follows perceived time rather than actual time in people with type 2 diabetes. *Proc Natl Acad Sci U S A* 2016; **113**: 8168–70.

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7 Sandler AD, Glesne CE, Bodfish JW. Conditioned placebo dose reduction: a new treatment in attention-deficit hyperactivity disorder? *J Dev Behav Pediatr* 2010; **31**: 369–75.

8 Sölle A, Worm M, Benedetti F, Sabine Bartholomäus T, Schwender-Groen L, Klinger R. Targeted Use of Placebo Effects Decreases Experimental Itch in Atopic Dermatitis Patients: A Randomized Controlled Trial. *Clin Pharmacol Ther* 2021; **110**: 486–97.

9 Van Ree JM, Schagen Van Leeuwen JH, Koppeschaar HP, Te Velde ER. Unexpected placebo response in premenstrual dysphoric disorder: implication of endogenous opioids. *Psychopharmacology (Berl)* 2005; **182**: 318–9.

Identified via literature search (n = 1)

1 Benedetti F, Shaibani A, Arduino C, Thoen W. Open-label nondeceptive placebo analgesia is blocked by the opioid antagonist naloxone. *Pain* 2022; **Publish Ahead of Print**. DOI:10.1097/j.pain.0000000000002791.

C) List of systematic reviews included in the umbrella review but not identified through the database search

Identified via citation search (n = 3)

1 de Craen AJ, Tijssen JG, de Gans J, Kleijnen J. Placebo effect in the acute treatment of migraine: subcutaneous placebos are better than oral placebos. *J Neurol* 2000; **247**: 183–8.

2 Hróbjartsson A, Gøtzsche PC. Placebo interventions for all clinical conditions. *Cochrane Database of Systematic Reviews* 2010; published online Jan 20. DOI:10.1002/14651858.CD003974.pub3.

3 Vase L, Petersen GL, Riley JL, Price DD. Factors contributing to large analgesic effects in placebo mechanism studies conducted between 2002 and 2007. *Pain* 2009; **145**: 36–44.

Identified via literature search (n = 2)

1 Amanzio M, Mitsikostas DD, Giovannelli F, Bartoli M, Cipriani GE, Brown WA. Adverse events of active and placebo groups in SARS-CoV-2 vaccine randomized trials: A systematic review. *Lancet Reg Health Eur* 2022; **12**: 100253.

2 Tang B, Barnes K, Geers A, Livesey E, Colagiuri B. Choice and the Placebo Effect: A Meta-analysis. *Ann Behav Med* 2022; **56**: 977–88.

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Supplementary appendix 5

List of studies excluded from the umbrella review after being read in their full length, with reasons for the exclusion

Systematic reviews

- *about non-pharmacological intervention (n = 6)*

1 Hesser H, Weise C, Rief W, Andersson G. The effect of waiting: A meta-analysis of wait-list control groups in trials for tinnitus distress. *Journal of Psychosomatic Research* 2011; **70**: 378–84.

2 Howick J, Webster R, Kirby N, Hood K. Rapid overview of systematic reviews of nocebo effects reported by patients taking placebos in clinical trials. *Trials* 2018; **19**: 674.

3 Kirsch I, Sapirstein G. Listening to Prozac but hearing placebo: A meta-analysis of antidepressant medication. *Prevention & Treatment* 1998; **1**. DOI:10.1037/1522-3736.1.1.12a.

4 Qiu Y, Mao Z, Yun D. Can the add-on placebo effect augment the physical and mental health outcomes of exercise? A meta-analysis. *Appl Psychol Health Well Being* 2022; **14**: 483–98.

5 Sherriff B, Clark C, Killingback C, Newell D. Impact of contextual factors on patient outcomes following conservative low back pain treatment: systematic review. *Chiropr Man Therap* 2022; **30**: 20.

6 Kube T, Glombiewski JA, Rief W. Using Different Expectation Mechanisms to Optimize Treatment of Patients With Medical Conditions: A Systematic Review. *Psychosom Med* 2018; **80**: 535–43.

- *pooled data not specific to either intervention type (pharmacological or non-pharmacological) or three-arm studies (active, placebo, no treatment) (n=1)*

1 Webster RK, Weinman J, Rubin GJ. A systematic review of factors that contribute to nocebo effects. *Health Psychology* 2016; **35**: 1334–55.

- *trials lacking of no-treatment groups (n = 4)*

1 Cao B, Liu YS, Selvitella A, *et al.* Differential power of placebo across major psychiatric disorders: a preliminary meta-analysis and machine learning study. *Sci Rep* 2021; **11**: 21301.

2 Kern A, Kramm C, Witt CM, Barth J. The influence of personality traits on the placebo/nocebo response. *Journal of Psychosomatic Research* 2020; **128**: 109866.

3 Meissner K, Fässler M, Rücker G, *et al.* Differential effectiveness of placebo treatments: a systematic review of migraine prophylaxis. *JAMA Intern Med* 2013; **173**: 1941–51.

4 Weimer K, Colloca L, Enck P. Age and Sex as Moderators of the Placebo Response - An Evaluation of Systematic Reviews and Meta-Analyses across Medicine. *Gerontology* 2015; **61**: 97–108.

- *lack of placebo control group and no-treatment group within the same trial (n = 2)*

1 Bélanger L, Vallières A, Ivers H, Moreau V, Lavigne G, Morin CM. Meta-analysis of sleep changes in control groups of insomnia treatment trials. *J Sleep Res* 2007; **16**: 77–84.

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2 Vallance AK. A systematic review comparing the functional neuroanatomy of patients with depression who respond to placebo to those who recover spontaneously: is there a biological basis for the placebo effect in depression? *J Affect Disord* 2007; **98**: 177–85.

Original research articles

- *Cited in systematic reviews included in the present meta-review (n = 1)*

1 Fratello F, Curcio G, Ferrara M, *et al.* Can an inert sleeping pill affect sleep? Effects on polysomnographic, behavioral and subjective measures. *Psychopharmacology* 2005; **181**: 761–70. *Cited in Yeung et al. (2018)*[45]

- *Cited in narrative reviews included in the present meta-review (n = 1)*

1 Ober K, Benson S, Vogelsang M, *et al.* Plasma Noradrenaline and State Anxiety Levels Predict Placebo Response in Learned Immunosuppression. *Clin Pharmacol Ther* 2012; **91**: 220–6. *Cited in Hadamitzky et al. (2020)*[90]

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Supplementary appendix 6

Mechanisms for placebo and nocebo effects in medical conditions and physiological systems

	Magnitude of placebo effect	Magnitude of nocebo effect	Mechanisms
Pain	The magnitude of placebo analgesia (expressed as pain relief) has been found to be large in nociceptive, idiopathic, and neuropathic pain, with Cohen's *d* = 1.01, 1.63, and 2.01, respectively.[66] The magnitude of placebo analgesia in placebo mechanism studies is large (*d* = 1.00, range = 0.95-1.14), and about five times larger than placebo analgesia effects in placebo control studies (*d* = 0.15–0.27).[37,39] Patients show to benefit from placebo treatment to a greater degree than healthy participants do, with an average effect size (Hedges' *g*) equal to 1.49 for patients and 1.24 for healthy individuals. Moreover, patients' clinical pain and experimentally induced pain respond to placebo to the same degree.[31] Brief expectation interventions: studies that assessed the effects of verbal suggestion of pain relief referred to a placebo treatment found a large pooled effect (placebo, *g* = 0.95) compared with a medium to large pooled effect in studies that assessed the effects of verbal suggestion of pain relief referred to an active treatment (placebo-related, *g* = 0.73).[32] Regarding the involvement of endogenous opioid, placebo administration has been shown to be associated with a reduction in self-report of pain (*d* = 0.89, p = 0.001), while naloxone administration has been shown to be associated with the anti-analgesic effects on pain perception (*d* = 0.55, p = 0.001).[38] Placebos elicit a very small effects (*g* = 0.08) on the neurologic pain signature.[30]	In nociceptive and idiopathic pain where nocebo effects were induced by verbal suggestions, the magnitude of nocebo hyperalgesic effects has been found to be moderate to large, with a Cohen's *d* around 0.66 to 0.90.[35] No nocebo hyperalgesic effects have been found in neuropathic pain.[66]	*Placebo analgesia* It is mediated by the endogenous opioid systems in some circumstances, as after pharmacological pre-exposure to μ-opioid receptor agonists. When mediated by the μ-opioid receptor, this analgesic placebo effect can be reversed by the opioid antagonist naloxone.[2,4,38,67] Proglumide (an indirect endorphin synergistic drug) has a synergistic effect of on placebo-induced analgesia.[40] After pharmacological pre-exposure to non-steroidal anti-inflammatory drugs (NSAIDs), the placebo effect is mediated by the activation of CB1 cannabinoid receptors, and can be reversed by the CB1 cannabinoid receptor antagonist rimonabant.[4,6,67] An activation of D2–D3 dopamine receptors and μ-opioid receptors in the nucleus accumbens (NAcc) occur during placebo analgesia.[2,4,6,67] In stress-induced analgesia, the increased arousal stems from an environmental stressor so that attention is diverted from the pain itself, leading to the activation of the endogenous opioid systems which, in turn, have an inhibitory effect on pain.[4,67] Genetic variants of both the fatty acid amide hydrolase (FAAH, Pro129Thr) — namely the major degrading enzyme of endocannabinoids — and the μ-opioid receptor (OPRM1, A118G) affect the magnitude of placebo analgesia.[68,69] Neuroanatomy:[34,36,67,70] reductions occur in brain regions involved in pain processing, including the dorsal anterior cingulate cortex (dACC), thalamus, and anterior insula, as well in regions implicated in studies of affect and valuation, namely in the amygdala and striatum. Activations occur in the dorsolateral prefrontal cortex, rostral ACC (rACC), and periacqueductal gray (PAG). Merely possessing a placebo analgesic (e.g. placebo cream), without using it, has been shown to reduce the intensity of acute pain sensation, which was induced using a cold compression task (placebo).[71] The open-label placebos (OLPs): effective in both laboratory (i.e., ischemic arm pain)[72] and clinical setting (i.e., low back pain).[20,62] Children: the influence of previous experience on subsequent treatment outcome has been shown to be stronger in children than in adults, indicating an increased relevance of learning processes for placebo treatment outcomes in children (placebo).[73] *Nocebo hyperalgesia* The pronociceptive cholecystokinin (CCK) system antagonizes the opioid system. Activated by anticipatory anxiety,[4] it also involves the activity of hypothalamic–pituitary–adrenal (HPA) axis.[2,4] Under hypoxic conditions (using high-altitude low-oxygen pressure as a model), negative expectation

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	about headache pain leads to the enhancement of the cyclooxygenase (COX) – prostaglandins (PG) pathway, which, in turn, induces pain worsening. Placebo administration to headache sufferers inhibits the nocebo-related component of pain and prostaglandins synthesis, indicating that the cyclooxygenase pathway can be modulated by both nocebos and placebos.[6] Deactivation of both D2–D3 and μ receptors occur in the NAcc during nocebo hyperalgesia.[2,4,6,67] Genetic variant (high-activity Val allele) of the catechol-O-methyltransferase (COMT, rs4680) — an enzyme that metabolizes dopamine and other catecholamines — has been associated with a higher frequency of nocebo effects.[74] Neuroanatomy: In experimental pain studies where pain occur as a result of verbal suggestions in the context of inert pharmacological substances, negative expectations led to significantly increased insula and somatosensory cortex activation.[33,75] *Moderators* Experimenters/clinicians' sex, status, and nonverbal behaviours are three factors capable of altering the perception of pain.[29] *Placebo/nocebo-related effects* Hidden (unexpected) injection of an active treatment is less effective than its open (expected) injection in both post-operative pain and in the experimental model of ischemic arm pain.[8]
Non-noxious somatic sensation	A top-down modulation on tactile perception has been demonstrated, probably due to an interaction between expectation and attention and which could be based on interactions between prefrontal and parietal brain regions (placebo). Changes in perception were supported by neurophysiological changes in brain-associated cortical responses (late somatosensory evoked potentials, SEP, N140, P200), whereas peripheral, subcortical and primary cortical responses (early SEP) remained stable. Possible therapeutic utility of these findings could be for those clinical conditions in which there is a pathological lack of sensation, e.g. due to a stroke.[76]
Disease of nervous system **Parkinson's disease (PD)**	Motor improvement is dependent by dopamine release in the dorsal striatum (placebo).[2,41,77–79] The magnitude of placebo-induced effects is modulated by an expectancy of improvement, which is in turn related to the release of dopamine within the ventral striatum (i.e., the NAcc) (placebo).[2,41,77–79] The functioning of the neural pathways underlying the placebo effect can be regulated by prior exposure and learning strategies (placebo and nocebo).[41,77,78] Placebo responders show a decrease in firing rate in the subthalamic nucleus, which is associated with a decrease in firing rate in the substantia nigra pars reticulata and, in turn, an increase in firing rate in the thalamic nuclei.[2,78] Also, the subthalamic nucleus neurons of all the placebo responders shift significantly from a pattern of bursting activity to a pattern of non-bursting discharge (placebo).[2,78] Strength of expectation can modulate dopamine release (placebo).[77]

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		Verbal suggestions have been shown to interfere with drug action. The supplementary motor area, source of the readiness potential, seems to be involved in this placebo effect (placebo).[6]
Disease of nervous system **Migraine**	In chronic migraine prevention trials, much of the effect of drugs (reduction in the number of days with migraine in the month) is still due to the high placebo effect, which contributes about 75% of the therapeutic gain.[42] In acute migraine treatment trials, the proportion of patients reporting adequate pain relief was 25.7% after oral placebo administration and 32.4% after subcutaneous placebo administration.[44]	Administration route impacts on placebo effects in chronic migraine preventive treatment, with the effect of application to the head being superior to the other routes (starting point for understanding placebo mechanisms).[42] In accordance with the expectation theory, adverse events (AEs) in placebo arms of clinical trials of anti-migraine medications were found to depend on the AEs of the active medication against which the placebo was compared (nocebo).[43]
Disease of nervous system **Sleep**	Placebo treatment leads to improved perceived global sleep quality (Hedges' g = 0.581), total sleep time (g = 0.322) and sleep onset latency (g = 0.272) when compared with no-treatment.[45]	Sleep seems to contribute to the consolidation of new expectations and consequently influence the generation of expectancy-mediated placebo effects (hypothetical placebo).[80] In particular, the relative duration of REM sleep can predict placebo-induced expectations of pain relief (placebo).[80]
Disease of nervous system **Intellectual disability (ID)** due to Fragile X, Down, Prader-Willi, and Williams syndromes	The effect of trial type on treatment outcomes (100% vs 50% probability of receiving genuine treatment) was statistically significant (p = 0.008). Higher effect sizes (treatment effects on core ID symptoms) were found in OLT (Hedges' g mean effect size = 0.65, placebo-related effect) compared to both the drug arm (mean g = 0.31, p = 0.043) and the placebo arm (mean g = 0.21, p = 0.009) in placebo-controlled RCTs.[46]	Certainty of genuine treatment, namely 100% likelihood of getting active drug, has been shown to increase drug responses among patients with an ID due to Fragile X, Down, Prader-Willi, and Williams syndromes compared to 50% likelihood (placebo-related).[46] In ID patients, it is likely that the expectations of surrounding parents, caretakers, and clinicians (i.e., implicit social influence of placebo by proxy) plays a role in treatment response (placebo-related).[46]
Mental and behavioural disorders **Depression**	A small placebo effect was observed in depression, whereby placebo conditions groups showed statistically significant improvements (assessed by clinical scales and number of relapses) when compared with the no-treatment or usual care (SMD 0.22, 95% CI 0.04–0.39).[47] Experimental evidence of large placebo effects on acute sadness in female depressed patients was provided: Hedge's g = 0.92. Since sadness is only one aspect of depressive affect, these results cannot be directly compared to placebo effects on symptoms of depression. Nevertheless, they're	Activity in the ventral striatum, rostral anterior cingulate cortex and other default mode network regions, orbitofrontal cortex, and dorsolateral prefrontal cortex correlates with placebo antidepressant effects (placebo), with overlap with some of the areas involved in placebo analgesia.[2,48] Regarding fluoxetine (inhibitor of serotonin re-uptake), while only a few brain areas are specifically affected by this drug, a unique ventral striatal (NAcc) and orbital frontal changes in both placebo and drug responders have been found at one week of treatment, that is, well before clinical benefit. These changes are not associated to the clinical response, but rather to expectation and anticipation of the clinical benefit. (placebo).[48] Important neurotransmitter systems could include the endogenous opioid system, dopamine, and serotonin,[48] with direct evidence for a role of the endogenous opioid system and dopamine (placebo).[69,74]

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	significant because demonstrate that experimentally induced placebo effects on mood can also prove powerful in clinical samples with depression.[81]	Regarding dopamine involvement, individuals with monoamine oxidase A (MAO-A) G/T polymorphisms (rs6323) coding for the low-activity form of the enzyme (T or T/T) and, therefore, higher basal dopamine tone, show a greater placebo-induced reduction in depressive symptoms than those with the high-activity MAOA genotypes (G o G/G) (placebo).[6,74,82] Medication (citalopram) plus expectancy (citalopram open administration, i.e. 100% chance receiving the active drug) produced greater depressive symptoms improvement in adult outpatients affected by major depressive disorder compared to the placebo-controlled group (50% chance of receiving active treatment) (placebo-related).[83] Patients affected by major depressive disorders have been shown to respond to OLPs (placebo).[20,62]
Mental and behavioural disorders **Anxiety**		Genetic variation in serotonin pathway polymorphisms, namely tryptophan hydroxylase-2 (TPH2) and serotonin transporter-linked polymorphic region (5-HTTLPR), are potential biomarkers of placebo effect in social anxiety disorder.[2,6,74] In particular, the TPH2 polymorphism is a significant predictor of clinical placebo effect: the genetic effect on symptomatic improvement with placebo is mediated by its effect on amygdala activity (placebo).[74] Diazepam hidden (unexpected) administration has been shown to be less effective than its open (expected) administration (placebo-related).[4,8] In the open (expected) interruption of diazepam, anxiety increased significantly, whereas in the hidden condition it did not change (nocebo-related).[8]
Mental and behavioural disorders **Dementia**		Alzheimer's disease (AD) patients are characterized by both an impairment of prefrontal executive functions and a reduced electroencephalographic connectivity between the prefrontal lobes and the rest of the brain. This results in a reduced effectiveness of many treatments for AD patients in moderate and later stages of the disease (placebo-related).[2,4] AD patients do not benefit from certainty of receiving genuine treatment (100% certainty) compared to the uncertainty of receiving active treatment or placebo (50% certainty) (placebo-related).[49] Intensive follow-up has been shown to improve dementia patients' cognition through the Hawthorne effect. [84]
Mental and behavioural disorders **Addiction**	In the alcohol-challenge studies conducted according to the balanced-placebo design, the placebo effect size was found to range from small to moderate according to variable classes: behavioural (d = 0.221), self-report (d = 0.348), physiological (d = 0.394). When physiological variables were utilized, expectancy effects were two standard deviations greater than pharmacological effects. Also, a moderate placebo effect size	Both expectations of benefit and reward mechanisms play a crucial role in placebo effects in addiction (placebo).[2,4] According to BPD design, when methylphenidate was expected (expecting drug, receiving drug), the increases in brain glucose metabolism were about 50% larger than when it was not, and the process was mediated by cerebellum (vermis) and thalamus. Unexpected methylphenidate (expecting placebo, receiving drug) induced greater increases in left lateral orbitofrontal cortex than when it was expected (placebo-related).[2,4,63,79] Nicotine: regardless of the actual treatment received, smokers who believed they had received nicotine had significantly better outcomes after six months than

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	was found when the studies were conducted in a natural environment, defined as situations where subjects were provided with an easy chair or environments that approximated a home setting (Cohen's *d* = 0.658).[51]	those who believed they had received the placebo (placebo-related).[86] Craving and cognitive performance in alcohol, caffeine, or nicotine consumers: i) expectations of alcohol consumption under placebo conditions produce an increase in craving, as it happens with alcohol consumption; ii) expectations of caffeine or nicotine consumption under placebo conditions produce a craving reduction; iii) expectations of having consumed alcohol slows reaction time even when alcohol is not consumed, while caffeine beliefs enhance accuracy (placebo).[50] Placebo alcohol and affect: evidence has been provided of the amendable nature of alcohol motives when confronted with a negative drinking experience, with an increase in emotional lability following placebo alcohol (placebo).[85] Alcohol-challenge studies: lab setting has been found to be a moderator for both pharmacological (alcohol) and expectancy effects. The natural environment paradigm seems thus plausible for producing the largest effects since subjects are likely to experience less tension and experimental reactivity than in experimental lab situations (placebo).[51]
Mental and behavioural disorders **Gynaecological disorders**		OLPs have been shown to be effective and safe in menopausal hot flushes (placebo).[87] In premenstrual dysphoric disorder, endogenous opioids seem to be involved: symptoms improvements after placebo administration are blocked by the opioid antagonist nalmefene) (placebo).[88]
Mental and behavioural disorders **Attention-deficit hyperactivity disorder (ADHD)**		Pairing stimulant medication with a visually distinctive placebo capsule administered in open-label fashion (OLPs) elicits a placebo effect that allows children with ADHD to be effectively treated on 50% of their optimal stimulant dose (placebo).[20,89]
Immune and endocrine systems		*Immune response* Cellular and humoral immune functions can be modulated via associative learning protocols (placebo).[2,4,79] The strength of the association between a conditioned stimulus (CS, e.g. an olfactory, gustatory, visual, auditory, or touch stimulus) and an unconditioned stimulus (US, i.e. a drug or substance with immunological properties) is not only affected by the temporal relation between the CS and US or the number of CS/US pairings. It is also affected by the history of the stimuli used as CS or US, as well as by states such as extinction, consolidation, reconsolidation, and partial reinforcement (placebo).[90] The "Immunological road map" for Pavlovian conditioning of immune functions has been drawn. For example, the conditioned immunosuppression by cyclosporine A (US) induces decreased cytokine production (interleukin-2 (IL-2), interferon-gamma (IFN-γ), IL-4, and IL-17) and diminished numbers of peripheral blood leukocytes subsets (B and T cells) (placebo).[2,90]

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	In asthmatic (male) patients, using grass-pollen or house dust as US and the procedure of inhalation of a neutral aerosol as CS, allergic attacks can be obtained as conditioned response (CR) (nocebo).[90] Allergic rhinitis has been shown to respond to OLPs (placebo).[20] Neuroanatomy: conditioned effects seem to be centrally mediated via the insular cortex and the amygdala, and peripherally mediated both via sympathetic innervation of lymphoid organs such as spleen and lymph nodes, and via noradrenaline and β-adrenoceptors on immune competent cells (placebo).[90] Predictors: Plasma noradrenaline and the subjects' state anxiety together with the baseline IL-2 levels predicted almost 60% of the variance in the conditioned IL-2 response.[90] *Endocrine response* Endocrine functions can be modulated via associative learning protocols, as demonstrated for the glucose-insulin system, HPA axis activity, growth hormone, and cortisol (placebo).[2,79] Compared to paradigms of conditioned immune responses, the basic mechanisms in endocrine system are less well understood. This is probably due to the complex temporal dynamics of HPA axis activity with its short- and long-term feedback mechanisms, and the partly pulsatile secretion of neuropeptides such as adrenocorticotropic hormone (ACTH) or corticotrophin-releasing hormone (CRH).[90] Cognition has been found to affect glucose levels in people with type 2 diabetes, whereby blood glucose levels a) increase in accordance with how much sugar participants believe they consumed rather than how much they actually consumed;[91] b) follow perceived time rather than actual time (placebo).[92]
Cardiovascular system	Most of what we know about placebo mechanisms in the cardiovascular system is the result of placebo analgesia studies. A reduction in heart rate has been found to be associated with placebo analgesia, whereby both placebo analgesia and the concomitant reduced heart rate were completely antagonized by the opioid antagonist naloxone.[2] A spectral analysis revealed that only the β-adrenergic low frequency (0.15 Hz) spectral component, which corresponds to sympathetic activity, was reduced during placebo analgesia, an effect that was reversed by naloxone.[2] Other placebo mechanisms include changes in coronary diameter and in systolic blood pressure.[79] Using the balanced placebo design, and employing the crossover design in which participants were sequentially exposed to four possible treatments, it was shown that expectations about caffeine effects consistently affect participants' diastolic and systolic blood pressure. Specifically, the greatest mean change in blood pressure occurred with non-blinded caffeine (told caffeine, get caffeine), the least effect occurred with non-blinded placebo (told placebo, get placebo). The two blinded treatments fell somewhere between, with blinded caffeine showing a greater blood pressure

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		effect than blinded placebo. These results are consistent with the possibility that the prefrontal cortex provides external, top-down control that modulates physiological outcomes (placebo).[93] In individuals affected by the rare Takotsubo cardiomyopathy, negative verbal suggestions paired to the injection of saline solution revealed both negative subjective and objective effects (nocebo).[94] Heart rate variability has proven to be the most reliable method to study placebo-analgesic and nocebo-hyperalgesic cardiac effects. Indeed, it can account for both sympathetic and parasympathetic influences on cardiac activity (placebo and nocebo).[52]
Respiratory system	In cough, a three-arm clinical trial of acute cough associated with the common cold showed that placebo treatment consisting of a single dose of vitamin E caused a significant reduction in cough frequency (50%, objective measure) compared with a 7% reduction in the no-treatment case.[95]	Involvement of endogenous opioids at the level of the respiratory centers: placebos can mimic the depressant effects of narcotics on ventilation, and these placebo respiratory-depressant effects can be prevented by the opioid antagonist naloxone (placebo).[2,79] The effects of placebos on respiratory function appear to be independent from those on pain. Indeed, based on experimental results, it has been hypothesized that these effects might involve different subpopulations of opioid receptors. Opioid μ1 receptors could mediate the effects of placebos on pain, while μ2 receptors those on respiration ((hypothetical placebo).[2,79] Procedures that combine conditioning and verbal suggestion seem to more reliably induce a placebo effect on dyspnoea (placebo).[96] Expectation-induced dyspnoea has been reproduced in the laboratory setting by using classical conditioning (nocebo). This psychophysiological phenomenon was associated, during the expectation phase, with deactivation of the dorsomedial prefrontal cortex and the rACC (nocebo).[79,97] *Asthma* Placebo effect may be mediated by inhibition of cholinergic outflow or activation of non-adrenergic parasympathetic outflow, or even regulation of inflammatory mediators active in the central nervous system (hypothetical placebo).[79,96] *Cough* Placebo antitussives are very effective in reducing cough and the urge-to-cough in clinical settings and under experimental conditions. This placebo effect could be mediated by endogenous opioids (hypothetical placebo).[95] An increase in activity in the prefrontal cortex likely contributes to the placebo-antitussive effects (hypothetical placebo).[95] Some interaction has been hypothesized between gustatory and cough pathways in the nucleus tractus solitarius, which may influence cough by the mediation of endogenous opioids (hypothetical placebo).[95]
Gastrointestinal disorders		*Nausea* Evidence has been found that conditioning procedures can alter nausea, with gender as important variable to be taken into account (i.e., women more susceptible to conditioning) (placebo).[53] *Visceral pain in irritable bowel syndrome (IBS)* Experimental placebo and nocebo studies highlight the role of expectancies and conditioning processes in shaping gastrointestinal symptoms not only at the level

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	of self-reports, but also within the brain and along the brain–gut axis (placebo and nocebo).[98] In individuals affected by IBS, both the desire to relieve pain and the expectation to relieve pain contribute to placebo analgesia, with ratings of desire for pain reduction, expected pain, and anxiety decreasing over time as the placebo effect increases (placebo).[99,100] Brain imaging studies revealed an altered activation of the cingulate cortex (and other regions) during placebo analgesia in patients with IBS, leading to speculate that IBS might be characterized by impaired cognitive pain modulation, to which affective disturbances might contribute (hypothetical placebo).[98] The COMT functional val158met polymorphism (i.e., rs4680) is associated with the placebo effect in IBS, whereby patients homozygous for the rs4680 low-activity met allele (met/met), known to have high levels of dopamine, show the greatest placebo effect (placebo).[6,74] IBS patients have been shown to respond to OLPs (placebo).[20,62]
Skin diseases	Expectations towards the benefit of a treatment — elicited by prior treatment experiences, verbal information, characteristics of the therapeutic context or intervention, social observation — have been shown to have an impact in itch, psoriasis, atopic dermatitis, allergic reactions, chronic wounds (placebo).[101] Negative product information (side-effects) paired with the administration of hydrating creams has been shown to be associated with more skin dryness (nocebo).[26] Psoriasis: positive response for placebo dose extension (OLPs) was found in psoriasis patients treated with corticosteroids (placebo).[62] *Itch* Placebo and nocebo effects can be induced through similar mechanisms across animal studies, studies with healthy volunteers, and studies with patients. In accordance with placebo research on pain: i) verbal suggestions or conditioning have shown to induce placebo and nocebo effects on itch, in which the combination of both procedures seems most promising;[96,102] ii) expectations (fewer or higher itch expectations) generally predict placebo and nocebo effects for itch (placebo and nocebo).[96] In both patients and healthy participants, self-reported outcomes and scratching behaviour were generally more likely to be affected by placebo and nocebo effects than physiological parameters (placebo and nocebo).[54] Brain areas likely involved in nocebo responding are those responsible for somatosensory processing of itch or are otherwise related to the itch-scratch cycle as well (nocebo). Placebo and nocebo effects may thus modulate itch through top-down processing in brain areas related to the specific condition or symptom in which they emerge (hypothetical placebo and nocebo).[54] In patients with chronic atopic dermatitis, the targeted application of placebo effects in addition to the pure pharmacological effectiveness of a drug (dimetindene)

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	was able to improve the overall drug action (placebo).[103] Moreover, placebo effects were stronger reflected on the subjective outcome "itching intensity" than on the objective outcome "wheal-size", suggesting that placebo effects in atopic dermatitis are more likely to be reflected in centrally mediated subjective experience than in peripherally mediated objective measurements (placebo).[87,103] Contagious itch: mirror neurons have been proposed to play a role in eliciting symptoms (nocebo).[54] Predictors of placebo and nocebo responding on itch and contagious itch: psychological characteristics and personality traits related to negative outcome expectancies seem to be of importance in predicting effects on itch, although evidence is mixed.[102]
Flu and related vaccines	*Influenza or influenza-like symptoms (ILS)* General expectations of getting influenza or ILS have been shown to be associated with an increased risk of developing actual symptoms over the entire winter season (nocebo).[104] The role of expectations as potential risk/protective factors remains stable even when accounting for the perception of general health and for previous ILS (nocebo).[104] Participants who expected their symptoms to be more intense and to last longer actually reported higher intensity and long duration of the illness, confirming the predictive value of expectations (nocebo).[104] *COVID-19 vaccines* A substantial proportion of AEs associated with COVID-19 vaccines are not a result of the vaccine per se, but may be related to the nocebo effect. Indeed, fatigue, headache, and pain (as local injection site reaction and myalgia) have been shown to be the most commonly reported AEs in both the active drug and the placebo arms, although in active vaccine arms they were higher. In addition, the AEs of fatigue, headache, and pain are more common in the younger population and in the first dose of mRNA placebo recipients.[55]
Oncology	The utility of conditioning both with and without a verbal suggestion in inducing a placebo effect on anticipatory nausea has been confirmed (placebo).[53,96] Nausea conditioning (rotation combined with cinnamon breath strips) and expectancy manipulation (instruction that cinnamon aroma would increase nausea) have been shown to lead to an exacerbation of the nausea symptom (nocebo).[26] The line of research using conditioning alone includes two strategies that are, as of yet, rarely applied in the rest of the placebo literature: overshadowing (the nausea-inducing stimulus is associated with a very salient stimulus which is then not present at test) and latent inhibition (participants are exposed to the environment where the nausea is induced several times before the nausea induction) (placebo).[96] Effective interventions tended to be those that were aimed at participants with high initial expectancies.[53] Cancer related fatigue has been shown to respond to OLPs (placebo).[20,62]

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Obesity			Improvements in biochemical (fasting glucose, insulin, lipids) and behavioural parameters (sleep duration/quality) occur between screening and randomization of the obese patients due to Hawthorne effect.[9] Interindividual propagation of behaviours and attitudes is common in the obesity condition, whereby negative expectations spread across different individuals (nocebo).[9] Supplements without weight loss effects may have nocebo effects through diminished weight loss self-efficacy (i.e., participants' belief about being able to resist temptations and exercise more). Participants who received a daily placebo capsule and were told that i) they were taking an active weight loss supplement or ii) they had a 50% random chance of receiving either the active or placebo, they showed decreased weight loss self-efficacy and increased expectations of benefit from dietary supplements. Participants not taking capsules showed the opposite. Also, adverse events were more frequently reported in groups taking capsules than those who were not (nocebo).[105] The potentially powerful influences of placebo and placebo-related effects should be taken into account when evaluating the outcomes in diet and lifestyle modification trials (placebo and placebo-related).[106]
Physical performance	Small to moderate placebo effects were found for sham nutritional ergogenic aids (d = 0.35 ± 0.44).[58,59] Specifically, large placebo effects on sport performance were found for purported anabolic steroids and an erythropoietin like substance (d = 1.44 ± 1.01 and d = 0.81, respectively). Small to moderate effect sizes were reported for placebos described as amino acids (d = 0.36) or caffeine (d = 0.40). Small effect was found for fictitious sports supplements (d = 0.21 ± 0.17).[58] Also, using pre-conditioning procedures resulted in large placebo effects (d = 0.82 ± 0.18). Small to moderate effect sizes were found for positive (d = 0.36 ± 0.44) and negative (d = 0.37 ± 0.25) expectations.[58] A very small, but significant, placebo effect on performance during exercise was found for caffeine and buffer supplements (Hedges' g = 0.09). In addition, the magnitude of this placebo effect could be influenced by the form of the supplement, with larger effects obtained when the placebo was presented	In studies on motor performance conducted on healthy individuals, where the effect of inert substances to evoke a nocebo effect was compared to a control condition or group, the mean effect size of nocebo effects has been found to be d = 0.60, suggesting a moderate effect.[56] Sports performance of healthy individuals (mainly force production and speed) seems to be the aspect of motor performance most susceptible to nocebo influences.[56] Nocebo effect on repeat-sprint performance (sprint time) has been found to have a small to moderate effect size (d = 0.32) when a dummy sports supplement thought to be detrimental to performance was administered.[58]	All available data in sport performance indicate athletes' expectations as important elements of physical performance (placebo and nocebo).[58] Regarding muscle performance and fatigue, central mechanisms would play a role through the concept of central command (placebo and nocebo).[107,108] Placebo caffeine has been found to reduce fatigue by acting at the central level on the preparatory/anticipatory phase of movement in the supplementary motor area (placebo).[108] Placebo ergogenic aid (presented as branched chain amino acids) significantly influenced frontal alpha asymmetry during maximum effort cycling (placebo).[108] Perceived fatigue has been found to be highly sensitive to placebo treatments, even more than pain. In hypoxic conditions at high altitude — differently from headache pain, perfusion, ventilation, and circulation — it is not necessary to perform a preconditioning procedure with real oxygen breathed through a mask to obtain robust placebo effects in fatigue, verbal suggestions alone being sufficient (placebo).[108] Neurotransmitter systems playing a role in fatigue: the involvement of opioid and endocannabinoid systems is intuitive considering the link between pain and fatigue (placebo).[2,108] Regarding the serotonin system, it has been most consistently linked with fatigue in sport (placebo).[108] Regarding dopamine system, it has been found to exert ergogenic effects and override inhibitory signals from the central nervous system (placebo). Conversely, a reduction of dopamine could impair activation of the basal ganglia and reduce stimulation of the motor cortex leading to central fatigue, as well as disruption of sensory inputs (nocebo).[108]

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	as a solution compared to a capsule (placebo).[57]	Histamine release and binding to H1 receptors mediates the exercise-induced fatigue reduction (placebo).[108] Individual variability of placebo and nocebo effects in physical performance: the ergogenic effects of caffeine are greater for homozygous carriers of the T allele of the adenosine A2A receptor subtype (placebo and nocebo).[108] Through mechanisms similar to those underpinning ergogenic placebo effects, also social environments that signal support and safety can reduce perceptions of pain and fatigue during physical exertion (placebo-related).[109] Social information provided by competitors and teammates can change the optimal physical output strategies for athletes and exercisers by altering the perceived costs (e.g., the consequences of resource depletion) and benefits (e.g., winning a competition) (placebo-related).[109]
Cognitive performance		Histamine release and binding to H1 receptors mediates the motivation to complete cognitive work (placebo).[108] A placebo for a psychotropic drug, i.e. R273, a mixture of baking soda and water which was described as a cognition-enhancing drug, was shown to help participants resist the misinformation effect (placebo).[110] Manipulation of cognitive performance expectation by means of the administration of an inactive nasal spray has been shown to affect the perceived change in cognitive performance and tiredness, but not the actual cognitive performance in healthy adults (placebo and nocebo).[26]

CI, confidence interval; OLPs, open-label placebos; OLT, open-label trial; RCTs, randomized clinical trials; SMD, standardized mean difference.

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PRISMA 2020 for Abstract Checklist

Section and Topic	Item #	Checklist item	Reported (Yes/No)
TITLE			
Title	1	Identify the report as an umbrella review.	YES, page 2
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	YES, page 2
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	YES, page 2
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	YES, page 2
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	YES, page 2
Synthesis of results	6	Specify the methods used to present and synthesise results.	YES, page 2
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	YES, page 2
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	YES, page 2
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	NO
Interpretation	10	Provide a general interpretation of the results and important implications.	YES, page 2
OTHER			
Funding	11	Specify the primary source of funding for the review.	YES, page 2
Registration	12	Provide the register name and registration number.	YES, page 2

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PRISMA 2020 Checklist

Section and Topic	Item #	Checklist item	Location where item is reported
TITLE			
Title	1	Identify the report as an umbrella review.	page 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist.	page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	pages 4 and 5
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	page 5
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	pages 5 and 6, and table 1
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	pages 5 and 6
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	supplementary appendix, 1B
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	page 6
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	page 6
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	page 5 and table 1
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	page 6 and table 1
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	pages 6 and 7, and supplementary appendix 2
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	page 7
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).	page 7
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	page 7
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	page 7
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	page 7
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	NA
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	pages 6 and 7
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	NA

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Section and Topic	Item #	Checklist item	Location where item is reported
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	page 7
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	pages 7 and 8, figure 1, and supplementary appendix 4
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	figure 1 and supplementary appendix 5
Study characteristics	17	Cite each included study and present its characteristics.	pages 7-13 and supplementary appendix 3
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	page 8 and supplementary appendix 2
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	page 11, table 2 and supplementary appendix 6
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	pages 7-13, and supplementary appendices 2 and 3
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	pages 7 and 8, page 11 and Table 2
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	NA
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	pages 8 and 11, and supplementary appendix 2
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	NA
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	11
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	pages 14-16
	23b	Discuss any limitations of the evidence included in the review.	page 16
	23c	Discuss any limitations of the review processes used.	page 16
	23d	Discuss implications of the results for practice, policy, and future research.	pages 14-16 and table 3
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	pages 2 and 5, and supplementary appendix 1A
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	pages 2 and 5, and supplementary appendix 1A
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	page 6
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	pages 2 and 17
Competing interests	26	Declare any competing interests of review authors.	page 17
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	page 17, supplementary appendices 3 and 6

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