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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 summarise 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 summarised through narrative synthesis, tables, 95% 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 per cent of the examined systematic reviews were of high quality.

Our findings revealed that mechanisms underlying placebo and/or nocebo effects have been characterised, 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, influenza and related vaccines, oncology, obesity, physical and cognitive performance. Their magnitude ranged from 0.08 to 2.01 (95% CI 0.37 to 0.89) for placebo effects and from 0.32 to 0.90 (95% CI 0.24 to 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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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.

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 emphasised 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-related 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 healthcare 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 *et al*,[12] along 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-related/nocebo-related effects associated with pharmacological interventions. Our threefold goal was to present findings regarding: (1) what are the conditions, that is, clinical or physiological, in which robust placebo/nocebo effects or placebo-related/nocebo-related effects have been documented to date; (2) what are the contexts/circumstances, that is, clinical or laboratory setting, in which they occur and (3) what do we know about the biological underpinnings of these effects.

METHODS

Review selection

The study was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (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 online supplemental 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 online supplemental 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-related/nocebo-related effects in non-pharmacological interventions (eg, 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.

The randomised clinical trials (RCTs) and OLPs clinical trials included in the present umbrella review were required to have a three-arm design (ie, 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: (1) different routes of placebo administration and reported improvements not attributable to spontaneous remission or regression to the mean; (2) different likelihoods of receiving active treatment or placebo; (3) 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: (1) addressed an underinvestigated topic in the field of placebo research that missed to be included in systematic or narrative reviews and (2) were too recent to be included in systematic or narrative reviews.

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: (1) different routes of placebo administration and reported improvements not attributable to spontaneous remission or regression to the mean; (2) different likelihoods of receiving active treatment or placebo; (3) the type of AEs occurring in both the active and placebo arms; ► Original research articles that: (1) addressed an underinvestigated topic in the field of placebo research that missed to be included in systematic or narrative reviews; (2) were too recent to be included in systematic or narrative reviews.

AEs, adverse events; OLPs, open-label placebos; PICOS, Population, Intervention, Comparison, Outcomes and Study; RCTs, randomised clinical trials.

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 preset 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 (ie, 7 out 16 items).[17] About the protocol domain, an 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 online supplemental appendix 2, the full assessment according to AMSTAR 2 tool was provided for each of the examined systematic reviews, including the seven 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 summarise 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 summarised as: (1) the percentage of all surveyed systematic reviews that received a positive final overall assessment and (2) the percentage of systematic reviews, distinguishing between those with and without meta-analysis, that received a positive final overall assessment.

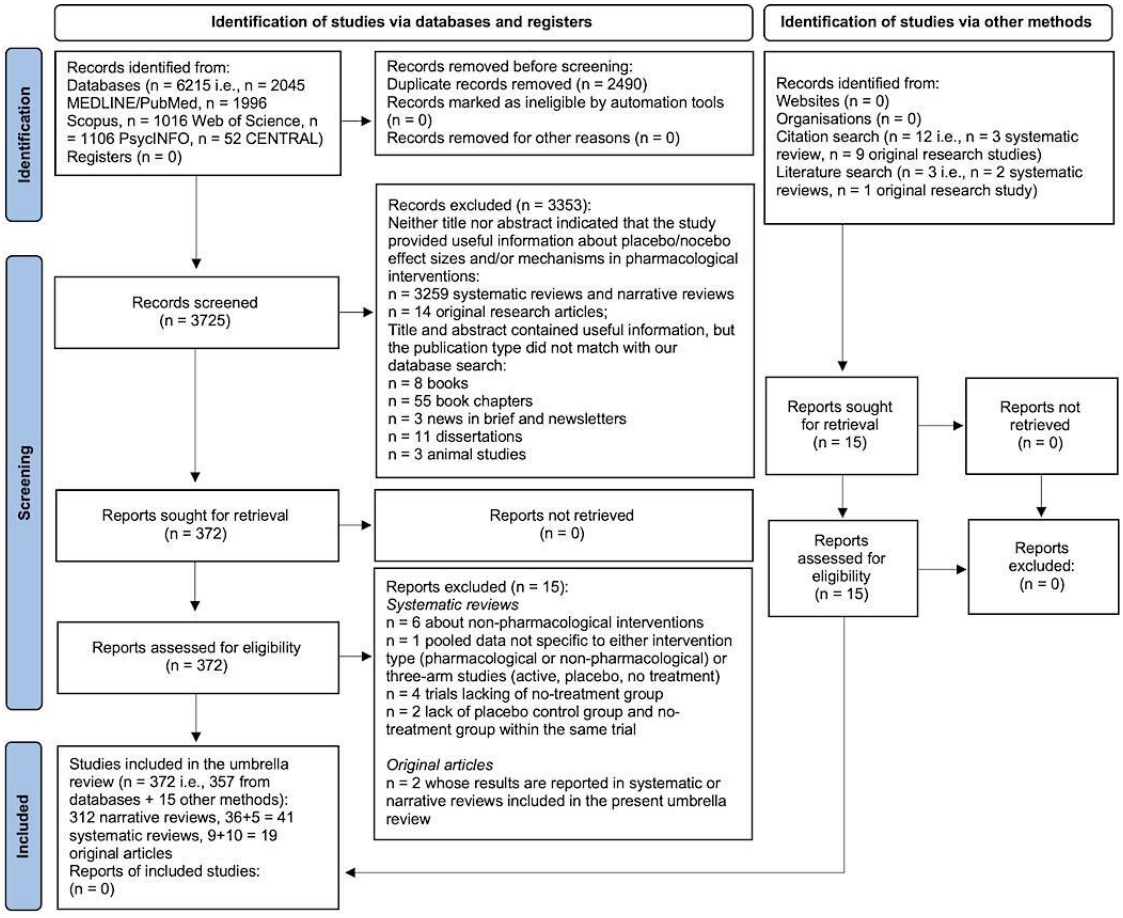

Figure 1 PRISMA flow chart. Trial flow of the selection process, showing both the number of events and reasons for the exclusion of most of the 6215 initially selected records. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Regarding the effect sizes expressed as Cohen's d, Hedges' g or standardised mean difference, they were summarised as a range with the smallest and largest placebo or nocebo effects, along with their respective 95% CI.

Patient and public involvement

No patient involved.

RESULTS

Umbrella 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 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 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 online supplemental appendix 3.[19–59] Furthermore, as documented in online supplemental 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.

Online supplemental 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). Online supplemental 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 (ie, 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 *et al*[21] extracted data about treatment effects from the last meta-analysis conducted by Hróbjartsson and Gøtzsche.[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 to 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 to 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 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=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 non-deceptive placebos compared with no-treatment (standardised mean difference 0.88 (95% CI 0.62 to 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 15 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 (ie, placebo without choice vs 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 (ie, 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 (ie, 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 towards effective treatments leads to substantial placebo effects. It is important to emphasise 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 specialised 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 emphasised 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—that is, 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 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 with females. Furthermore, endogenous opioid transmission has been reported to be more effective in males compared with 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-related/nocebo-related effects associated with pharmacological interventions, together with their effect sizes, are reported in online supplemental 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 (PD),[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] influenza 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 to 0.89) in the case of placebo effects, and from 0.32 to 0.90 (95% CI 0.24 to 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 with those using placebos as control 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 neurological pain signature, which is a brain-based pattern that can reliably distinguish between responses to painful and non-painful stimuli, and is sensitive and specific to pain.[30] This finding suggests that placebos might modulate non-specific affective and cognitive processes rather than affecting nociception.[30 70]

The neuroanatomy of nocebo hyperalgesia has been characterised 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

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 measures)
	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 no 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	50% 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, for example, 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 measures)
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 measures)
	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] Total sleep time Hedges' g=0.322[45] Perceived global sleep quality Hedges' g=0.58[45]	Global sleep quality, total sleep time, sleep onset latency (patients' subjective self-reported measures)
	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, for example, power output, speed or time to completion (objective measures)

Continued

Table 2 Continued

Magnitude of the effect size	Type of effect	Condition	Values	Outcome 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 (objective measure)
	Placebo	Depression	Standardised Mean Difference 0.22[47]	Validated clinical scale for major depression, filled in by patients (subjective measure); no of relapses (objective measure)
	Placebo	Sport performance assuming a fictitious sport supplement	Cohen's d=0.21[58]	Direct measure of performance, for example, 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 (ie, performance test)/time to exhaustion (ie, capacity test).

potentially threatening stimuli receive more attention and are reliably detected.[33 75]

In antimigraine clinical trials, adequate control 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 *et al*) 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 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 with 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]

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 characterised in both clinical and non-clinical contexts, as extensively described in online supplemental 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 OLPs administration were documented for: pain (low back pain and ischaemic arm pain),[20 62 72] depression,[20 62] menopausal hot flushes,[87] ADHD,[20 89] allergic rhinitis,[20] IBS,[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 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 characterised by a pathological lack of sensation, eg, stroke), PD, 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 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

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 summarise the treatment information they were provided with, to prevent negative biases and misunderstandings. Favour positive associations and minimise 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 non-adherence to the treatment regimen or discontinuation of the drug. Teach and train strategies to cope with adverse effects.	Standardise the language used to present the benefit–risk profile of the intervention under investigation. Standardise framing strategies used to present information about side effects. Standardise questions and use structured checklists to collect data on side effects. Standardise the duration and no 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. Optimise 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' (ie, 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 (eg, 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 pretreatments 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.

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, that is, is it possible for placebos to act, in part or entirely, on a pre-existing nocebo effect under certain conditions? How do placebo and 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, for example, 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.

This 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 this 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 minimise potential nocebo effects associated with pharmacological interventions. In addition, this 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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