Routledge
Taylor & Francis Group

Health Psychology Review

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/rhpr20

A scoping review of placebo and nocebo responses and effects: insights for clinical trials and practice

Arianna Bagnis, Stefanie H. Meeuwis, Julia W. Haas, Mary O'Keeffe, Elzbieta Anita Bajcar, Przemyslaw Babel, Andrea W.M. Evers, Eveliina Glogan, Marek Oleszczyk, Antonio Portoles, Johan W.S. Vlaeyen, Katia Mattarozzi & on behalf of PANACEA Consortium

To cite this article: Arianna Bagnis, Stefanie H. Meeuwis, Julia W. Haas, Mary O'Keeffe, Elzbieta Anita Bajcar, Przemyslaw Babel, Andrea W.M. Evers, Eveliina Glogan, Marek Oleszczyk, Antonio Portoles, Johan W.S. Vlaeyen, Katia Mattarozzi & on behalf of PANACEA Consortium (03 Mar 2025): A scoping review of placebo and nocebo responses and effects: insights for clinical trials and practice, Health Psychology Review, DOI: 10.1080/17437199.2025.2471792

To link to this article: https://doi.org/10.1080/17437199.2025.2471792

HEALTH PSYCHOLOGY REVIEW
https://doi.org/10.1080/17437199.2025.2471792

Routledge
Taylor & Francis Group

REVIEW ARTICLE

OPEN ACCESS Check for updates

A scoping review of placebo and nocebo responses and effects: insights for clinical trials and practice

Arianna Bagnis[a], Stefanie H. Meeuwis[b], Julia W. Haas[c,d], Mary O'Keeffe[e], Elzbieta Anita Bajcar[f], Przemyslaw Babel[f], Andrea W.M. Evers[b], Eveliina Glogan[c], Marek Oleszczyk[g], Antonio Portoles[h], Johan W.S. Vlaeyen[c], Katia Mattarozzi[a] and on behalf of PANACEA Consortium[a]

[a]Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy; [b]Institute of Psychology, Leiden University, Leiden, Netherlands; [c]Faculty of Psychology and Educational Sciences, Katholieke Universiteit Leuven, Leuven, Belgium; [d]Department of Psychology, University of Kaiserslautern-Landau (RPTU), Landau, Germany; [e]European Pain Federation EFIC, Brussels, Belgium; [f]Institute of Psychology, Jagiellonian University, Krakow, Poland; [g]Department of Family Medicine, Jagiellonian University Medical College, Krakow, Poland; [h]Department of Farmacología y Toxicología, Universidad Complutense Madrid, Madrid, Spain

ABSTRACT

Placebo and nocebo responses and effects influence treatment outcomes across a variety of conditions. The current scoping review aims to synthesise evidence from systematic reviews and meta-analyses in both clinical and healthy populations, elucidating key determinants of placebo and nocebo responses and effects, including individual, clinical, psychological and contextual factors. Among the 306 publications identified, 83% were meta-analyses and 17% systematic reviews, with a predominance of research in medical specialties (81.7%) such as psychiatry and neurology. Placebo responses were significantly more studied than nocebo responses. Individual determinants (e.g., age), clinical determinants (e.g., baseline symptom severity) and psychological determinants (e.g., expectations) were found to influence placebo and nocebo outcomes. Contextual determinants, including trial design and the method of treatment administration, also played critical roles. Several key underinvestigated areas in the current body of systematic reviews and meta-analyses were also identified. This scoping review highlights valuable insights into the determinants of placebo and nocebo responses and effects on a group level, potentially offering practical implications for optimising clinical trial designs and enhancing patient care strategies in clinical practice. However, to fully leverage these benefits, it is crucial to address the underexplored topics through more rigorous investigations using a person-centred perspective.

ARTICLE HISTORY
Received 7 November 2024
Accepted 20 February 2025

KEYWORDS
Clinical practice; clinical trials; healthcare; nocebo; placebo; scoping review

1. Introduction

The phenomena of placebo and nocebo have garnered increasing attention in health and neuro-psycho-biological research across a wide range of clinical conditions, due to their significant impact on patient outcomes and treatment responses (Amanzio & Benedetti, 1999; Benedetti

CONTACT Arianna Bagnis arianna.bagnis@unibo.it
Supplemental data for this article can be accessed online at https://doi.org/10.1080/17437199.2025.2471792.

et al., 2005). However, a comprehensive overview of common and disease-specific determinants influencing these phenomena remains elusive.

The term 'placebo', introduced in the eighteenth century, denoted the administration of inert substances to elicit positive responses in patients (Beecher, 1955; Shapiro & Shapiro, 2000), capturing the prevailing conception of the placebo word within both the public and the medical community. However, this reflects only a type of intervention where the placebo is considered as an inert treatment. Nonetheless, with the increase of robust evidence, researchers have proposed broader and more intricate definitions of the placebo phenomena, including the behavioural and psychophysiological processes that become active whenever an individual perceives symptoms and approaches treatment and/or a context of care (Benedetti, 2008).

Traditionally, literature distinguishes between placebo responses and placebo effects (Evers et al., 2018). The placebo response has been defined as the positive health outcome of a patient that occurs following an inert treatment (e.g., a placebo pill) and it includes placebo effects, but also other non-specific factors, such as the natural course of disease (Enck et al., 2013; Evers et al., 2018; Kelley, 2018). Placebo responses are generally observed and measured within randomised controlled trials (RCTs), which are clinical studies usually structured with two arms, one administered the active drug under investigation and the other, the control arm, given an inert substance known as a placebo. The placebo effect, a less broad term, refers to the positive health changes that occur specifically due to mechanisms activated by individual and contextual factors, e.g., treatment expectations (Enck et al., 2013; Evers et al., 2018; Finniss et al., 2010; Häuser et al., 2012; Kaptchuk et al., 2008), whenever a patient enters a caring context and is either administered an inert treatment or engages with an active treatment.

Conversely, nocebo effects are driven by individual and contextual factors, such as negative verbal suggestions and treatment expectations, leading to negative health outcomes (Colloca & Barsky, 2020). They refer to the occurrence of negative symptoms or worsening of symptoms in response to an inert or active treatment, and they are measured by comparison to a no treatment condition or group. Nocebo responses include any negative health outcomes, such as unfavourable symptoms or adverse events, following an inert treatment, which are partly due to nocebo effects and partly due to a variety of artefacts, including natural history and regression to the mean (Colloca, 2019; Schedlowski et al., 2015).

Placebo and nocebo responses and effects are evident across various clinical conditions (Benedetti, 2014; Colloca & Barsky, 2020; Rossettini et al., 2020). To date, most studies have primarily focused on pain (Atlas, 2021). Nevertheless, these effects have been observed across a diverse range of symptoms conditions, encompassing neurological disorders (e.g., Parkinson's disease, migraine, dementia, ADHD), psychiatric conditions (e.g., depression, anxiety, addiction), gynaecological issues (e.g., premenstrual dysphoric disorder, menopausal hot flashes), cardiovascular (e.g., cardiomyopathy, hypertension), gastrointestinal disorders (e.g., irritable bowel syndrome, Crohn's disease, nausea), dermatological conditions (e.g., itch, atopic dermatitis, psoriasis), respiratory issues (e.g., cough, dyspnoea), immunological challenges (e.g., allergy, asthma) and sleep disorders (e.g., insomnia) (for a comprehensive review, refer to Frisaldi et al., 2023).

Several studies have attempted to identify the neurobiological correlates of placebo and nocebo effects (Rossettini et al., 2023; Wager & Atlas, 2015; Zubieta et al., 2005). Neuroimaging studies have revealed the activation of endogenous opioid systems and the modulation of neurotransmitter release in response to placebo interventions (Benedetti et al., 2005). For example, the dopaminergic reward circuitry is implicated in mediating placebo analgesia (Lidstone et al., 2010; Scott et al., 2008; Wager et al., 2004). Additionally, other studies highlight the involvement of specific brain regions, such as the prefrontal cortex and anterior cingulate cortex, in modulating placebo-induced pain relief, reflecting the engagement of cognitive and emotional processing during placebo analgesia (Bingel et al., 2006; Freeman et al., 2015).

Placebo and nocebo responses and effects derive from a complex interplay of determinants – that work together to produce and influence these phenomena – such as individual, clinical,

psychological and contextual factors (Bishop et al., 2017; Di Blasi et al., 2001). These determinants, either uniquely or in combination, shape behaviours and health outcomes in both healthy individuals and patients. Individual determinants refer to specific personal characteristics or attributes such as age, sex, race, genetic profiles and personality traits (e.g., Colagiuri et al., 2015; Hall et al., 2015; Kern et al., 2020; Okusogu et al., 2020; Świder & Bąbel, 2013; Weimer et al., 2015). Given the pivotal role these determinants play in shaping an individual's health outcomes and susceptibility to various health conditions or diseases, there have been efforts to identify people susceptible to placebo effects (i.e., 'placebo responders'), albeit with inconsistent results (Kaptchuk et al., 2008). Similarly, clinical determinants, intrinsic to the medical condition being treated, may impact placebo and nocebo responses or effects. They include, among others, the severity of the disease, the development of the disease, baseline symptoms at enrolment and the presence of other diseases. For example, diseases with unclear aetiologies or unpredictable courses may leave patients more vulnerable to the influence of suggestion that alter their expectations and make them more open to accept placebo treatments (Kisaalita et al., 2011; Lembo et al., 2021; Neogi & Colloca, 2023; Vollert et al., 2020). Psychological factors, including learning experiences, expectations, beliefs, attitudes and emotional states of healthy individuals and patients as well as experimenters and practitioners, can also heavily influence placebo and nocebo responses and effects, potentially enhancing therapeutic outcomes (Benedetti et al., 2003). Finally, contextual determinants include factors around the patient and the therapy, patient-provider interaction, clinical setting and treatment characteristics. For example, effective communication, positive patient-practitioner interaction and clear information enhance therapeutic responses (Kaptchuk et al., 2008; Kelley et al., 2014). Also, contextual characteristics that researchers and clinicians decided to implement into the experiment or clinical trial, such as the trial design, the sample size, the study location, the type of treatment in the active arm, the administration route, the frequency of visits, have been proven to influence placebo and nocebo phenomena (Colloca & Miller, 2011; Geuter et al., 2017). Table 1 shows an overview of these determinants.

Exploring these factors within both placebo and nocebo responses and effects is essential for understanding the intricate relationship between mind and body in health and disease and for harnessing their potential in clinical practice. This paper encompasses a thorough scoping review, synthesising both basic and clinical evidence related to placebo and nocebo responses and

Table 1. Determinants of placebo and nocebo effects.

Determinant category	Definition	Example	Reference(s)
Individual	Individual invariant characteristics shaping an individual's health outcomes and susceptibility to various health conditions or diseases; associated with concept of 'placebo responder' in RCT	Age, sex, race, genetic profiles, personality traits	Colagiuri et al., 2015; Hall et al., 2015; Kern et al., 2020; Okusogu et al., 2020; Świder & Bąbel, 2013; Weimer et al., 2015
Clinical	Intrinsic to the individual's medical condition being treated	Severity of the disease, the development of the disease, baseline symptoms at enrolment and the presence of other disease	Enck & Klosterhalfen, 2020; Kisaalita et al., 2011; Lembo et al., 2021; Neogi & Colloca, 2023; Vollert et al., 2020
Psychological	Psychological processes (cognitive, affective and emotional) and variant characteristics that shape an individual's behaviour and decision-making processes, including health outcomes	Classical conditioning, operant conditioning, verbal suggestions, observational learning, expectations, beliefs and emotional states	Bąbel, 2020; Benedetti et al., 2003; Colloca & Miller, 2011; Lidstone et al., 2010; Meeuwis et al., 2023
Contextual	Factors around the patient and the therapy, patient-provider interaction, clinical setting and treatment characteristics	Quality of the relationship between patients and practitioners, study design, administration route, frequency of visits	Colloca & Miller, 2011; Geuter et al., 2017; Kaptchuk et al., 2008; Kelley et al., 2014

RCT = randomised controlled trial.

effects, with a specific focus on elucidating their determinants, including individual, clinical, psychological and contextual factors, along with their neurobiological correlates. There exists a gap between scientific evidence on placebo and nocebo effects and their application in clinical practice (Evers et al., 2018). By identifying and comprehensively summarising and analysing these factors, we aim to provide clinicians and researchers with valuable insights into how to effectively implement and exploit placebo and nocebo effects in clinical settings and potential research needs. This knowledge can contribute to the development of strategies to optimise treatment outcomes, tailor interventions to individual patient needs, enhance patient care and minimise adverse effects, ultimately improving the overall efficacy and efficiency of healthcare delivery.

As we aimed to analyse and present the most robust scientific evidence, only systematic reviews and meta-analyses were considered. The results were discussed to draw insights from the determinants mentioned above. Finally, underinvestigated topics and implications for clinical trials and clinical practice were discussed.

2. Materials and methods

2.1. Study design and registration

Scoping reviews are commonly employed to map the existing literature within a specific field, posing a broader research question compared to systematic reviews. They prove particularly valuable when the literature is extensive, complex, or heterogeneous (Peters et al., 2015), as in this case. We reported this scoping review according to the PRISMA extension for Scoping Reviews (PRISMA-ScR) (Peters et al., 2015, 2022; Tricco et al., 2018). We followed a protocol developed a priori, that was registered on Open Science Framework on October 6, 2023 (https://osf.io/9uxk6).

2.2. Eligibility criteria

Only systematic reviews and meta-analyses were included in the scoping review. These study designs were selected for inclusion due to their ability to provide a comprehensive overview of existing evidence, reduce bias in evidence synthesis and offer standardised methodologies for data extraction and analysis. Specifically, we included peer-reviewed systematic reviews or meta-analyses investigating placebo or nocebo responses and effects in healthy individuals or clinical samples that were available in English. We thus excluded non-peer reviewed publications (e.g., conference proceedings, preprints), primary research articles, narrative reviews and publications on animals. We also excluded systematic reviews and meta-analyses of clinical trials that used placebo purely as an experimental paradigm to assess drug efficacy and safety.

2.3. Search strategy

We searched six databases from their inception to April 11, 2023: PubMed, Scopus, Cochrane Library, PsychINFO, Embase, Web of Science. To identify potentially eligible studies, the following two search strategies were used in PubMed: (1) Placebo [Title] OR nocebo [Title]; (2) Placebo [Title] OR nocebo [Title] AND (clinic*[Title/Abstract] OR clinical practice [Title/Abstract] OR implementation [Title/Abstract]). Vocabulary and syntax were adjusted across the databases.

2.4. Selection of evidence

Following the search, the output of each database was uploaded on Rayyan (Ouzzani et al., 2016) separately for each search strategy to start the screening against the inclusion criteria. All identified studies were collated, and duplicates were removed. Five independent researchers (AB, EAB, JWH,

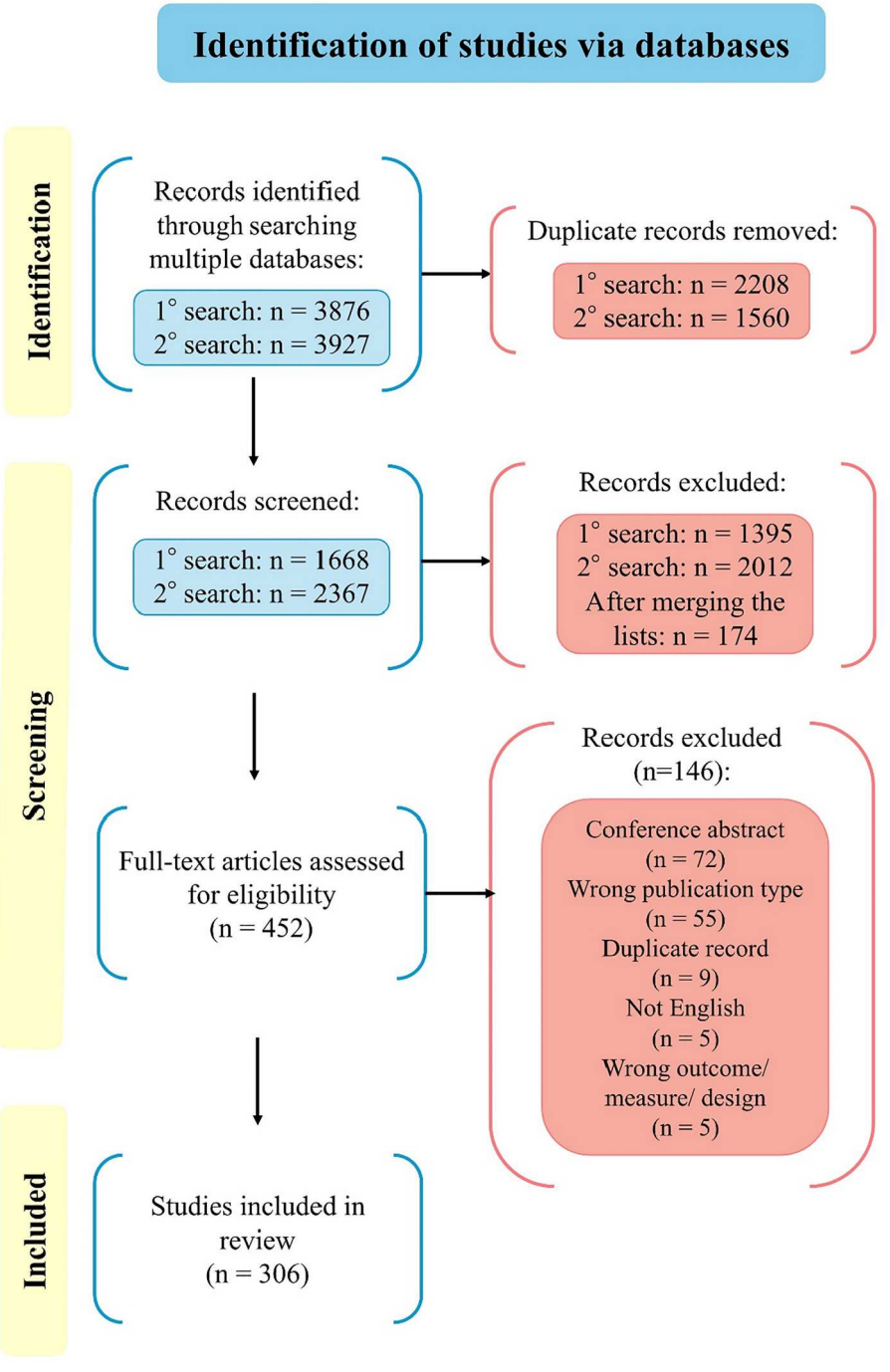

Figure 1. PRISMA flow chart.

MOK, SHM) screened studies in pairs, first by reading title and abstracts. Reasons for exclusion were reported on Rayyan. Disagreements were resolved by discussion and consensus. The full texts of potentially eligible articles were then read, and, if included, information was extracted. See Figure 1 in section 3.1 for the selection process.

2.5. Data collection

All data were extracted electronically in a pre-developed form using Microsoft Excel software (Microsoft Corporation, Seattle, USA). From each publication, we independently extracted bibliographic information, publication characteristics and other key information related to placebo and nocebo responses and effects. Bibliographic information included authors, title, journal, year of publication and Doi. Publication characteristics included the type of evidence (meta-analysis or systematic review) and topic (placebo/nocebo response or effect); the research setting of included studies (healthcare setting, lab setting, both); the field of research (e.g., medical specialties, psychology, neuroscience); the determinants and biological correlates; the publication aim; information about studies included in the review or meta-analysis (number of studies, sample size, age range/mean); the study population (healthy vs. clinical). When applicable, the investigated clinical condition, the type of intervention (e.g., pharmacological, psychological), control group (e.g., placebo, no treatment), outcomes (e.g., pain, anxiety, adherence) and outcome measures (e.g., rating scales, questionnaires), key findings and their interpretation were collected. Other important information including healthy individuals'/patients' beliefs and characteristics, experimenters'/practitioners' beliefs and characteristics, experimental condition and treatment characteristics, relationship (between experimenter/clinician and subject/patient), biological correlates, clinical implications, bioethical issues were collected to help discuss the main results.

2.6. Quality assessment

Quality assessment of included papers was performed using the R-AMSTAR checklist, a validated tool to assess the methodological quality of systematic reviews and meta-analyses (Kung et al., 2010). A total score of 11 indicates that none of the AMSTAR criteria were met across the established 11 domains. In contrast, a score of 44 indicates that all the criteria for systematic review excellence were confirmed in each domain (Kung et al., 2010). Due to the heterogeneity of the articles included in the scoping review and the potential exclusion bias resulting from the higher scores typically associated with meta-analyses of RCTs compared to systematic reviews, we opted to conduct a sensitivity analysis on the meta-analyses of RCTs instead of excluding studies based solely on their scores.

2.7. Synthesis of results

We use a narrative approach to report information from the included studies, in addition to summarising it in tables and figures, without attempting to aggregate findings from various studies, as this is not the aim of this scoping review. Where appropriate, we include graphical representations to visualise the data.

The selection of evidence is reported in the PRISMA flowchart (Moher et al., 2009). The number of publications by year is summarised in a trend chart. Descriptive statistics are used to report quality assessment and sensitivity analysis, the type of evidence (systematic reviews vs. meta-analyses) and topic (placebo /nocebo responses vs. effects), and the research setting (healthcare vs. lab setting). The fields of research and determinants are presented as a pie chart and a Sankey plot, respectively. The determinants of meta-analyses and systematic reviews are described separately, as these two types of research do not necessarily contain the same type of key information. The results associated with determinants influencing placebo and nocebo responses are presented in a summary table, whereas the biological correlates are presented in a narrative form. When possible, the pooled response rate (PRR, %), effect size (ES), including standard (Cohen's d or Hedges' g) or weighted mean difference (SMD, WMD), the prevalence of placebo-treated patients with at least one adverse event (AE) and placebo-treated patients who withdrew treatment due to AEs are reported. Outcomes and their measurement were quite heterogeneous, depending on the clinical conditions.

Describing each clinical outcome summarised in each review and meta-analysis was outside of the scope of this review. However, when results were split in multiple different outcomes that cannot be merged, we reported them separately. For example, clinical outcomes in diabetes patients were usually reported for both HbA1c (i.e., glycated haemoglobin, an index of the average blood sugar levels) and weight, two indices that cannot be merged in one single summary outcome.

3. Results

3.1. Selection of evidence

As shown in Figure 1, we identified a total of 3876 publications in the first search strategy and 3927 in the second search strategy. Following the removal of duplicates, these numbers were reduced to 1668 and 2367, respectively. Upon screening titles and abstracts for relevance, 452 papers underwent more detailed full-text evaluation. Of these, 146 were excluded for the reasons listed in Figure 1. Ultimately, 306 articles met the full inclusion criteria.

3.2. Study quality assessment

Quality assessment of the included reviews and meta-analyses is based upon R-AMSTAR checklist. The mean AMSTAR score is 27.83 ± 7.01 (range = 11–44), indicating overall moderate quality. Scores from 11 to 16, classified as Critically Low, encompass 17 publications (5.56%). Scores between 17 and 22 fell into the Low category, including 60 publications (19.61%). Publications with scores ranging from 23 to 33, categorised as Moderate, represent the largest group with 157 publications (51.31%). Finally, scores between 34 and 44 were classified as High, comprising 72 publications (23.53%). No differences are found between systematic reviews and meta-analyses containing RCTs ($N = 270$, $M = 28.10 \pm 7.09$) and other studies ($N = 36$, $M = 25.81 \pm 6.10$), $t(304) = 1.85$, $p = .06$. Therefore, results on the whole set of selected studies are presented. Sensitivity analyses results can be found in the Supplementary Materials.

3.3. Summary of evidence

3.3.1. Trends in publication of evidence

To visualise the trends in publication of systematic reviews and meta-analyses on placebo and nocebo responses and effects over time, we plotted the number of articles published by year against the years of publications. Figure 2 depicts the overall publication trends, encompassing both placebo and nocebo research collectively. Additionally, it showcases the comparative trends in placebo and nocebo publications (along with publications on both responses and effects), from the inception of the first published systematic review in 1995 to the most recent article available, at the time of our literature search, on April 11, 2023. As indicated in the figure, the number of systematic reviews or meta-analyses published annually was quite limited before 2008, with fewer than 10 articles per year. Despite notable fluctuations in the total number of publications each year, a gradual increase can be observed since 2008, with peaks in 2020 (23 articles) and 2022 (45 articles). When comparing the trends in publications addressing placebo research to those addressing nocebo research, it is evident that very few systematic reviews or meta-analyses on nocebo were published before 2014.

3.3.2. Types and topic of evidence

Of the 306 selected records, 254 were meta-analyses (83%) and 52 were systematic reviews (17%). Most of the records ($n = 270$, 88%) referred to placebo and nocebo responses in RCTs.

The distribution of publications on placebo and nocebo was assessed, highlighting the frequency and corresponding percentages of publications. 240 systematic reviews and meta-analyses on placebo were identified, constituting 78.43% of the total. Within this category, the majority focused on placebo responses (195 publications, 81.25%), followed by placebo effects (36

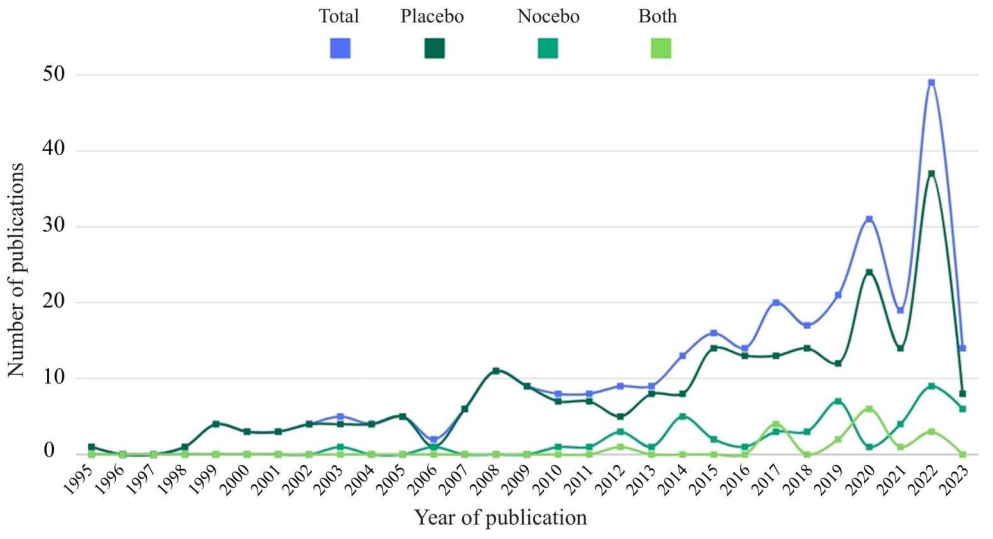

Figure 2. Trends in publication of systematic reviews and meta-analyses on placebo and nocebo.

Note: It should be noted that we only considered publications from January to April of 2023. As a result, the apparent decline in the number of publications may not reflect the actual trend, but rather the fact that we have only screened a portion of the literature for 2023.

publications, 15.00%), and a smaller subset addressing both responses and effects (9 publications, 3.75%). On the other hand, 49 systematic reviews and meta-analyses on nocebo were identified, representing 16.01% of the total. Among these, the predominant focus was on nocebo responses (41 publications, 83.67%), followed by publications investigating nocebo effects (8 publications, 16.33%). A subset of systematic reviews and meta-analyses examined both placebo and nocebo, comprising 17 publications, with placebo and nocebo responses being the primary focus in 11 publications (64.71%) and effects in 6 publications (35.29%).

3.3.3. Research setting

The selected meta-analyses and systematic reviews consist of placebo and nocebo studies across different research settings (i.e., the laboratory setting, the healthcare setting or both). The majority, accounting for 260 (84.97%), referred to studies within healthcare settings, reflecting a strong focus on real-world clinical scenarios. It is noteworthy that these publications predominantly analysed RCTs that investigated placebo responses. A total of 16 (5.23%) publications consisted of studies conducted in a laboratory setting, namely in a controlled experimental environment. Additionally, 30 publications (9.80%) were based on studies conducted in both laboratory and healthcare settings (e.g., medical centres and university hospitals) indicating a blended approach that encompasses controlled experimental conditions as well as practical healthcare settings.

3.3.4. Field of research

As shown in Figure 3, most systematic reviews and meta-analyses on placebo and nocebo fall under the umbrella of Medical Specialties, constituting 81.70% of the total, with a diverse range of disciplines within this category. Notably, Psychiatry emerges as a prominent field with 28.40% of the total, highlighting the substantial focus on placebo and nocebo responses and effects in mental health. Neurology follows closely with 24.20%, indicating a significant presence of studies within neurological research. Gastroenterology and Rheumatology also show notable engagement, contributing 14.00% and 7.20%, respectively. Other Medical Specialties such as Dermatology and Urology are also represented (3.60% and 3.20%, respectively). Among fields beyond Medical Specialties, Various disciplines (i.e., publications including studies on more than one medical specialty) account for 5.20%, followed by Psychology at 3.60%, and Neuroscience at 3.30%. Together these

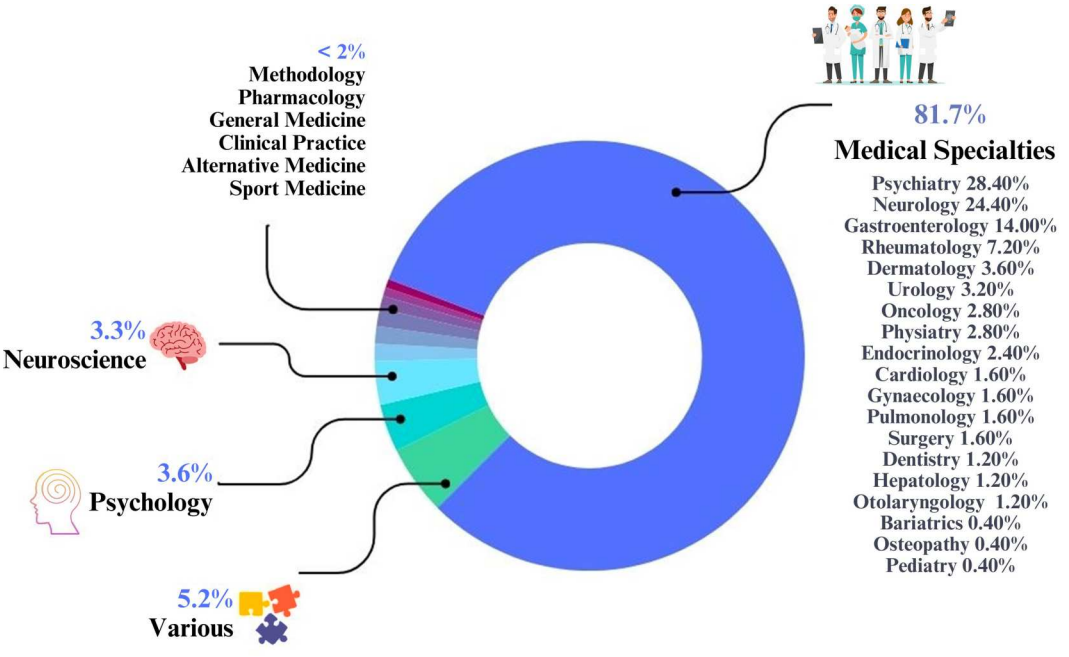

Figure 3. Pie chart of selected studies by field of research.

results reflect the interdisciplinary nature of research on placebo and nocebo responses and effects. Methodology, Pharmacology, General Medicine, Alternative Medicine, and Sport Medicine are less represented with less than 2.00% each. It is worth noting that there are only three systematic reviews providing data about the implementation of placebo and nocebo into Clinical Practice in general (i.e., not within specific specialties).

3.3.5. Determinants and biological correlates

Figure 4 illustrates the frequency and percentage of publications categorised by publication type, based on the determinants and biological correlates associated with placebo and nocebo effects.

Most systematic reviews and meta-analyses on placebo studies aimed to determine the magnitude of placebo responses by summarising the pooled response rate (PRR, %) or effect size (ES),

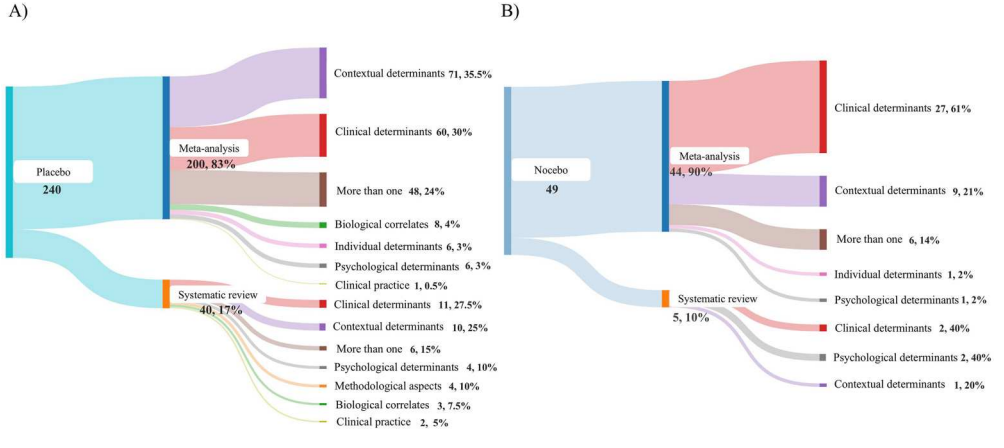

Figure 4. Sankey plot of publications on placebo (A) and nocebo (B) by publication type (*N*, %).

including standardised (Cohen's d, Hedges' g, SMD) or weighted (WMD) mean differences. PRR indicates the measured improvement of a patient in a clinical trial after receiving a placebo treatment, with higher values meaning a higher improvement. ESs are associated with patient health improvement (positive ES values) or symptom reduction (negative ES values) in the placebo arms in clinical RCTs compared to baseline (i.e., no treatment). Systematic reviews and meta-analyses on nocebo response studies aimed to determine the prevalence and magnitude of nocebo responses by determining the prevalence of placebo-treated patients with at least one adverse event (AE) and placebo-treated patients who withdrew treatment due to AEs. Systematic reviews and meta-analyses on nocebo effect studies, instead, report on the effect size of induced nocebo effects compared to control.

Table 2 reports narrative results of systematic reviews. Table 3 summarises the meta-analytic results for healthy and clinical patients by research field and condition. Only research field categories (see Figure 3) with a frequency of at least 3% are listed, except for Medical Specialties, which are all reported. When possible, results in the 'Various' category were sorted into the other categories according to the clinical conditions investigated. Finally, when these were measured in the original studies, individual, clinical, psychological and contextual determinants influencing results were reported.

Regarding individual factors, age appears as an individual determinant across multiple conditions. Younger age is associated with greater placebo and nocebo effects in obsessive-compulsive disorder (Mohamadi et al., 2023), schizophrenia (Agid et al., 2013; Fraguas et al., 2019; Leucht et al., 2018), bipolar disorder (Dodd et al., 2019), epilepsy (Rheims et al., 2008), neuropathic pain (Arakawa et al., 2015), genetically determined intellectual disability (Curie et al., 2015), fibromyalgia (Mitsikostas et al., 2012), asthma (Yang et al., 2014) and non-alcoholic steatohepatitis (Ng et al., 2022). Age seems to have less impact on placebo responses in gastroenterological diseases and with an opposite effect, as placebo responses increased with the mean age in participants with chronic idiopathic constipation (Nee et al., 2019). Similarly, older individuals with attention deficit hyperactivity disorder (ADHD) (Ramírez-Saco et al., 2022) and those with osteoporosis (Kravvariti et al., 2023) showed higher nocebo responses. The impact of sex appears less consistent. Reduced placebo responses and adverse event rates have been shown in bipolar (Yildiz et al., 2011) and depressive (Meister et al., 2017) disorders, in placebo arms with a greater proportion of men. Similarly, it has been found that women report more pain after a nocebo intervention (Bagarić et al., 2022; Vambheim & Flaten, 2017). Instead, increased placebo effects in pain (Vambheim & Flaten, 2017) and in itch (Lee et al., 2020) were found in studies with male predominance. Moreover, it has been found that the placebo effects in nausea (Quinn & Colagiuri, 2015) and pain (Vambheim & Flaten, 2017) varied depending on sex, with men more susceptible to suggestion and women to conditioning. Finally, only one systematic review took into consideration the role of the experimenter's or clinician's sex on placebo effect, showing that participants reported lower pain when tested by an experimenter of the opposite sex (Daniali & Flaten, 2019). However, only two studies included in the review investigated the role of experimenter/clinician sex on placebo/nocebo effects, showing no reliable tendency.

Clinical determinants such as baseline disease and symptom severity, disease duration and disorder subtype show relevance across various conditions, albeit with some distinctions. Higher placebo and nocebo responses correlate with lower baseline symptoms severity in schizophrenia (Fraguas et al., 2019; Palermo et al., 2019), depression (Papakostas & Fava, 2009) and in neuropathy (Arakawa et al., 2015; Jutzeler et al., 2018), but with greater severity of illness or symptoms in individuals with alcohol use disorder (Del Re et al., 2013), obstructive sleep apnoea (Labarca et al., 2023), arthritis (Erre et al., 2022), fibromyalgia (Chen et al., 2017) and atopic dermatitis (Lee et al., 2020). In gastroenterology, higher disease activity or a disease duration exceeding five years before enrolment were associated with lower placebo response rates (Jairath et al., 2017; Sedano et al., 2022). Higher entry scores (i.e., baseline symptom scores required for eligibility) were positively correlated with placebo response rates in Crohn's disease (Su et al., 2004); however, ulcerative colitis showed an

Table 2. Narrative results of systematic reviews across clinical conditions.

Field of research	Condition	Topic of evidence	Results	Individual determinants	Clinical determinants	Psychological determinants	Contextual determinants
Psychiatry	Mood disorders	Placebo	Despite evidence that placebo determinants may influence patient outcomes, antidepressant trials often fail to report on many of these, including the healthcare environment, practitioner characteristics, patient-practitioner interactions and non-pharmaceutical aspects of medication.[116]	None	None	None	None
Neurology	Headache	Nocebo	Placebo arms in anti-migraine medication RCTs showed high rates of adverse events, mirroring those of the active medication. These included anorexia and memory difficulties often associated with anticonvulsants, suggesting a link to the active medication's side effects. These findings support the expectation theory of placebo and nocebo effects and are unaffected by variables, such as race, age, weight, or migraine characteristics.[9]	None	None	None	None
Dermatology	Various cutaneous conditions	Placebo and Nocebo	Placebo and nocebo effects were induced via verbal suggestions, conditioning and social induction, but differences in study designs, conditioning paradigms, medical conditions and outcome measures, hinder comparability between studies. In healthy participants, outcomes were most consistent for self-reported itch and histamine responding. Self-reported and behavioural (e.g., scratching) outcomes were more consistent than physiological outcomes. Most studies focussed on atopic dermatitis and allergic rhinitis, while research on other conditions,	None	None	Placebo response/effect induction[185]	None

(*Continued*)

Table 2. Continued.

Field of research	Condition	Topic of evidence	Results	Individual determinants	Clinical determinants	Psychological determinants	Contextual determinants
			such as psoriasis and chronic urticarial was limited.[185]				
Physiatry	Pain	Placebo	Nine studies showed that sham oral, compared to sham laser, medications significantly improved average self-reported pain scores for non-specific LBP across acute, subacute and chronic conditions.[225*]	None	None	None	Route of administration[225*]
Otolaryngology	Burning mouth syndrome	Placebo	A positive placebo response was observed in 13 studies. In 7 of these, the placebo response was statistically equivalent to the active treatment. This effect was particularly strong in patients receiving the placebo compared to ALA in a crossover trial where the placebo preceded ALA.[141]	None	None	None	Active treatment type[141], trial design[141]
Psychology	Pain	Placebo	Experimenters/clinicians of the opposite-sex tended to induce lower pain reports. Greater confidence, competence, professionalism and positive nonverbal behaviours contributed to lower pain reports and higher placebo effects.[47*] Men showed a stronger response to placebo treatment, with larger placebo effects induced by verbal information.[275*]	Patients' sex[47*,275*], clinicians' sex[47*], clinicians' confidence[47*], clinicians' competence[47*], clinicians' professionalism[47*], clinicians' status[47*]	None	Nonverbal behaviours[47*], placebo response/effect induction[275*]	None
		Nocebo	Lower clinician status resulted in higher pain reports and stronger nocebo effects; negative nonverbal behaviours led to higher pain reports and increased nocebo effects.[47*] Females responded more strongly to nocebo interventions and showed larger nocebo effects induced by conditioning procedures.[275*]	Patients' sex[275*], clinicians' status[47*]	None	Nonverbal behaviours[47*], nocebo response/effect induction[275*]	None
	Various	Placebo	Optimism was relatively consistently associated with increased placebo responses.[138] The evidence supports strategies to enhance patient expectancies by (1)	Personality traits[138]	None	Patients' expectations[44]	None

			improving their expectations about medical procedures and teaching them how to cope with these, (2) strengthening their self-management skills and ability to communicate with health-care providers and (3) enhancing their belief in the benefits of effective treatments.[44]				
		Nocebo	Pessimism was relatively consistently associated with nocebo responses; fear and anxiety seem to increase the likelihood of perceiving negative treatment effects.[138]	Personality traits[138]	None	None	None
	Research with healthy participants	Placebo	Caffeine and nicotine expectancies typically reduce cravings; where expecting caffeine tends to improve accuracy, the effects on reaction time are unclear.[81]	None	None	Expectations[81]	None
		Nocebo	Believing one is under the influence of alcohol may increase cravings, but the differential effects between alcohol and placebo is unclear; alcohol expectancies result in similar cognitive performance, slower reaction times and impaired inhibitory control, compared to actual alcohol use; nicotine expectancies improve attentional filtering of distractor stimuli.[81] The nocebo response varied based on learning circumstances, expectations, emotional state and participant characteristics. It can be reduced or prevented through latent inhibition, positive mood induction, or a previous placebo induction.[15*]	Patients' sex[15*]	Presence of anxiety or depression[15*]	Expectations[15*,81], emotional state[15*], nocebo response/ effect induction[15*]	Conditioning duration[15*], generalisation[15*]
Various	Various	Placebo	Placebo interventions are most effective at reducing nausea in people with high expectations or existing symptoms, especially when accompanied by convincing instructions. Purely instructional effects are harder to	Patients' sex[227]	None	Patients' expectations[227], placebo response/ effect induction[227]	None

(*Continued*)

Table 2. Continued.

Field of research	Condition	Topic of evidence	Results	Individual determinants	Clinical determinants	Psychological determinants	Contextual determinants
			achieve, with combined or conditioning manipulations generally proving more effective.[227]				
		Nocebo	Many studies focused on the psychomotor performance of healthy individuals. A subset reported nocebo effects, which were prominent in studies of healthy people's sports performance. In Parkinson's disease, the nocebo effect only influenced reaction time, but not finger tapping or diadochokinesia.[108*]	None	None	None	Nocebo agent[108*], trial design[108*]

Note: *Placebo or nocebo effects (i.e., involving no-treatment or natural history control conditions).
The numbers associated with the results refer to the systematic reviews from which the data were extracted; the full list with corresponding numbers can be found in the Supplementary Materials.
Abbreviations: ALA = Alpha Lipoic Acid; LBP = Low Back Pain.

Table 3. Magnitude of placebo and nocebo effects/response across clinical conditions.

Field of research	Condition	Topic of evidence	Results	Individual determinants	Clinical determinants	Psychological determinants	Contextual determinants
Psychiatry	Mood disorders	Placebo	Pooled response rate: - Depression: 30–50%[24,40,79,120,121,140,163,188,189,209,217,257,282] - Bipolar disorder: 31–39%[17,267,294] Pooled effect size: - Depression: d = 0.80–1.85[25,236] g = 0.33–1.60[230,246,28,171,131]; SMD = 0.17–1.22[67,69,159], SMD = −2.51[23] - Bipolar disorder: g = 0.29[28]	Patients'age[294], patients' sex[294]	Baseline disease severity[23,24,217], depression onset[189] depression type[236], refractoriness[25]	None	Number of sites[79,159,163,188,294], publication year[131,159,163,217,282], probability of receiving placebo[67,189,209,217], trial duration[79,159], subj. vs obj. measures[188,236], funding source[131,163], country[163,159] sample size[189], placebo type[198], hospitalisation length[198], run-in period[246], comparator drug[23], number of failed interventions[131], number of sites[24]
		Nocebo	AE rate: - Depression: 45–76%[36,57,189,195] - Bipolar disorder: 68%[58] Drop-out rate: - Depression: 4–5%[57,189,195,297]	Patients' age[58], weight[58], patients' sex[189]	Depression onset[189]	Patients' expectations (treatment naïve vs experienced)[58]	Country [58], study phase [58], publication year[189]
	Anxiety-related disorders	Placebo	Pooled response rate: - Social phobia: 23%[212] - Anxiety: 38–40%[40,56] - OCD: 31%[40] Pooled effect size: - Anxiety: g = 1.03[171]; SMD = 0.45–1.01[69,159] - OCD: g = 0.50–0.60[171,264]; SMD = 0.58[159]; d = 0.32[197] - Panic disorder = d = 0.57[2]	Patients' age[197]	None	None	Measurement tools[2,197], number of site[56,212], subj. vs obj. measures[2], analysis methods[197], publication year[2], funding source[56], country[56], sample size[212]

(*Continued*)

Table 3. Continued.

Field of research	Condition	Topic of evidence	Results	Individual determinants	Clinical determinants	Psychological determinants	Contextual determinants
	Schizophrenia	Placebo	Pooled response rate: 21.3%[51] Pooled effect size: g = 0.13–0.64[28,46]; d = 2.91[75]; SMD = −0.33[1]	Patients' age[1,75,157]	Baseline severity of positive symptoms[75], disease duration[1]	None	Trial duration[46,75,182,288], sample size[75,157], ratio of patients assigned to active vs. placebo arm[46], active arm number[75], funding source[75], publication year[75], number of site[75], number of country[182], country[75], treatment setting[182]
		Nocebo	AE rate: 66.3%[214] Drop-out rate: 5–7%[214,297]	None	Level of psychiatric symptomatology[214]	None	None
	ADHD	Placebo	Pooled response rate: 23–33%[30,207] Pooled effect size: SMD = −0.36 – −0.75[66]	Patients' ethnicity[207]	Inattentive subtype[207], presence of comorbidities[207], baseline disease severity[66]	None	Publication year[30,66], country[30], raters[66], lack of previous stimulant treatment[207]
		Nocebo	AE rate: 55.5%[229] Drop-out rate: 2.4%[66]	Patients' age[229]	None	None	Treatment duration[229], AE collection method[229], active treatment type[229], psychotherapy[229], raters[66]
	Substance use disorders	Placebo	Pooled effect size: g = 0.90[53]	None	Baseline disease severity[53]	None	Subj. vs obj. measures[53], treatment duration[53], administration frequency[53]
		Nocebo	Drop-out rate: 3.5%[297]	None	None	None	None
	Pervasive development disorders	Placebo	Pooled response rate:19%[252] Pooled effect size: g = 0.45[181]	None	Baseline irritability level[252], response to active intervention[181]	None	Raters (caregiver vs. clinicians)[252,181], risk of bias[252], dosing regimen[252], sample size[252], number of site[252], publication year[252], use of symptoms threshold[252], active treatment type[181], country[181]
Neurology	Epilepsy	Placebo	Pooled response rate: 10% – 17%[27,90,233]	Patients' age[233]	Active arm efficacy[90]	None	None
		Nocebo	AE rate: 60–61%[296,303] Drop-out rate: 1–6%[233,296,297,303]	Patients' age[233]	None	None	None
	Headache	Placebo	Pooled response rate: - CM: 24% – 68%[71,142] - EM: 24% – 66%[68,71,142] - Migraine: 21% – 38%[50,89,172,177,178,187]	None	None	None	Trial design[68,177,178], country[68,177,178], route of administration[50,178,266]

		Pooled effect size: - Migraine: SMD = −1.76[266]				
	Nocebo	AE rate: - EM: 18– 33%[142,194,299] - Migraine: 10 - 30%[172,177,232] Drop-out rate: - EM: 0–10%[142, 194,297,299] - CM: 1%[142]	None	None	None	Country[177]
Neurodegenerative diseases	Nocebo	AE rate: - Multiple sclerosis: 25% – 89%[86,215] - Motor neuron disease: 78.3%[248] - Parkinson's: 56–65%[151,258] - Multiple system atrophy: 64.2%[283] - Cerebellar ataxia: 13.8%[4] Drop-out rate: - Parkinson's: 5–10%[151, 222, 258,297] - Motor neuron disease: 8.4%[248] - Multiple system atrophy: 7.5%[283] - Cerebellar ataxia: 4.8%[4]	None	None	None	Trial design[215,86], sample size[258], publication year[258], treatment duration[258]
Neuromuscular disorders	Placebo	Pooled response rate: - Restless legs syndrome: 40.09%[78] Pooled effect size: - Restless legs syndrome: g = −1.41[253] - Myasthenia gravis: d = 0.24[76]	None	None	None	Trial duration[253,78], funding source[253], subj. vs. obj. measures[253]
	Nocebo	AE rate: - Myasthenia gravis: 80.1%[278] - Restless legs syndrome: 45.36%[253]	None	None	None	None

(*Continued*)

Table 3. Continued.

Field of research	Condition	Topic of evidence	Results	Individual determinants	Clinical determinants	Psychological determinants	Contextual determinants
			Drop-out rate: - Myasthenia gravis: 2.4%[278]				
	Neuropathy	Placebo	Pooled response rate: - HIV pain: 35% – 43%[31,137] - DPN: 18–27%[12,31,137,274] - p-Nep: 23%[12] - PHN: 11 −19%[12,31] - PT: 15%[12] - c-NeP: 14%[12] Central pain: 7.2%[31] Pooled effect size: Neuropathic pain: SMD = -0.62[134]	Patients' age[12], patients' sex[134]	Baseline pain[12,134], time course[274]	None	Treatment duration[12], dosing regimen[12], active treatment type[31]
		Nocebo	AE rate: Neuropathic pain: 52%[216] CIDP: 42%[302] Drop-out rate: Neuropathic pain: 6%[216, 297] DPN: 5.8%[98] CIDP: 2.1%[302]	None	None	None	None
	Chronic fatigue syndrome	Placebo	Pooled response rate: 9.6%[38]	None	None	None	Active treatment type[38]
	Sleep-related disorders	Placebo	Pooled response rate: Insomnia: 63–74%[127,129,291] Pooled effect size: Insomnia: d = 0.70–1.61[100,184]; g = 0.27–0.66[128,293*]; SMD = −0.09 – −0.36[203]; SMD = 0.30–0.54[203] Obstructive sleep apnoea: SMD = −1.88 – −2.84[148]	None	Baseline hypersomnia[148]	None	Subj. vs obj. measures[100,128,148,184,203,293*], treatment duration [128,129], placebo type[148], publication year[128], sample size[128], dosing regimen[128]
	Intellectual disability	Placebo	Pooled effect size: g = 0.47[45]	IQ level[45], patients' age[45]	Presence of dementia[45]	None	Subj. vs. obj. measures[45]
	Stroke	Placebo	Pooled effect size: g = 0.47[130]	None	None	None	None

Gastroenterology	- Bowel disorders	Placebo	Pooled response rate: - Crohn's disease: 16–56%[6,73,89,123,218,262] - IBS: 36–43%[20,59,63,70,72,219,221] - AP-RFGD: 41%[104] - Colitis: 20–34%[83,95,122,124,176,247,263] - Constipation: 13–29%[34,206] Pooled effect size: - Constipation: SMD = 0.71–1.29[269] - Faecal incontinence: SMD = −1.26 – −1.53[269]	Patients' age[206], patients' sex[206]	Entry score [122,176,262,247], disease duration before enrollment[122,124,176], disease activity[89,122,263], baseline symptoms severity[6,206], baseline disease severity[122], presence of comorbidities[70]	None	Trial design[20,122,123,124,176,247], number of visits[6,59,73,262,263], treatment duration[59,72,73,104], country[20,72,83], trial duration[83,221], active treatment type[218], subj. vs obj. measures[72], outcome definition rigidity[263], diary keeping[83], follow-up duration[6], publication year[20], dosing regimen[20], sample size[20], run-in period duration[20], intervention frequency[221]
		Nocebo	AE rate: - IBS: 32% – 71%[162,174] Drop-out rate: - IBS: 5%[87]	None	None	None	Trial design[174]
	Functional dyspepsia	Placebo	Pooled response rate: 40–44%[21,114] Pooled effect size: SMD = −0.32 – −0.54[169]; WMD = −0.11 – −3.35[169]	None	None	None	Trial duration[114], assessment frequency[114], responder definition[21]
		Nocebo	Drop-out rate: 7%[87]	None	None	None	None
	Oesophageal disorders		Pooled response rate: - Gastro-oesophageal reflux disease: 18.85%[43] - Esophagitis: 4–14%[175,213]	None	Esophagitis type [43], natural disease history[175]	None	Outcome parameters (histological vs symptomatic)[175,213], PPI therapy at baseline[175,43]
	Ulcer	Placebo	Pooled response rate: 36–44%[49]	None	None	None	Dosing regimen[49]
Rheumatology	Arthritis	Placebo	Pooled response rate: - JIA:17–55%[54] - Osteoarthritis: 30–44%[115] - Rheumatoid arthritis (ACR20): 29–33%[18,204,265] - Psoriatic arthritis: 20.3%[62] - Knee osteoarthritis: 47–52%[224]	None	Rate of patient with systemic JIA at enrollment[13], baseline symptom severity[298]	Patients' expectations (blinded vs open placebo)[298]	Route of administration[16,204,298], subj. vs obj. measures[115, 298], publication year[62,204], country[204], active treatment strength[298], sample size[298]

(*Continued*)

Table 3. Continued.

Field of research	Condition	Topic of evidence	Results	Individual determinants	Clinical determinants	Psychological determinants	Contextual determinants
			Pooled effect size: - Osteoarthritis: g = 0.12–0.77[16, 298]				
		Nocebo	AE rate: - Rheumatoid arthritis: 44–54%[249,265]	None	None	None	None
	Fibromyalgia	Placebo	Pooled response rate: 18.6%[94] Pooled effect size: SMD = 0.42–0.52[35*,99]	Patients' age[35*], patients' sex[35]	Disease duration[35*], baseline pain[35*]	None	Active treatment strenght[35*]
		Nocebo	AE rate: 67.2%[193] Drop-out rate: 9–11%[94,98,193]	Patients' age[193]	Presence of other conditions[193]	None	Sample size[193]
Dermatology	Chronic inflammatory skin diseases	Placebo	Pooled response rate: - Atopic dermatitis: 6–39.9%[5,11,152] - Hidradenitis suppurativa: 10–30%[5] - Psoriasis: 0–5%[5,10,149] Pooled effect size: - Chronic idiopathic urticaria: SMD = 1.71[276] - Psoriasis: SMD = 1.04[276] - Atopic dermatitis: SMD = 0.75[276]	Patients' sex[152]	Itch severity at baseline[152]	None	Trial design[152], trial duration[152], active arm number[152], concomitant topical therapy[152]
		Nocebo	AE rate: - Psoriasis: 52–53%[3]	None	None	None	None
	Allergic skin diseases	Placebo	Pooled response rate: 32%[5]	None	None	None	Subj. vs obj. measures[5]
Urology	Urinary conditions	Placebo	Pooled effect size: - Overactive bladder: SMD = −0.45 – −1.18[96,201]	Patients' age[201]	None	None	None
		Nocebo	AE rate: 3–5%[202]	None	None	Patients' expectations (previous medications)[202]	None

	Sexual dysfunctions	Placebo	Pooled effect size: - Erectile dysfunction: g = 0.35[260]	None	Presence of PTSD[260]	None	None
Oncology	Cancer	Placebo	Pooled response rate: - Cancer-related fatigue: 29%[133] - Cancer: 1%[26]	None	Cancer type[26,170]	None	None
		Nocebo	AE rate: 85–95%[170,238,254] Drop-out rate: 2–4%[231,238,254]	None	None	None	None
Physiatry	Pain	Placebo	Pooled response rate: - LBP: 20–53%[61,125] Pooled effect size: - LBP: SMD = −0.19 – −2.71[261*] - Neck pain: d = 1.03[113]	None	None	None	Follow-up time[261*]
Endocrinology	Diabetes	Placebo	Pooled effect size: - T1DM: WMD $_{HbA1c}$ = −0.06[164]; WMD $_{weight}$ = 0.33[164] - T2DM: WMD$_{HbA1c}$ = −0.12 – −0.26[52,91,101,164]; WMD $_{weight}$ = −0.40 – −1.33[52,91,160,164]	Patients' age[164], patients' sex[164]	Diabetes duration[164], diabetes type[164]	None	Route of administration[52,164], country[101]
		Nocebo	AE rate: 18–75%[52]	None	None	None	Route of administration[52]
	Osteoporosis	Nocebo	Drop-out rate: 8%[145]	Patients' age[145]	None	None	None
Cardiology	Hypertension	Placebo	Pooled effect size: g = −0.27 – −0.49[290]	None	None	None	Study quality[290], number of site visits[290]
Gynaecology	Menopause	Placebo	Pooled effect size: SMD = −24.38 – −51.2[161,196]	BMI[196]	Presence of breast cancer[196]	None	Active treatment type[161], treatment duration [196], active arm number[196]
	Sexual dysfunction	Placebo	Pooled effect size: WMD = 3.62[287]	None	None	None	None
Pulmonology	Asthma	Placebo	Pooled response rate: 34–51%[228,292] Pooled effect size: WMD = 0.11[132]	Patients' age[292]	FEV1 at baseline[292]	None	Season of treatment[292], subj. vs obj. measures[228]

(*Continued*)

Table 3. Continued.

Field of research	Condition	Topic of evidence	Results	Individual determinants	Clinical determinants	Psychological determinants	Contextual determinants
	Allergic rhinitis	Placebo	Pooled response rate: 57%[228]	None	None	None	Subj. vs obj. measures[228]
	Cough	Placebo	Pooled effect size: SMD = −0.94[155]	None	Cough type[155]	None	Treatment duration[155]
	Cystic fibrosis	Placebo	Pooled effect size: SMD_{BMI} = 0.09[41]	None	None	None	None
Surgery	Various	Placebo	Pooled effect size: SMD = 0.13–0.55[136,284,285]	None	None	None	Subj. vs obj. Measures[284,285]
Dentistry	Pain	Placebo	Pooled response rate: 10–29%[14,223]	None	None	None	Active treatment type[223]
		Nocebo	AE rate: 22.8%[286] Drop-out rate: 0.24%[286]	None	None	None	None
Hepatology	Pancreatitis	Placebo	Pooled response rate: 19.9%[29]	None	None	None	Trial design[29], run-in period[29], washout period[29]
	Non-alcoholic steatohepatitis	Placebo	Pooled response rate: 11.65–33%[173,208]	Patients' age[208], ethnicity[208]	None	None	None
		Nocebo	AE rate: 68%[271] Drop-out rate: 3.1%[271]	None	None	None	Study phase[271], funding source[271]
Otolaryngology	Meniere disease	Nocebo	AE rate: 42.3%[55]	None	None	None	None
	Burning mouth syndrome	Placebo	Pooled response rate: 72%[147]	None	None	None	None
Bariatrics	Obesity	Placebo	Pooled response rate: 20.4%[37]	None	Presence of diabetes[37]	None	Trial duration[37]
		Nocebo	AE rate: 73.7%[37] Drop-out rate: 5.2%[37]	None	None	None	None
Various	Various	Placebo	Pooled effect size: - OLP vs controls: SMD = 0.72–0.88[33*,280*] - Chronic peripheral diseases: g = 0.21[186*]	None	None	None	Control condition[280*], outcome parameters[186*]
		Nocebo	AE rate: - Sham TMS: 13.6%[304] Drop-out rate: - Sham TMS: 2.7%[304]	None	None	None	Coil type[304]

Psychology	Pain	Placebo	Pooled effect size: d = 0.45–1.37[244*,279*]; g = 0.64–1.73[74,84]	None	None	Placebo response/ effect induction[279*]	Clinical vs exp. study [244*,279*], pain induction[244*]
		Nocebo	Pooled effect size: g = 0.62–1.03[220*] Drop-out rate: 6.1%[297]	None	None	None	Nocebo induction[220*]

Note. *Placebo or nocebo effects (i.e., involving no-treatment or natural history control conditions).

Scores are reported from highest to lowest within each condition. Larger values indicate a stronger placebo or nocebo response or a larger placebo or nocebo effect. The numbers associated with the results refer to the meta-analyses from which the data were extracted; the full list with corresponding numbers can be found in the Supplementary Materials. Abbreviations: ACR20 = American College of Rheumatology 20% improvement; AE = adverse event; AP- RFGD = Abdominal Pain-Related Functional Gastrointestinal Disorders; CIDP = chronic inflammatory demyelinating polyneuropathy; CM = chronic migraine; c-NeP = central neuropathic pain; d = Cohen's d; DGBI = disorders of gut-brain interaction; DMT = disease-modifying treatments; DPN = diabetic polyneuropathy; EM = episodic migraine; FEV1 = forced expiratory volume in 1 sec; g = Hedges' g; IBS = irritable blow syndrome; JIA = Juvenile Idiopathic Arthritis; LBP = low back pain; OCD = obsessive compulsive disorder; OLP = open label placebo; PHN = postherpetic neuralgia; p-NeP = peripheral neuropathic pain; PT = post-traumatic peripheral neuropathic pain; PTSD = post-traumatic stress disorder; RCT = randomised controlled trial; SMD = standardised mean difference; ST = symptomatic treatments; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus; TMS = transcranial magnetic stimulation; WMD = weight mean difference.

opposite trend, with lower endoscopy scores correlating with higher placebo response rates (Jairath et al., 2017; Sedano et al., 2022).

Systematic reviews, compared to meta-analyses, provide more in-depth insight into psychological determinants. Notably, the way placebo effects are induced (i.e., through processes such as verbal suggestions, conditioning, or social learning) significantly impacts placebo and nocebo responses, yet variations in study designs, including differences in instructions and conditioning paradigms, complicate comparability of effect sizes across studies (Meeuwis et al., 2020; Petersen et al., 2014; Vase et al., 2002). It has been shown that higher placebo responses often occur in individuals with high positive expectations or existing symptoms, with combined or conditioning manipulations proving more effective (Quinn & Colagiuri, 2015). An extensive systematic review reported evidence for a global influence of positive outcome expectancy on treatment enhancement (Crow et al., 1999). Additionally, patients' expectations were highlighted as a psychological determinant influencing nocebo response in psychiatric and urological conditions: being treatment-naive (Dodd et al., 2019) was protective against adverse events, while having already received the same medications (Mostafaei et al., 2022) facilitated adverse events. Finally, it has been shown that unawareness of an inert treatment is crucial to trigger a more pronounced placebo effect (Zhang et al., 2008), while meta-analyses on open-label placebo indicate that deception might not be necessary to trigger placebo effects (Charlesworth et al., 2017; von Wernsdorff et al., 2021).

Contextual determinants associated with the RCT context, such as trial duration, trial design, sample size, the number of study sites, frequently influence placebo and nocebo responses. Trial duration was positively associated with the magnitude of placebo improvement in depression (Furukawa et al., 2016; Li et al., 2019), atopic dermatitis (Lee et al., 2020), restless legs syndrome (Fulda & Wetter, 2008; Silva et al., 2017), irritable bowel syndrome (Pitz et al., 2005), ulcerative colitis (Garud et al., 2008) and obesity (Chin et al., 2022). However, greater placebo improvement was found to be associated with shorter trial duration in schizophrenia (Agid et al., 2013; Czobor et al., 2022; Matsusaki et al., 2018; Welge & Keck, 2003) and functional dyspepsia (Huang et al., 2021). It has been shown that placebo and nocebo response rates in migraine were notably higher in studies with a parallel design compared to cross-over studies (Fernandes et al., 2008; Macedo et al., 2006, 2008; Papadopoulos & Mitsikostas, 2010), and that response rates vary depending on whether trials are designed for induction or maintenance, with higher rates observed in induction colitis trials (Jairath et al., 2016, 2017; Macaluso et al., 2019; Sedano et al., 2022). Moreover, the larger the trial, as reflected by either the number of participants or the number of study sites, the higher was the response to placebo and the nocebo drop-out rate across conditions (Bosman et al., 2021; Bridge et al., 2009; Dobson & Strawn, 2016; Fraguas et al., 2019; Leucht et al., 2018; Meister et al., 2017; Mitsikostas et al., 2012; Oosterbaan et al., 2001; Siafis et al., 2020; Zhang et al., 2008). Interestingly, the higher probability of receiving the most effective treatment increases the magnitude of placebo effects in arthritis (Zhang et al., 2008), fibromyalgia (Chen et al., 2017), chronic fatigue syndrome (Cho et al., 2005), menopause (Li et al., 2017) and dentistry (Porporatti et al., 2019) trials. The route of administration affects responses in several clinical conditions as well. In diabetes (de Wit et al., 2016; Lin et al., 2020), migraine (de Craen et al., 2000; Macedo et al., 2006; Swerts et al., 2022) and arthritis (Bannuru et al., 2015; Nagai et al., 2020; Zhang et al., 2008) trials, injectable placebo compared to oral or topical placebos was associated with higher placebo responses. Additionally, it has been observed that the placebo response rate increases with more frequent visits in gastroenterology (Almradi et al., 2022; Dorn et al., 2007; Su et al., 2004, 2007) and cardiology (Wilhelm et al., 2016).

Finally, the choice between subjective and objective outcome measures can impact results, with less subjectivity usually resulting in smaller observed effects, for example in conditions such as asthma (Radziwill & Kruszewski, 2011), allergic rhinitis (Radziwill & Kruszewski, 2011), alcohol use disorders (Del Re et al., 2013), restless leg syndrome (Silva et al., 2017), osteoarthritis (Huang et al., 2019; Zhang et al., 2008), allergic skin diseases (Ali et al., 2020) and surgical trials (Wartolowska et al., 2016, 2017). In sleep-related disorders, some meta-analyses report greater placebo responses when self-report measures are used (Labarca et al., 2023; McCall et al., 2003; Yeung et al., 2018), while others indicate smaller placebo responses in subjective compared to objective measures

(He et al., 2020), or no differences (Jiang et al., 2020; Muench et al., 2022). It is noteworthy that, within subjective measurement in psychiatric disorders, discrepancies exist between observer ratings and self-ratings when assessing clinical outcomes, as clinician-rated evaluations yielded higher placebo response rates compared to patient-reported data (Ahmadzad-Asl et al., 2022; Meister et al., 2020; Rief et al., 2009).

Most of the results of systematic reviews and meta-analyses on neurobiological correlates of placebo and nocebo effects were based on neuroimaging studies of experimentally induced acute pain. During painful stimulation, placebo effects, compared to controls (e.g., the same inert substance without expected pain relief), lead to reliable reductions in activation in regions linked to pain processing, including the dorsal anterior cingulate, thalamus and insula (Amanzio et al., 2013; Atlas & Wager, 2014; Zunhammer et al., 2021). Additionally, consistent reductions are observed in affect- and valuation-associated regions such as the amygdala and striatum (Atlas & Wager, 2014). Notably, there are increases in activation in various brain regions, including the prefrontal cortex (encompassing dorsolateral, ventromedial and orbitofrontal cortices), which are involved in cognitive and emotional processes, the midbrain surrounding the periaqueductal grey, which is crucial in the descending pain modulation system, and the anterior cingulate, which handles the affective and evaluative aspects of pain (Amanzio et al., 2013; Atlas & Wager, 2014; Romanella et al., 2023; Zunhammer et al., 2021). The right ventral striatum shows placebo-specific concordance, while the dorsal anterior cingulate cortex (dACC), left posterior insula, and left parietal operculum exhibit nocebo-specific concordance (Fu et al., 2021). Meta-analyses on clinical conditions showed that placebo responses in depression are mainly associated with activity in the dorsal prefrontal cortex, rostral anterior cingulate and ventral striatum (Burke et al., 2022; Huneke et al., 2022). In Parkinson's disease, motor improvement is dependent on the activation of the entire nigrostriatal pathway induced by dopamine release in the dorsal striatum, whereas placebo-induced motor improvement is modulated by an expectancy of improvement, which is instead related to the release of dopamine within the ventral striatum (Quattrone et al., 2018). Finally, it has been shown that in healthy participants, the endogenous opioid, endocannabinoid and vasopressinergic systems were peripherally involved in placebo effects (Skyt et al., 2020; Ter Riet et al., 1998).

4. Discussion

Considering the critical role of placebo and nocebo responses and effects in healthcare, it is essential to comprehensively understand the existing literature to support evidence-based clinical practice and guide future research endeavours. This scoping review synthetised the most robust scientific evidence, namely meta-analyses and systematic reviews, to explore the individual, clinical, psychological and contextual determinants influencing placebo and nocebo responses and effects. Specifically, this discussion will focus on the unique contributions of this scoping review, emphasising the key determinants influencing placebo and nocebo responses and effects that are highlighted in the literature, identifying underinvestigated topics, and highlighting the clinical relevance of our findings through actionable recommendations.

4.1. Summary of studies characteristics

We identified 306 meta-analyses and systematic reviews, published between 1995 and 2023 that were overall evaluated as being of moderate quality. Most selected records were meta-analyses (270), primarily focusing on randomised controlled trials (RCTs). A relatively limited number of studies focused on nocebo compared to placebo, suggesting a potential gap in understanding the determinants underlying the nocebo phenomena. Moreover, a significant portion of systematic reviews and meta-analyses focused on placebo and nocebo responses, while fewer investigated placebo and nocebo effects. This distribution highlights a predominant clinical interest in understanding how individuals perceive and respond to placebo treatment and to contextual factors.

It also emphasises the exploration of negative outcomes associated with expectations of harm, often without controlling for a variety of artefacts, such as regression to the mean and the natural history of the disorder. The high volume of RCTs, which routinely include placebo arms as part of their design, significantly contributes to the abundance of available literature for meta-analyses on placebo responses.

Moreover, the frequency distribution of the field of research suggests a robust interest in understanding placebo and nocebo responses and effects across various healthcare disciplines with most of the studies falling under the category of medical specialties. Psychiatry and neurology emerged as prominent fields, reflecting a significant focus on mental health aspects, but gastroenterology, rheumatology, and dermatology were quite represented as well. Additionally, the involvement of disciplines such as psychology and neuroscience underscores the complex nature of placebo and nocebo concepts. Conversely, the general implementation of placebo and nocebo effects into clinical practice is poorly investigated in systematic reviews and meta-analyses.

4.2. Determinants of placebo and nocebo

To understand the nuances of placebo and nocebo responses and effects across various clinical conditions, we delved into the individual, clinical, psychological and contextual determinants that may influence them.

First, findings suggest that individual determinants like age and sex significantly affect susceptibility to placebo and nocebo responses across conditions. Younger age is generally linked to greater placebo and nocebo responses in psychiatric conditions (Agid et al., 2013; Dodd et al., 2019; Fraguas et al., 2019; Leucht et al., 2018; Mohamadi et al., 2023). However, in chronic idiopathic constipation (Nee et al., 2019) and osteoporosis (Kravvariti et al., 2023), older age shows stronger responses, indicating disease-specific age effects. It's worth noting that larger responses may also reflect age-related differences in disease progression. Sex differences are also disease-specific but less consistent. While some studies report reduced placebo responses in bipolar (Yildiz et al., 2011) and depressive (Meister et al., 2017) disorders with more male participants, others suggest women report more pain following nocebo treatments (Bagarić et al., 2022; Vambheim & Flaten, 2017). These findings emphasise the need to consider factors like patient' s age and sex in clinical trials and treatment, as tailoring interventions based on these characteristics may improve treatment outcomes and patient care.

Clinical determinants significantly influence placebo and nocebo responses across conditions. For instance, it's important to consider baseline symptom severity and illness severity, as both have been shown to correlate with placebo and nocebo responses in different ways, depending on the clinical condition (Arakawa et al., 2015; Chen et al., 2017; Del Re et al., 2013; Erre et al., 2022; Fraguas et al., 2019; Jutzeler et al., 2018; Labarca et al., 2023; Lee et al., 2020; Palermo et al., 2019; Papakostas & Fava, 2009). For example, in gastroenterology, thorough patient evaluation in clinical trial enrolment is key as patients with more active disease or long disease duration generally exhibit lower placebo response rates in bowel disorders (Jairath et al., 2017; Sedano et al., 2022), while higher baseline severity correlates with stronger placebo responses in Crohn's disease (Su et al., 2004) and lower responses in in colitis (Jairath et al., 2017; Sedano et al., 2022). These findings highlight the importance of clinical characteristics in shaping placebo and nocebo responses, as symptomatology and disease severity influence patient expectations and treatment outcomes (Benedetti, 2008; Enck et al., 2013; Kaptchuk & Miller, 2015), guiding more personalised therapeutic interventions.

Although psychological determinants play a significant role in placebo and nocebo responses and effects according to the literature, they are often inadequately explored in meta-analytic studies. This may be due to the primary focus of meta-analyses on RCTs, which typically lack comprehensive data on psychological variables (Hughes et al., 2012). Systematic reviews provide more insight into psychological determinants. Notably, the way placebo effects are induced (i.e., through processes such as verbal suggestions, conditioning, or social learning) significantly

impacts placebo and nocebo responses, yet variations in study designs, including differences in instructions and conditioning paradigms, complicate comparability of effect sizes across studies (Meeuwis et al., 2020; Petersen et al., 2014; Vase et al., 2002).

Individuals with high expectations or existing symptoms often show stronger placebo responses and effects, especially when using conditioning manipulations (Quinn & Colagiuri, 2015). Indeed, positive outcome expectancy is crucial in enhancing treatment effects, emphasising the importance of improving patients' understanding of treatment (Crow et al., 1999). For example, in psychiatric and urological conditions, treatment-naïve patients (i.e., individuals who have never received any prior treatment for a specific condition or disease) were less likely to experience nocebo effects (Dodd et al., 2019), while prior treatment increased adverse events due to sensitisation and conditioning (Colloca et al., 2008; Mostafaei et al., 2022). Finally, expecting active treatment, even when receiving an inert one, produces stronger placebo effects, highlighting again the role of patient expectations in influencing outcomes (Zhang et al., 2008). However, meta-analyses show that open-label placebos (OLPs), where patients know they are receiving a placebo, can still improve clinical outcomes without deception (Charlesworth et al., 2017; von Wernsdorff et al., 2021), suggesting OLP may work through different mechanisms like hope or patient engagement (Ballou et al., 2022; Haas et al., 2022).

Contextual determinants associated with RCT design, such as trial duration, design type and sample size, consistently influence placebo and nocebo responses across medical specialties. Longer trial duration generally increases placebo responses (e.g., Lee et al., 2020; Li et al., 2019; Silva et al., 2017). This may be because individuals treated over a longer period are more likely to believe they are receiving substantial care, increasing their expectation of a positive response. Additionally, extended immersion in the treatment process can amplify their anticipation of benefits or intensify their experience of adverse events (Pitz et al., 2005). Trial design also plays a role, as placebo responses are higher in parallel vs. cross-over designs (e.g., Fernandes et al., 2008; Papadopoulos & Mitsikostas, 2010), and larger trials tend to have stronger placebo/nocebo responses (e.g., Bosman et al., 2021; Leucht et al., 2018; Meister et al., 2017; Mitsikostas et al., 2012; Siafis et al., 2020), probably due to increased statistical power.

Placebo response magnitude is influenced also by the strength and type of active treatment, with greater symptom relief seen when patients expect the most effective treatments, such as in arthritis, fibromyalgia, ADHD, and chronic fatigue syndrome (e.g. Chen et al., 2017; Cho et al., 2005; Ramírez-Saco et al., 2022; Zhang et al., 2008). Injectable placebos often result in higher responses than oral or topical ones, likely due to stronger expectations of healing when a route of administration typically considered as the most 'powerful' is used (Schwartz et al., 2000). Frequent healthcare visits also boost placebo effects, as observed in gastroenterology and cardiology (Almradi et al., 2022; Wilhelm et al., 2016). Lastly, discrepancies between different types of assessments may arise because patients, particularly in psychiatric disorders (Ahmadzad-Asl et al., 2022; Meister et al., 2020), might be unable to detect small changes in their health, leading to underreporting in self-assessments, while clinicians may overestimate improvements. These differences can result in varying placebo responses depending on whether self-report, clinician, or physiological assessments are used. These findings highlight the importance of RCT design and assessment methods in understanding placebo/nocebo effects.

Finally, some meta-analyses and systematic reviews have attempted to summarise neurobiological correlates of placebo and nocebo responses and effects, particularly in pain perception (e.g. Amanzio et al., 2013; Atlas & Wager, 2014; Zunhammer et al., 2021), depression (Burke et al., 2022; Huneke et al., 2022), and Parkinson's disease (Quattrone et al., 2018). Not surprisingly, the brain regions implicated are primarily frontal and subcortical, closely linked to the pain circuitry. However, these results are hard to interpret considering the complexity of individual variability. Indeed, recent neuroimaging studies suggest that group averages may not fully capture the nuances of individual differences in brain responses (Gratton et al., 2018; Kohoutová et al., 2022; Siddiqi et al., 2022), highlighting the need for more personalised approaches in understanding the neurobiology of placebo and nocebo effects.

4.3. Underinvestigated topics

While synthetising evidence, we identified several underinvestigated topics in the current meta-analyses and systematic reviews on placebo and nocebo responses and effects. Future research should prioritise these overlooked areas to provide a more comprehensive understanding of this area of research.

First, nocebo phenomena remain understudied compared to placebo phenomena, largely due to ethical concerns, as studying nocebo requires harm and deception (Cohen, 2014), leading review boards to hesitate in approving such research (Rojas-Mirquez et al., 2014). Meta-analyses seldom address these ethical issues but suggest integrating nocebo-related information into informed consent and emphasising the unlikelihood of adverse events (Haas et al., 2022; Hinwood et al., 2022). Studies also stress the need to inform patients about placebo group assignment, as awareness of active treatment can enhance placebo effects (Kerschbaumer et al., 2023). Additionally, open-label placebo (OLP) studies show promise, demonstrating positive clinical effects when other treatments are unavailable or ineffective for an individual, but more research is needed due to small sample sizes and heterogeneity (Bąbel, 2024; Charlesworth et al., 2017; von Wernsdorff et al., 2021).

Patient expectations, a key element of placebo responses, are rarely measured consistently. Similarly, the beliefs and characteristics of clinicians, including their expectations and empathy, which can significantly impact health outcomes (e.g. Crow et al., 1999; Hinwood et al., 2022; Hrobjartsson & Gøtzsche, 2001), are underexplored in systematic reviews due to limited data. Additionally, empathic relationships with patients, involving physical touch and compassionate communication, are acknowledged as contributors to placebo effects (e.g., Ali et al., 2020; Flik et al., 2017), but these factors are largely uninvestigated.

There is a notable gap in meta-analyses and systematic reviews addressing the mechanisms behind placebo effects, particularly psychological and learning processes, despite growing interest in this area (Bąbel, 2020). For example, misattribution, a key psychological determinant of the nocebo effect, involves attributing unrelated symptoms to a treatment (Petrie & Rief, 2019), with studies showing that 70-80% of reported symptoms are unrelated but perceived as treatment effects (Mahr et al., 2017). This phenomenon significantly influences adverse effect perceptions but is also underexplored due to its complexity.

Eventually, research focusing on determinants of placebo effects in clinical practice are needed for achieving a deeper understanding and drawing more nuanced conclusions. From this scoping review, it's clear that this aspect is underinvestigated in systematic reviews and meta-analyses. While clinical trials and basic research studies provide valuable insights into treatment efficacy, they may not fully capture the complexity of real-world patient scenarios where multiple factors influence outcomes. For instance, within the realm of patient care, one significant implication often described in literature involves managing clinical conditions for which effective treatments are not readily available (Price et al., 2008), a conclusion not readily inferable from clinical trial data alone.

4.4. Implications for clinical trials and clinical practice

As mentioned above, most meta-analyses and systematic reviews in this scoping review primarily rely on clinical trials and thus it is possible to outline some strategies that clinical research may want to consider in designing clinical trials. However, even within this framework, it's possible to delineate certain clinical implications that can be invaluable in real-world clinical practice as well.

This scoping review highlights key determinants of placebo and nocebo responses relevant for both clinical trial design and real-world practice. Extrinsic and modifiable determinants like trial duration, design and treatment procedures can be adjusted to enhance drug-placebo distinctions or improve treatment efficacy, while intrinsic factors, tied to patient and disease characteristics, pose greater challenges. To enhance clarity, the strategies to control or minimise placebo and nocebo responses in randomised controlled trials have been summarised in Figure 5.

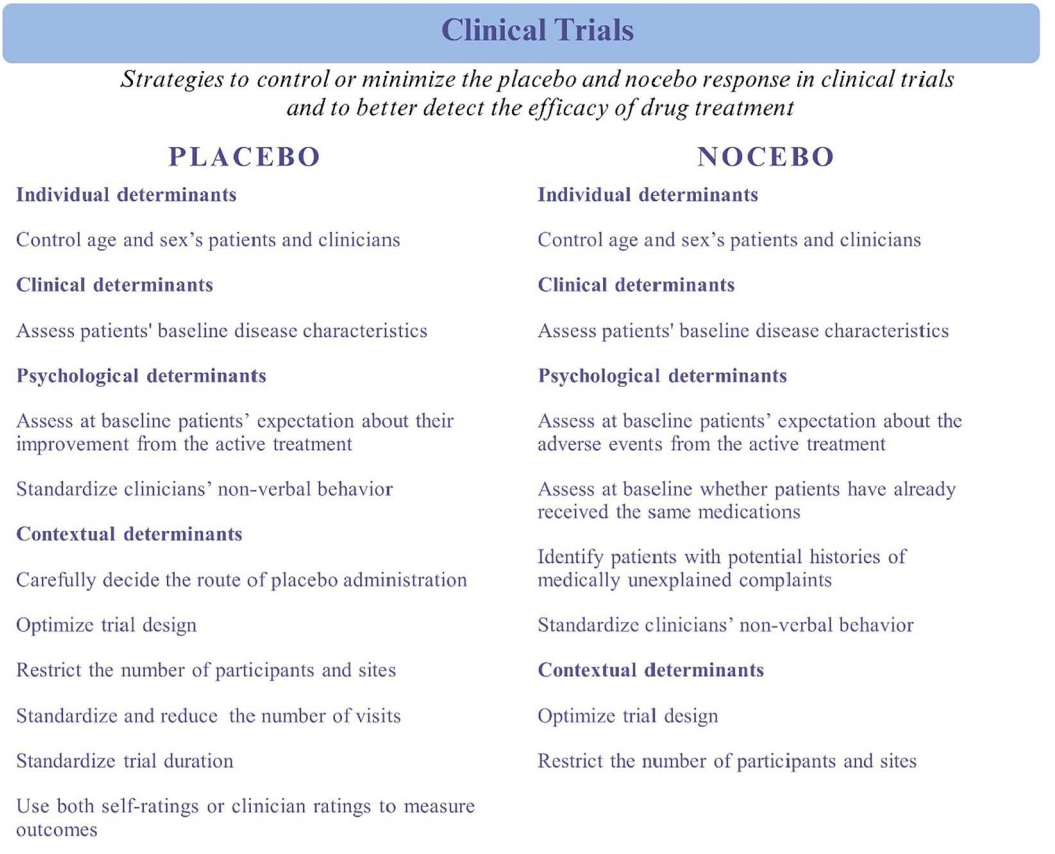

Figure 5. Potential strategies to control or minimise placebo and nocebo responses in clinical trials.

Although more research is needed on their impact in practice, incorporating insights from clinical trials can optimise patient care. While in clinical trials researchers aim to control and minimise the placebo responses, in clinical practice placebo responses and effects can serve as valuable tools, potentially influencing clinical outcomes. Strategies here aim to maximise the placebo responses and effects to optimise treatment efficacy, regardless of whether improvements stem from specific treatment effects, placebo mechanisms, or a combination. In the case of nocebo, instead, the intention of the clinicians is always to minimise its risk and effects both in clinical trials and clinical practice. The recommendations derived from the studies analysed in this scoping review suggest that optimising treatment outcomes involves not only enhancing the efficacy of active medications by activating placebo effects but also re-evaluating appropriate dosages for these medications (e.g., Arakawa et al., 2015; Bosman et al., 2021). Additionally, selecting the most appropriate route of administration by considering both the clinical context and the patient's individual preferences and prior experiences can optimise efficacy while also improving adherence to treatment plans (e.g., de Wit et al., 2016; Nagai et al., 2020). The number of visits to a healthcare provider can significantly influence treatment success by fostering stronger therapeutic relationships and reinforcing positive expectations. More frequent visits provide opportunities for ongoing communication, monitoring and reassurance, which have been shown to amplify placebo effects and improve patients' overall satisfaction with care (e.g., Almradi et al., 2022; Su et al., 2004). However, balancing this frequency is crucial to avoid patient fatigue or the perception of unnecessary medicalisation. Strategically scheduling visits to align with key milestones in the treatment process can maximise their

impact on adherence and outcomes. As such, fostering patient-centred care involves a comprehensive approach that includes understanding, evaluating, and managing patients' beliefs, expectations, and perceptions regarding treatment (e.g., Dodd et al., 2019; Quinn & Colagiuri, 2015). This necessitates refining clinicians' communication skills to effectively convey complex medical concepts and address patient concerns. This includes the need to frame information about side effects positively to reduce anxiety and improve adherence, thereby fostering trust and cooperation. Clinicians should pay attention to their nonverbal behaviour as well, as it plays a crucial role in enhancing the therapeutic alliance and reinforcing the intended message (Daniali & Flaten, 2019).

However, the presence of non-stationarity and heterogeneity in individual data poses significant challenges to the generalisation of findings from group averages to individual cases. Non-stationarity, where statistical properties of data change over time, undermines the assumption of consistent patterns across different time points. Heterogeneity, reflecting uniqueness of individual trajectories and responses, further complicates matters (Fisher et al., 2018; Molenaar & Campbell, 2009). Consequently, relying on group averages to make inferences about individual behaviour or experiences can lead to erroneous conclusions, emphasising the need for more nuanced, person-specific approaches in placebo research (Vlaeyen et al., 2020). In this context, it is essential for healthcare professionals to be guided by evidence-based research, leveraging findings to recognise, assess and address individual patient characteristics through a personalised approach. This involves integrating tailored strategies into clinical practice to optimise outcomes. Furthermore, training healthcare professionals in effective communication is critical. By considering individual differences and aligning communication strategies with patients' personalities, expectations and cultural contexts, clinicians can enhance placebo effects while mitigating nocebo effects. The other side of the patient-clinician relationship (i.e., the patient) is equally important. Indeed, educating patients about placebo and nocebo effects can enhance their awareness and ability to manage their expectations, potentially improving treatment outcomes. Greater patient awareness can also assist clinicians by providing deeper insights into patients' needs and preferences, enabling the development of more personalised and effective therapies. It's also important to note that educating patients requires a careful balance; when informing them about nocebo effects, it is essential to avoid making them feel responsible for the success or failure of the treatment. Finally, recognising the multifaceted nature of illness is paramount, requiring attention not only to its physical aspects but also to the psychological and social dimensions that influence treatment outcomes.

4.5. Strengths and limitations

The scoping review exclusively includes meta-analyses and systematic reviews, covering both basic and clinical research without restrictions on clinical conditions, and thus provides a comprehensive synthesis of high-quality evidence. This broad approach allowed for the identification of overarching trends and key determinants across diverse medical fields, offering valuable insights that are applicable to both clinical research and practice.

However, the broad scope of the review necessarily results in a trade-off with depth. Since the review aims to cover a wide range of aspects, including studies with varying characteristics and findings, it cannot delve deeply into any one area. Second, the lack of terminological consistency in the placebo and nocebo literature poses a challenge, as it prevents assurance that all relevant papers were captured during the search process. Thirdly, by restricting inclusion criteria to meta-analyses and systematic reviews, there may be a loss of some detailed information from individual studies. Furthermore, it would have been valuable to differentiate between responses and effects and isolate the influence of other nonspecific factors such as regression to the mean or the natural progression of the disease on health outcomes. However, it is crucial to acknowledge that very few meta-analyses and systematic reviews included here rely on RCTs with a third control group necessary to distinguish the effect from the response (Charlesworth et al., 2017; Chen et al., 2017; Fernández-López et al., 2022; Howick et al., 2013; Meissner et al., 2007; Zhang et al., 2008). Likewise, this might limit the generalizability of the findings to real-world settings, as there may be

differences between the patients included in RCTs and those encountered in daily clinical practice. Nevertheless, we believe that these limitations do not undermine the key objectives and significance of this scoping review, that is reducing the gap between basic research and clinical practice.

5. Conclusion

The current scoping review aimed to synthesise a comprehensive body of both basic and clinical evidence concerning placebo and nocebo responses and effects sourced from meta-analyses and systematic reviews. Specifically, our focus was elucidating various determinants that influence placebo and nocebo responses and effects, spanning individual, clinical, psychological and contextual factors, which healthcare professionals and clinical researchers should recognise and take into consideration in their practice. Particularly, psychological and contextual factors, such as beliefs, patient-clinician interactions, study design and the treatment setting, offer significant potential for manipulation in designing new research. Understanding these determinants may help in designing targeted interventions and healthcare strategies tailored to the unique needs of individuals and specific patients' groups, albeit using a person-centred perspective. This translational aspect is essential for refining established treatment approaches and optimising patient care by harnessing the mechanisms underlying placebo effects and mitigating nocebo effects (Evers et al., 2018, 2020). To further advance the field, bridging the gap between scientific evidence on placebo and nocebo phenomena and their integration into clinical practice is paramount. Educating healthcare professionals on the implications of these findings and providing training opportunities to effectively apply them in clinical settings will enhance patient care and improve overall healthcare delivery.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

The research was supported by Erasmus+ Programme of the European Union, under Grant IT02–KA220–HED–000088065–Cooperation partnerships in Higher Education. PB is supported by the National Science Centre in Poland under grants no. 2019/35/B/HS6/04320 and 2020/38/A/HS6/00470.

Author contributions

Conceptualisation: AB, KM, PB, AWME, AP, JWSV; Formal analysis: AB; Investigation: AB, EAB, JWH, MOK, SHM; Data Curation: AB; Writing – Original Draft: AB; Writing – Review & Editing: All Authors; Visualisation: AB, Supervision: KM; Project Administration: AB; Funding Acquisition: KM.

Data availability statement

The data that support the findings of this study are available from the corresponding author (AB) upon reasonable request. The studies included in this scoping review are listed in Supplementary Materials (References included in Tables 2 and 3).

References

Agid, O., Siu, C. O., Potkin, S. G., Kapur, S., Watsky, E., Vanderburg, D., Zipursky, R. B., & Remington, G. (2013). Meta-regression analysis of placebo response in antipsychotic trials, 1970-2010. *American Journal of Psychiatry*, *170* (11), 1335–1344. https://doi.org/10.1176/appi.ajp.2013.12030315

Ahmadzad-Asl, M., Davoudi, F., Mohamadi, S., Hadi, F., Nejadghaderi, S. A., Mirbehbahani, S. H., Jabbarinejad, R., Saneh, S., Arshadi, M., Naserbakht, M., Sinyor, M., Kabir, A., & Shamshiri, A. (2022). Systematic review and meta-analysis of the

placebo effect in panic disorder: Implications for research and clinical practice. *Australian & New Zealand Journal of Psychiatry*, *56* (9), 1130–1141. https://doi.org/10.1177/00048674211068793

Ali, A. A., Seng, E. K., Alavi, A., & Lowes, M. A. (2020). Exploring changes in placebo treatment arms in hidradenitis suppurativa randomized clinical trials: A systematic review. *Journal of the American Academy of Dermatology*, *82* (1), 45–53. https://doi.org/10.1016/j.jaad.2019.05.065

Almradi, A., Sedano, R., Hogan, M., Zou, G. Y., MacDonald, J. K., Parker, C. E., Hanzel, J., Crowley, E., Singh, S., D'Haens, G., Sandborn, W. J., Feagan, B. G., Ma, C., & Jairath, V. (2022). Clinical, endoscopic, and safety placebo rates in induction and maintenance trials of Crohn's disease: Meta-analysis of randomised controlled trials. *Journal of Crohn's and Colitis*, *16* (5), 717–736. https://doi.org/10.1093/ecco-jcc/jjab194

Amanzio, M., & Benedetti, F. (1999). Neuropharmacological dissection of placebo analgesia: Expectation- activated opioid systems versus conditioning-activated specific subsystems. *The Journal of Neuroscience*, *19* (1), 484–494. https://doi.org/10.1523/jneurosci.19-01-00484.1999

Amanzio, M., Benedetti, F., Porro, C. A., Palermo, S., & Cauda, F. (2013). Activation likelihood estimation meta-analysis of brain correlates of placebo analgesia in human experimental pain. *Human Brain Mapping*, *34* (3), 738–752. https://doi.org/10.1002/hbm.21471

Arakawa, A., Kaneko, M., & Narukawa, M. (2015). An investigation of factors contributing to higher levels of placebo response in clinical trials in neuropathic pain: A systematic review and meta-analysis. *Clinical Drug Investigation*, *35* (2), 67–81. https://doi.org/10.1007/s40261-014-0259-1

Atlas, L. Y. (2021). A social affective neuroscience lens on placebo analgesia. *Trends in Cognitive Sciences*, *25* (11), 992–1005. https://doi.org/10.1016/j.tics.2021.07.016

Atlas, L. Y., & Wager, T. D. (2014). A meta-analysis of brain mechanisms of placebo analgesia: Consistent findings and unanswered questions. *Handbook of Experimental Pharmacology*, *225* (7223), 37–69. https://doi.org/10.1007/978-3-662-44519-8_3

Bąbel, P. (2020). Operant conditioning as a new mechanism of placebo effects. *European Journal of Pain*, *24* (5), 902–908. https://doi.org/10.1002/ejp.1544

Bąbel, P. (2024). Rethinking placebo: Exploring the effectiveness of open-label placebos. *European Journal of Pain*, *28* (3), 357–358. https://doi.org/10.1002/EJP.2226

Bagarić, B., Jokić-Begić, N., & Sangster Jokić, C. (2022). The nocebo effect: A review of contemporary experimental research. *International Journal of Behavioral Medicine*, *29* (3), 255–265. https://doi.org/10.1007/s12529-021-10016-y

Ballou, S., Haas, J. W., Iturrino, J., Nee, J., Kirsch, I., Rangan, V., Cheng, V., Lembo, A., Kaptchuk, T. J., & Kelley, J. M. (2022). Psychological predictors of response to open-label versus double-blind placebo in a randomized controlled trial in irritable bowel syndrome. *Psychosomatic Medicine*, *84* (6), 738–746. https://doi.org/10.1097/PSY.0000000000001078

Bannuru, R. R., McAlindon, T. E., Sullivan, M. C., Wong, J. B., Kent, D. M., & Schmid, C. H. (2015). Effectiveness and implications of alternative placebo treatments: A systematic review and network meta-analysis of osteoarthritis trials. *Annals of Internal Medicine*, *163* (5), 365–372. https://doi.org/10.7326/M15-0623

Beecher, H. K. (1955). The powerful placebo. *Journal of the American Medical Association*, *159* (17), 1602–1606. https://doi.org/10.1001/jama.1955.02960340022006

Benedetti, F. (2008). Mechanisms of placebo and placebo-related effects across diseases and treatments. *Annual Review of Pharmacology and Toxicology*, *48* (1), 33–60. https://doi.org/10.1146/annurev.pharmtox.48.113006.094711

Benedetti, F. (2014). Placebo effects: From the neurobiological paradigm to translational implications. *Neuron*, *84* (3), 623–637. https://doi.org/10.1016/j.neuron.2014.10.023

Benedetti, F., Mayberg, H. S., Wager, T. D., Stohler, C. S., & Zubieta, J. K. (2005). Neurobiological mechanisms of the placebo effect. *Journal of Neuroscience*, *25* (45), 10390–10402. https://doi.org/10.1523/JNEUROSCI.3458-05.2005

Benedetti, F., Pollo, A., Lopiano, L., Lanotte, M., Vighetti, S., & Rainero, I. (2003). Conscious expectation and unconscious conditioning in analgesic, motor, and hormonal placebo/nocebo responses. *Journal of Neuroscience*, *23* (10), 4315–4323. https://doi.org/10.1523/jneurosci.23-10-04315.2003

Bingel, U., Lorenz, J., Schoell, E., Weiller, C., & Büchel, C. (2006). Mechanisms of placebo analgesia: rACC recruitment of a subcortical antinociceptive network. *Pain*, *120* (1–2), 8–15. https://doi.org/10.1016/j.pain.2005.08.027

Bishop, F. L., Coghlan, B., Geraghty, A. W. A., Everitt, H., Little, P., Holmes, M. M., Seretis, D., & Lewith, G. (2017). What techniques might be used to harness placebo effects in non-malignant pain? A literature review and survey to develop a taxonomy. *BMJ OPEN*, *7* (6), e015516. https://doi.org/10.1136/bmjopen-2016-015516

Bosman, M., Elsenbruch, S., Corsetti, M., Tack, J., Simrén, M., Winkens, B., Boumans, T., Masclee, A., & Keszthelyi, D. (2021). The placebo response rate in pharmacological trials in patients with irritable bowel syndrome: A systematic review and meta-analysis. *The Lancet Gastroenterology and Hepatology*, *6* (6), 459–473. https://doi.org/10.1016/S2468-1253(21)00023-6

Bridge, J. A., Birmaher, B., Iyengar, S., Barbe, R. P., & Brent, D. A. (2009). Placebo response in randomized controlled trials of antidepressants for pediatric major depressive disorder. *American Journal of Psychiatry*, *166* (1), 42–49. https://doi.org/10.1176/appi.ajp.2008.08020247

Burke, M. J., Romanella, S. M., Mencarelli, L., Greben, R., Fox, M. D., Kaptchuk, T. J., Pascual-Leone, A., & Santarnecchi, E. (2022). Placebo effects and neuromodulation for depression: A meta-analysis and evaluation of shared mechanisms. *Molecular Psychiatry*, *27* (3), 1658–1666. https://doi.org/10.1038/s41380-021-01397-3

Charlesworth, J. E. G., Petkovic, G., Kelley, J. M., Hunter, M., Onakpoya, I., Roberts, N., Miller, F. G., & Howick, J. (2017). Effects of placebos without deception compared with no treatment: A systematic review and meta-analysis. *Journal of Evidence-Based Medicine*, *10* (2), 97–107. https://doi.org/10.1111/jebm.12251

Chen, X., Zou, K., Abdullah, N., Whiteside, N., Sarmanova, A., Doherty, M., & Zhang, W. (2017). The placebo effect and its determinants in fibromyalgia: Meta-analysis of randomised controlled trials. *Clinical Rheumatology*, *36* (7), 1623–1630. https://doi.org/10.1007/s10067-017-3595-8

Chin, Y. H., Ng, C. H., Chew, N. W., Kong, G., Lim, W. H., Tan, D. J. H., Chan, K. E., Tang, A., Huang, D. Q., Chan, M. Y., Figtree, G., Wang, J.-W., Shabbir, A., Khoo, C. M., Wong, V. W.-S., Young, D. Y., Siddiqui, M. S., Noureddin, M., Sanyal, A., … Muthiah, M. D. (2022). The placebo response rate and nocebo events in obesity pharmacological trials: A systematic review and meta-analysis. *eClinicalMedicine*, *54*, 101685. https://doi.org/10.1016/j.eclinm.2022.101685

Cho, H. J., Hotopf, M., & Wessely, S. (2005). The placebo response in the treatment of chronic fatigue syndrome: A systematic review and meta-analysis. *Psychosomatic Medicine*, *67* (2), 301–313. https://doi.org/10.1097/01.psy.0000156969.76986.e0

Cohen, S. (2014). The nocebo effect of informed consent. *Bioethics*, *28* (3), 147–154. https://doi.org/10.1111/j.1467-8519.2012.01983.x

Colagiuri, B., Schenk, L. A., Kessler, M. D., Dorsey, S. G., & Colloca, L. (2015). The placebo effect: From concepts to genes. *Neuroscience*, *307*, 171–190. https://doi.org/10.1016/j.neuroscience.2015.08.017

Colloca, L. (2019). The placebo effect in pain therapies. *Annual Review of Pharmacology and Toxicology*, *59* (1), 191–211. https://doi.org/10.1146/annurev-pharmtox-010818-021542

Colloca, L., & Barsky, A. J. (2020). Placebo and nocebo effects. *The New England Journal of Medicine*, *382* (6), 87–89. https://doi.org/10.1002/9781119540687.ch2

Colloca, L., & Miller, F. G. (2011). The nocebo effect and its relevance for clinical practice. *Psychosomatic Medicine*, *73* (7), 598–603. https://doi.org/10.1097/PSY.0b013e3182294a50

Colloca, L., Sigaudo, M., & Benedetti, F. (2008). The role of learning in nocebo and placebo effects. *PAIN*, *136* (1–2), 211–218. https://doi.org/10.1016/J.PAIN.2008.02.006

Crow, R., Gage, H., Hampson, S., Hart, J., Kimber, A., & Thomas, H. (1999). The role of expectancies in the placebo effect and their use in the delivery of health care: A systematic review. *Health Technology Assessment*, *3* (3), 1–38. https://doi.org/10.3310/hta3030

Curie, A., Yang, K., Kirsch, I., Gollub, R. L., Des Portes, V., Kaptchuk, T. J., & Jensen, K. B. (2015). Placebo responses in genetically determined intellectual disability: A meta-analysis. *PLoS One*, *10* (7), e0133316. https://doi.org/10.1371/journal.pone.0133316

Czobor, P., Kakuszi, B., & Bitter, I. (2022). Placebo response in trials of negative symptoms in schizophrenia: A critical reassessment of the evidence. *Schizophrenia Bulletin*, *48* (6), 1228–1240. https://doi.org/10.1093/schbul/sbac061

Daniali, H., & Flaten, M. A. (2019). A qualitative systematic review of effects of provider characteristics and nonverbal behavior on pain, and placebo and nocebo effects. *Frontiers in Psychiatry*, *10*, 242. https://doi.org/10.3389/fpsyt.2019.00242

de Craen, A. J., Tijssen, J. G., de Gans, J., & Kleijnen, J. (2000). Placebo effect in the acute treatment of migraine: Subcutaneous placebos are better than oral placebos. *Journal of Neurology*, *247* (3), 183–188. https://doi.org/10.1007/s004150050560

Del Re, A. C., Maisel, N., Blodgett, J. C., Wilbourne, P., & Finney, J. W. (2013). Placebo group improvement in trials of pharmacotherapies for alcohol use disorders. *Journal of Clinical Psychopharmacology*, *33* (5), 649–657. https://doi.org/10.1097/JCP.0b013e3182983e73

de Wit, H. M., te Groen, M., Rovers, M. M., & Tack, C. J. (2016). The placebo response of injectable GLP-1 receptor agonists vs. Oral DPP-4 inhibitors and SGLT-2 inhibitors: A systematic review and meta-analysis. *British Journal of Clinical Pharmacology*, *82* (1), 301–314. https://doi.org/10.1111/bcp.12925

Di Blasi, Z., Harkness, E., Ernst, E., Georgiou, A., & Kleijnen, J. (2001). Influence of context effects on health outcomes: A systematic review. *Lancet*, *357* (9258), 757–762. https://doi.org/10.1016/S0140-6736(00)04169-6

Dobson, E. T., & Strawn, J. R. (2016). Placebo response in pediatric anxiety disorders: Implications for clinical trial design and interpretation. *Journal of Child and Adolescent Psychopharmacology*, *26* (8), 686–693. https://doi.org/10.1089/cap.2015.0192

Dodd, S., Walker, A. J., Brnabic, A. J. M., Hong, N., Burns, A., & Berk, M. (2019). Incidence and characteristics of the nocebo response from meta-analyses of the placebo arms of clinical trials of olanzapine for bipolar disorder. *Bipolar Disorders*, *21* (2), 142–150. https://doi.org/10.1111/bdi.12662

Dorn, S. D., Kaptchuk, T. J., Park, J. B., Nguyen, L. T., Canenguez, K., Nam, B. H., Woods, K. B., Conboy, L. A., Stason, W. B., & Lembo, A. J. (2007). A meta-analysis of the placebo response in complementary and alternative medicine trials of irritable bowel syndrome. *Neurogastroenterology & Motility*, *19* (8), 630–637. https://doi.org/10.1111/j.1365-2982.2007.00937.x

Enck, P., Bingel, U., Schedlowski, M., & Rief, W. (2013). The placebo response in medicine: Minimize, maximize or personalize? *Nature Reviews Drug Discovery*, *12* (3), 191–204. https://doi.org/10.1038/nrd3923

Enck, P., & Klosterhalfen, S. (2020). Placebo responses and placebo effects in functional gastrointestinal disorders. *Frontiers in Psychiatry*, *11*, 522970. https://doi.org/10.3389/fpsyt.2020.00797

Erre, G. L., Mavridis, D., Woodman, R. J., & Mangoni, A. A. (2022). Placebo response in psoriatic arthritis clinical trials: A systematic review and meta-analysis. *Rheumatology*, *61* (4), 1328–1340. https://doi.org/10.1093/rheumatology/keab774

Evers, A. W. M., Colloca, L., Blease, C., Annoni, M., Atlas, L. Y., Benedetti, F., Bingel, U., Büchel, C., Carvalho, C., Colagiuri, B., Crum, A. J., Enck, P., Gaab, J., Geers, A. L., Howick, J., Jensen, K. B., Kirsch, I., Meissner, K., Napadow, V., … Kelley, J. M. (2018). Implications of placebo and nocebo effects for clinical practice: Expert consensus. *Psychotherapy and Psychosomatics*, *87* (4), 204–210. https://doi.org/10.1159/000490354

Evers, A. W. M., Colloca, L., Blease, C., Gaab, J., Jensen, K. B., Atlas, L. Y., Beedie, C. J., Benedetti, F., Bingel, U., Büchel, C., Bussemaker, J., Colagiuri, B., Crum, A. J., Finniss, D. G., Geers, A. L., Howick, J., Klinger, R., Meeuwis, S. H., Meissner, K., … Kirsch, I. (2020). What should clinicians tell patients about placebo and nocebo effects? Practical considerations based on expert consensus. *Psychotherapy and Psychosomatics*, *90* (1), 49–56. https://doi.org/10.1159/000510738

Fernandes, R., Ferreira, J. J., & Sampaio, C. (2008). The placebo response in studies of acute migraine. *Journal of Pediatrics*, *152* (4), 527–534. https://doi.org/10.1016/j.jpeds.2007.09.024

Fernández-López, R., Riquelme-Gallego, B., Bueno-Cavanillas, A., & Khan, K. S. (2022). Influence of placebo effect in mental disorders research: A systematic review and meta-analysis. *European Journal of Clinical Investigation*, *52* (7), e13762. https://doi.org/10.1111/eci.13762

Finniss, D. G., Kaptchuk, T. J., Miller, F., & Benedetti, F. (2010). Biological, clinical, and ethical advances of placebo effects. *The Lancet*, *375* (9715), 686–695. https://doi.org/10.1016/S0140-6736(09)61706-2

Fisher, A. J., Medaglia, J. D., & Jeronimus, B. F. (2018). Lack of group-to-individual generalizability is a threat to human subjects research. *Proceedings of the National Academy of Sciences of the United States of America*, *115* (27), E6106–E6115. https://doi.org/10.1073/pnas.1711978115

Flik, C. E., Bakker, L., Laan, W., van Rood, Y. R., Smout, A. J., & de Wit, N. J. (2017). Systematic review: The placebo effect of psychological interventions in the treatment of irritable bowel syndrome. *World Journal of Gastroenterology*, *23* (12), 2223–2233. https://doi.org/10.3748/wjg.v23.i12.2223

Fraguas, D., Díaz-Caneja, C. M., Pina-Camacho, L., Umbricht, D., & Arango, C. (2019). Predictors of placebo response in pharmacological clinical trials of negative symptoms in schizophrenia: A meta-regression analysis. *Schizophrenia Bulletin*, *45* (1), 57–68. https://doi.org/10.1093/schbul/sbx192

Freeman, S., Yu, R., Egorova, N., Chen, X., Kirsch, I., Claggett, B., Kaptchuk, T. J., Gollub, R. L., & Kong, J. (2015). Distinct neural representations of placebo and nocebo effects. *NeuroImage*, *112*, 197–207. https://doi.org/10.1016/j.neuroimage.2015.03.015

Frisaldi, E., Shaibani, A., Benedetti, F., & Pagnini, F. (2023). Placebo and nocebo effects and mechanisms associated with pharmacological interventions: An umbrella review. *BMJ Open*, *13* (10), e077243. https://doi.org/10.1136/BMJOPEN-2023-077243

Fu, J., Wu, S., Liu, C., Camilleri, J. A., Eickhoff, S. B., & Yu, R. (2021). Distinct neural networks subserve placebo analgesia and nocebo hyperalgesia. *NeuroImage*, *231*(117833), 1–18. https://doi.org/10.1016/j.neuroimage.2021.117833

Fulda, S., & Wetter, T. C. (2008). Where dopamine meets opioids: A meta-analysis of the placebo effect in restless legs syndrome treatment studies. *Brain*, *131* (4), 902–917. https://doi.org/10.1093/brain/awm244

Furukawa, T. A., Cipriani, A., Atkinson, L. Z., Leucht, S., Ogawa, Y., Takeshima, N., Hayasaka, Y., Chaimani, A., & Salanti, G. (2016). Placebo response rates in antidepressant trials: A systematic review of published and unpublished double-blind randomised controlled studies. *The Lancet Psychiatry*, *3* (11), 1059–1066. https://doi.org/10.1016/S2215-0366(16)30307-8

Garud, S., Brown, A., Cheifetz, A., Levitan, E. B., & Kelly, C. P. (2008). Meta-analysis of the placebo response in ulcerative colitis. *Digestive Diseases and Sciences*, *53* (4), 875–891. https://doi.org/10.1007/s10620-007-9954-6

Geuter, S., Koban, L., & Wager, T. D. (2017). The cognitive neuroscience of placebo effects: Concepts, predictions, and physiology. *Annual Review of Neuroscience*, *40* (1), 167–188. https://doi.org/10.1146/annurev-neuro-072116-031132

Gratton, C., Laumann, T. O., Nielsen, A. N., Greene, D. J., Gordon, E. M., Gilmore, A. W., Nelson, S. M., Coalson, R. S., Snyder, A. Z., Schlaggar, B. L., Dosenbach, N. U. F., & Petersen, S. E. (2018). Functional brain networks are dominated by stable group and individual factors, Not cognitive or daily variation. *Neuron*, *98* (2), 439–452.e5. https://doi.org/10.1016/j.neuron.2018.03.035

Haas, J. W., Bender, F. L., Ballou, S., Kelley, J. M., Wilhelm, M., Miller, F. G., Rief, W., & Kaptchuk, T. J. (2022). Frequency of adverse events in the placebo arms of COVID-19 vaccine trials: A systematic review and meta-analysis. *JAMA Network Open*, *5* (1), e2143955–e2143955. https://doi.org/10.1001/JAMANETWORKOPEN.2021.43955

Hall, K. T., Loscalzo, J., & Kaptchuk, T. J. (2015). Genetics and the placebo effect: The placebome. *Trends in Molecular Medicine*, *21* (5), 285–294. https://doi.org/10.1016/j.molmed.2015.02.009

Häuser, W., Hansen, E., & Enck, P. (2012). Nocebo phenomena in medicine. *Deutsches Arzteblatt International*, *109* (26), 459–465. https://doi.org/10.3238/arztebl.2012.0459

He, D., Jiang, B., Guo, Z., Mu, Q., & McClure, M. A. (2020). Biphasic feature of placebo response in primary insomnia: Pooled analysis of data from randomized controlled clinical trials of orexin receptor antagonists. *Sleep*, *43* (3), zsz238. https://doi.org/10.1093/sleep/zsz238

Hinwood, M., Wall, L., Lang, D., Balogh, Z. J., Smith, A., Dowsey, M., Clarke, P., Choong, P., Bunzli, S., & Paolucci, F. (2022). Patient and clinician characteristics and preferences for increasing participation in placebo surgery trials: A scoping review of attributes to inform a discrete choice experiment. *Trials*, *23* (1), 296. https://doi.org/10.1186/s13063-022-06277-x

Howick, J., Friedemann, C., Tsakok, M., Watson, R., Tsakok, T., Thomas, J., Perera, R., Fleming, S., & Heneghan, C. (2013). Are treatments more effective than placebos? A systematic review and meta-analysis. *PLoS One*, *8* (5), e62599. https://doi.org/10.1371/journal.pone.0062599

Hrobjartsson, A., & Gøtzsche, P. C. (2001). Is the placebo powerless? An analysis of clinical trials comparing placebo with no treatment. *Obstetrical and Gynecological Survey*, *56* (10), 628–629. https://doi.org/10.1097/00006254-200110000-00021

Huang, Z., Chen, J., Hu, Q. S., Huang, Q., Ma, J., Pei, F. X., Shen, B., & Kraus, V. B. (2019). Meta-analysis of pain and function placebo responses in pharmacological osteoarthritis trials. *Arthritis Research & Therapy*, *21* (1), 1–10. https://doi.org/10.1186/s13075-019-1951-6

Huang, X., Oshima, T., Tomita, T., Fukui, H., & Miwa, H. (2021). Meta-analysis: Placebo response and its determinants in functional dyspepsia. *American Journal of Gastroenterology*, *116* (11), 2184–2196. https://doi.org/10.14309/ajg.0000000000001397

Hughes, J., Gabbay, M., Funnell, E., & Dowrick, C. (2012). Exploratory review of placebo characteristics reported in randomised placebo controlled antidepressant drug trials. *Pharmacopsychiatry*, *45* (1), 20–27. https://doi.org/10.1055/s-0031-1286260

Huneke, N. T. M., Aslan, I. H., Fagan, H., Phillips, N., Tanna, R., Cortese, S., Garner, M., & Baldwin, D. S. (2022). Functional neuroimaging correlates of placebo response in patients with depressive or anxiety disorders: A systematic review. *International Journal of Neuropsychopharmacology*, *25* (6), 433–447. https://doi.org/10.1093/ijnp/pyac009

Jairath, V., Zou, G. Y., Parker, C. E., Macdonald, J. K., Alameel, T., Al Beshir, M., Almadi, M. A., Al-Taweel, T., Atkinson, N. S. S., Biswas, S., Chapman, T., Dulai, P. S., Glaire, M. A., Hoekman, D. R., Koutsoumpas, A., Minas, E., Mosli, M. H., Samaan, M., Khanna, R., … Feagan, B. G. (2017). Placebo response and remission rates in randomised trials of induction and maintenance therapy for ulcerative colitis. *The Cochrane Database of Systematic Reviews*, *2017* (9), 1–39. https://doi.org/10.1002/14651858.CD011572.PUB2

Jairath, V., Zou, G., Parker, C. E., Macdonald, J. K., Mosli, M. H., Khanna, R., Shackelton, L. M., Vandervoort, M. K., AlAmeel, T., Al Beshir, M., AlMadi, M., Al-Taweel, T., Atkinson, N. S. S., Biswas, S., Chapman, T. P., Dulai, P. S., Glaire, M. A., Hoekman, D., Koutsoumpas, A., … Feagan, B. G. (2016). Systematic review and meta-analysis: Placebo rates in induction and maintenance trials of ulcerative colitis. *Journal of Crohn's & Colitis*, *10* (5), 607–618. https://doi.org/10.1093/ecco-jcc/jjw004

Jiang, B., He, D., Guo, Z., & Gao, Z. (2020). Dynamic features of placebo effects addressing persistent insomnia disorder: A meta-analysis of placebo-controlled randomized clinical trials. *Journal of Sleep Research*, *29* (4), e12997. https://doi.org/10.1111/jsr.12997

Jutzeler, C. R., Warner, F. M., Cragg, J. J., Haefeli, J., Richards, J. S., Andresen, S. R., Finnerup, N. B., Mercier, C., & Kramer, J. L. K. (2018). Placebo response in neuropathic pain after spinal cord injury: A meta-analysis of individual participant data. *Journal of Pain Research*, *11*, 901–912. https://doi.org/10.2147/JPR.S155979

Kaptchuk, T. J., Kelley, J. M., Deykin, A., Wayne, P. M., Lasagna, L. C., Epstein, I. O., Kirsch, I., & Wechsler, M. E. (2008). Do "placebo responders" exist? *Contemporary Clinical Trials*, *29* (4), 587–595. https://doi.org/10.1016/j.cct.2008.02.002

Kaptchuk, T. J., & Miller, F. G. (2015). Placebo effects in medicine. *New England Journal of Medicine*, *373* (1), 8–9. https://doi.org/10.1056/nejmp1504023

Kelley, J. M. (2018). Lumping and splitting: Toward a taxonomy of placebo and related effects. In *International review of neurobiology* (Vol. 139 (1st ed., pp. 29–48). Elsevier Inc. https://doi.org/10.1016/bs.irn.2018.07.011

Kelley, J. M., Kraft-Todd, G., Schapira, L., Kossowsky, J., & Riess, H. (2014). The influence of the patient-clinician relationship on healthcare outcomes: A systematic review and meta-analysis of randomized controlled trials. *PLoS One*, *9* (4), e94207. https://doi.org/10.1371/journal.pone.0094207

Kern, A., Kramm, C., Witt, C. M., & Barth, J. (2020). The influence of personality traits on the placebo/nocebo response: A systematic review. *Journal of Psychosomatic Research*, *128*, 109866. https://doi.org/10.1016/j.jpsychores.2019.109866

Kerschbaumer, A., Stimakovits, N. M., Smolen, J. S., Stefanova, T., Chwala, E., & Aletaha, D. (2023). Influence of active versus placebo control on treatment responses in randomised controlled trials in rheumatoid arthritis. *Annals of the Rheumatic Diseases*, *82* (4), 476–482. https://doi.org/10.1136/ard-2022-223349

Kisaalita, N. R., Roditi, D., & Robinson, M. E. (2011). Factors affecting placebo acceptability: Deception, outcome, and disease severity. *The Journal of Pain*, *12* (8), 920–928. https://doi.org/10.1016/j.jpain.2011.02.353

Kohoutová, L., Atlas, L. Y., Büchel, C., Buhle, J. T., Geuter, S., Jepma, M., Koban, L., Krishnan, A., Lee, D. H., Lee, S., Roy, M., Schafer, S. M., Schmidt, L., Wager, T. D., & Woo, C. W. (2022). Individual variability in brain representations of pain. *Nature Neuroscience*, *25* (6), 749–759. https://doi.org/10.1038/s41593-022-01081-x

Kravvariti, E., Kasdagli, M. I., Diomatari, K. M., Mouratidou, P., Daskalakis, K., Mitsikostas, D. D., Sfikakis, P. P., & Yavropoulou, M. P. (2023). Meta-analysis of placebo-arm dropouts in osteoporosis randomized-controlled trials and implications for nocebo-associated discontinuation of anti-osteoporotic drugs in clinical practice. *Osteoporosis International*, *34* (3), 585–598. https://doi.org/10.1007/s00198-022-06658-7

Kung, J., Chiappelli, F., Cajulis, O. O., Avezova, R., Kossan, G., Chew, L., & Maida, C. A. (2010). From systematic reviews to clinical recommendations for evidence-based health care: Validation of revised assessment of multiple systematic reviews (R-AMSTAR) for grading of clinical relevance. *The Open Dentistry Journal*, *4* (2), 84. https://doi.org/10.2174/1874210601004020084

Labarca, G., Montenegro, R., Oscullo, G., Henriquez-Beltran, M., Uribe, J. P., Gómez-Olivas, J. D., Garcia-Ortega, A., & Martínez-García, MÁ. (2023). Placebo response in objective and subjective measures of hypersomnia in randomized

clinical trials on obstructive sleep apnea. A systematic review and meta-analysis. *Sleep Medicine Reviews*, *67*, 101720. https://doi.org/10.1016/J.SMRV.2022.101720

Lee, H. H., Patel, K. R., Rastogi, S., Singam, V., Vakharia, P. P., Chopra, R., & Silverberg, J. I. (2020). Placebo responses in randomized controlled trials for systemic therapy in atopic dermatitis: A systematic review and meta-analysis. *Journal of the American Academy of Dermatology*, *82* (1), 62–71. https://doi.org/10.1016/j.jaad.2019.05.102

Lembo, A., Kelley, J. M., Nee, J., Ballou, S., Iturrino, J., Cheng, V., Rangan, V., Katon, J., Hirsch, W., Kirsch, I., Hall, K., Davis, R. B., & Kaptchuk, T. J. (2021). Open-label placebo vs double-blind placebo for irritable bowel syndrome: A randomized clinical trial. *Pain*, *162* (9), 2428–2435. https://doi.org/10.1097/j.pain.0000000000002234

Leucht, S., Chaimani, A., Leucht, C., Huhn, M., Mavridis, D., Helfer, B., Samara, M., Cipriani, A., Geddes, J. R., Salanti, G., & Davis, J. M. (2018). 60 years of placebo-controlled antipsychotic drug trials in acute schizophrenia: Meta-regression of predictors of placebo response. *Schizophrenia Research*, *201*, 315–323. https://doi.org/10.1016/j.schres.2018.05.009

Li, Y., Huang, J., He, Y., Yang, J., Lv, Y., Liu, H., Liang, L., Li, H., Zheng, Q., & Li, L. (2019). The impact of placebo response rates on clinical trial outcome: A systematic review and meta-analysis of antidepressants in children and adolescents with major depressive disorder. *Journal of Child and Adolescent Psychopharmacology*, *29* (9), 712–720. https://doi.org/10.1089/cap.2019.0022

Li, L., Xu, L., Wu, J., Dong, L., Lv, Y., & Zheng, Q. (2017). Quantitative analysis of placebo response and factors associated with menopausal hot flashes. *Menopause-The Journal of the North American Menopause Society*, *24* (8), 932–937. https://doi.org/10.1097/GME.0000000000000085

Lidstone, S. C., Schulzer, M., Dinelle, K., Mak, E., Sossi, V., Ruth, T. J., De La Fuente-Fernández, R., Phillips, A. G., & Stoessl, A. J. (2010). Effects of expectation on placebo-induced dopamine release in Parkinson disease. *Archives of General Psychiatry*, *67* (8), 857–865. https://doi.org/10.1001/archgenpsychiatry.2010.88

Lin, C., Cai, X., Yang, W., Lv, F., Nie, L., & Ji, L. (2020). Age, sex, disease severity, and disease duration differences in placebo response: Implications from a meta-analysis of diabetes mellitus. *BMC Medicine*, *18* (1), 322. https://doi.org/10.1186/s12916-020-01787-4

Macaluso, F. S., Maida, M., Ventimiglia, M., Renna, S., Cottone, M., & Orlando, A. (2019). Factors affecting clinical and endoscopic outcomes of placebo arm in trials of biologics and small molecule drugs in ulcerative colitis: A meta-analysis. *Inflammatory Bowel Diseases*, *25* (6), 987–997. https://doi.org/10.1093/ibd/izy365

Macedo, A., Baños, J. E., & Farré, M. (2008). Placebo response in the prophylaxis of migraine: A meta-analysis. *European Journal of Pain*, *12* (1), 68–75. https://doi.org/10.1016/j.ejpain.2007.03.002

Macedo, A., Farré, M., & Baños, J. E. (2006). A meta-analysis of the placebo response in acute migraine and how this response may be influenced by some of the characteristics of clinical trials. *European Journal of Clinical Pharmacology*, *62* (3), 161–172. https://doi.org/10.1007/s00228-005-0088-5

Mahr, A., Golmard, C., Pham, E., Iordache, L., Deville, L., & Faure, P. (2017). Types, frequencies, and burden of nonspecific adverse events of drugs: Analysis of randomized placebo-controlled clinical trials. *Pharmacoepidemiology and Drug Safety*, *26* (7), 731–741. https://doi.org/10.1002/pds.4169

Matsusaki, A., Kaneko, M., & Narukawa, M. (2018). Meta-analysis of placebo response in randomized clinical trials of antipsychotic drugs using PANSS focusing on different approaches to the handling of missing data. *Clinical Drug Investigation*, *38* (8), 751–761. https://doi.org/10.1007/s40261-018-0661-1

McCall, W. V., D'Agostino, R., & Dunn, A. (2003). A meta-analysis of sleep changes associated with placebo in hypnotic clinical trials. *Sleep Medicine*, *4* (1), 57–62. https://doi.org/10.1016/s1389-9457(02)00242-3

Meeuwis, S. H., van Middendorp, H., van Laarhoven, A. I. M., van Leijenhorst, C., Pacheco-Lopez, G., Lavrijsen, A. P. M., Veldhuijzen, D. S., & Evers, A. W. M. (2020). Placebo and nocebo effects for itch and itch-related immune outcomes: A systematic review of animal and human studies. *Neuroscience and Biobehavioral Reviews*, *113* (January), 325–337. https://doi.org/10.1016/j.neubiorev.2020.03.025

Meeuwis, S. H., Wasylewski, M. T., Bajcar, E. A., Bieniek, H., Adamczyk, W. M., Honcharova, S., Di Nardo, M., Mazzoni, G., & Bąbel, P. (2023). Learning pain from others: A systematic review and meta-analysis of studies on placebo hypoalgesia and nocebo hyperalgesia induced by observational learning. *Pain*, *164* (11), 2383–2396. https://doi.org/10.1097/j.pain.0000000000002943

Meissner, K., Distel, H., & Mitzdorf, U. (2007). Evidence for placebo effects on physical but not on biochemical outcome parameters: A review of clinical trials. *BMC Medicine*, *5* (3), 1–11. https://doi.org/10.1186/1741-7015-5-3

Meister, R., Abbas, M., Antel, J., Peters, T., Pan, Y., Bingel, U., Nestoriuc, Y., & Hebebrand, J. (2020). Placebo response rates and potential modifiers in double-blind randomized controlled trials of second and newer generation antidepressants for major depressive disorder in children and adolescents: A systematic review and meta-regression analysis. *European Child and Adolescent Psychiatry*, *29* (3), 253–273. https://doi.org/10.1007/S00787-018-1244-7

Meister, R., Jansen, A., Härter, M., Nestoriuc, Y., & Kriston, L. (2017). Placebo and nocebo reactions in randomized trials of pharmacological treatments for persistent depressive disorder. A meta-regression analysis. *Journal of Affective Disorders*, *215*, 288–298. https://doi.org/10.1016/j.jad.2017.03.024

Mitsikostas, D. D., Chalarakis, N. G., Mantonakis, L. I., Delicha, E. M., & Sfikakis, P. P. (2012). Nocebo in fibromyalgia: Meta-analysis of placebo-controlled clinical trials and implications for practice. *European Journal of Neurology*, *19* (5), 672–680. https://doi.org/10.1111/j.1468-1331.2011.03528.x

Mohamadi, S., Ahmadzad-Asl, M., Nejadghaderi, S. A., Jabbarinejad, R., Mirbehbahani, S. H., Sinyor, M., Richter, M. A., & Davoudi, F. (2023). Systematic review and meta-analysis of the placebo effect and its correlates in obsessive compulsive disorder. *Canadian Journal of Psychiatry*, *68* (7), 479–494. https://doi.org/10.1177/07067437221115029

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., Antes, G., Atkins, D., Barbour, V., Barrowman, N., Berlin, J. A., Clark, J., Clarke, M., Cook, D., D'Amico, R., Deeks, J. J., Devereaux, P. J., Dickersin, K., Egger, M., Ernst, E., Gøtzsche, P. C., … Tugwell, P. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *Annals of Internal Medicine*, *151* (4), 264–269. https://doi.org/10.7326/0003-4819-151-4-200908180-00135

Molenaar, P. C. M., & Campbell, C. G. (2009). The new person-specific paradigm in psychology. *Current Directions in Psychological Science*, *18* (2), 112–117. https://doi.org/10.1111/j.1467-8721.2009.01619.x

Mostafaei, H., Janisch, F., Mori, K., Quhal, F., Pradere, B., Hajebrahimi, S., Roehrborn, C. G., & Shariat, S. F. (2022). Placebo response in patients with oral therapy for overactive bladder: A systematic review and meta-analysis. *European Urology Focus*, *8* (1), 239–252. https://doi.org/10.1016/j.euf.2021.02.005

Muench, J., Giller, K., Morales, K. H., Culnan, E., Khader, W., Kaptchuk, T. J., McCall, W. V., & Perlis, M. L. (2022). Do placebos primarily affect subjective as opposed to objective measures? A meta-analysis of placebo responses in insomnia RCTs. *Behavioral Sleep Medicine*, *21* (4), 500–512. https://doi.org/10.1080/15402002.2022.2115046

Nagai, K., Matsubayashi, K., Ide, K., Seto, K., Kawasaki, Y., & Kawakami, K. (2020). Factors influencing placebo responses in rheumatoid arthritis clinical trials: A meta-analysis of randomized, double-blind, placebo-controlled studies. *Clinical Drug Investigation*, *40* (3), 197–209. https://doi.org/10.1007/s40261-020-00887-6

Nee, J., Sugarman, M. A., Ballou, S., Katon, J., Rangan, V., Singh, P., Zubiago, J., Kaptchuk, T. J., & Lembo, A. (2019). Placebo response in chronic idiopathic constipation: A systematic review and meta-analysis. *American Journal of Gastroenterology*, *114* (12), 1838–1846. https://doi.org/10.14309/ajg.0000000000000399

Neogi, T., & Colloca, L. (2023). Placebo effects in osteoarthritis: Implications for treatment and drug development. *Nature Reviews Rheumatology*, *19* (10), 613–626. https://doi.org/10.1038/s41584-023-01021-4

Ng, C. H., Xiao, J., Lim, W. H., Chin, Y. H., Yong, J. N., Tan, D. J. H., Tay, P., Syn, N., Foo, R., Chan, M., Chew, N., Tan, E. X., Huang, D. Q., Dan, Y. Y., Tamaki, N., Siddiqui, M. S., Sanyal, A. J., Loomba, R., & Noureddin, M. (2022). Placebo effect on progression and regression in NASH: Evidence from a meta-analysis. *Hepatology*, *75* (6), 1647–1661. https://doi.org/10.1002/hep.32315

Okusogu, C., Wang, Y., Akintola, T., & Pain, N. H.-U. (2020). Placebo hypoalgesia: Racial differences. *Pain*, *161* (8), 1872–1883. https://doi.org/10.1097/j.pain.0000000000001876

Oosterbaan, D. B., van Balkom, A. J., Spinhoven, P., & van Dyck, R. (2001). The placebo response in social phobia. *Journal of Psychopharmacology*, *15* (3), 199–203. https://doi.org/10.1177/026988110101500314

Ouzzani, M., Hammady, H., Fedorowicz, Z., & Elmagarmid, A. (2016). Rayyan-a web and mobile app for systematic reviews. *Systematic Reviews*, *5* (1), 1–10. https://doi.org/10.1186/s13643-016-0384-4

Palermo, S., Giovannelli, F., Bartoli, M., & Amanzio, M. (2019). Are patients with schizophrenia spectrum disorders more prone to manifest nocebo-like-effects? A meta-analysis of adverse events in placebo groups of double-blind antipsychotic trials. *Frontiers in Pharmacology*, *10* (502), 1–10. https://doi.org/10.3389/fphar.2019.00502

Papadopoulos, D., & Mitsikostas, D. D. (2010). Nocebo effects in multiple sclerosis trials: A meta-analysis. *Multiple Sclerosis*, *16* (7), 816–828. https://doi.org/10.1177/1352458510370793

Papakostas, G. I., & Fava, M. (2009). Does the probability of receiving placebo influence clinical trial outcome? A meta-regression of double-blind, randomized clinical trials in MDD. *European Neuropsychopharmacology*, *19* (1), 34–40. https://doi.org/10.1016/j.euroneuro.2008.08.009

Peters, M. D. J., Godfrey, C. M., Khalil, H., McInerney, P., Parker, D., & Soares, C. B. (2015). Guidance for conducting systematic scoping reviews. *International Journal of Evidence-Based Healthcare*, *13* (3), 141–146. https://doi.org/10.1097/XEB.0000000000000050

Peters, M. D. J., Godfrey, C., McInerney, P., Khalil, H., Larsen, P., Marnie, C., Pollock, D., Tricco, A. C., & Munn, Z. (2022). Best practice guidance and reporting items for the development of scoping review protocols. *JBI Evidence Synthesis*, *20* (4), 953–968. https://doi.org/10.11124/JBIES-21-00242

Petersen, G. L., Finnerup, N. B., Colloca, L., Amanzio, M., Price, D. D., Jensen, T. S., & Vase, L. (2014). The magnitude of nocebo effects in pain: A meta-analysis. *PAIN®*, *155* (8), 1426–1434. https://doi.org/10.1016/J.PAIN.2014.04.016

Petrie, K. J., & Rief, W. (2019). Psychobiological mechanisms of placebo and nocebo effects: Pathways to improve treatments and reduce side effects. *Annual Review of Psychology*, *70* (August 2018), 599–625. https://doi.org/10.1146/annurev-psych-010418-102907

Pitz, M., Cheang, M., & Bernstein, C. N. (2005). Defining the predictors of the placebo response in irritable Bowel Syndrome. *Clinical Gastroenterology and Hepatology*, *3* (1), 237–247. https://doi.org/10.1016/S1542-3565(04)00626-3

Porporatti, A. L., Costa, Y. M., Reus, J. C., Stuginski-Barbosa, J., Rodrigues Conti, P. C., Velly, A. M., & Canto, G. D. L. (2019). Placebo and nocebo response magnitude on temporomandibular disorder-related pain: A systematic review and meta-analysis. *Journal of Oral Rehabilitation*, *46* (9), 862–882. https://doi.org/10.1111/joor.12827

Price, D. D., Finniss, D. G., & Benedetti, F. (2008). A comprehensive review of the placebo effect: Recent advances and current thought. *Annual Review of Psychology*, *59* (1), 565–590. https://doi.org/10.1146/annurev.psych.59.113006.095941

Quattrone, A., Barbagallo, G., Cerasa, A., & Stoessl, A. J. (2018). Neurobiology of placebo effect in Parkinson's disease: What we have learned and where we are going. *Movement Disorders*, *33* (8), 1213–1227. https://doi.org/10.1002/mds.27438

Quinn, V. F., & Colagiuri, B. (2015). Placebo interventions for nausea: A systematic review. *Annals of Behavioral Medicine*, *49* (3), 449–462. https://doi.org/10.1007/s12160-014-9670-3

Radziwill, K., & Kruszewski, J. (2011). Evaluation of the size of the placebo effect in treatments of allergic diseases and asthma based on a meta-analysis of efficacy trials of drugs. *Advances in Dermatology and Allergology/Postępy Dermatologii i Alergologii*, *28* (5), 372–377.

Ramírez-Saco, D., Barcheni, M., Cunill, R., Sáez, M., Farré, M., & Castells, X. (2022). Nocebo response in attention deficit hyperactivity disorder: Meta-analysis and meta-regression of 105 randomized clinical trials. *Journal of Attention Disorders*, *26* (11), 1412–1421. https://doi.org/10.1177/10870547221075845

Rheims, S., Cucherat, M., Arzimanoglou, A., & Ryvlin, P. (2008). Greater response to placebo in children than in adults: A systematic review and meta-analysis in drug-resistant partial epilepsy. *PLoS Medicine*, *5* (8), e166. https://doi.org/10.1371/journal.pmed.0050166

Rief, W., Nestoriuc, Y., Weiss, S., Welzel, E., Barsky, A. J., & Hofmann, S. G. (2009). Meta-analysis of the placebo response in antidepressant trials. *Journal of Affective Disorders*, *118* (1-3), 1–8. https://doi.org/10.1016/j.jad.2009.01.029

Rojas-Mirquez, J. C., Rodriguez-Zuñiga, M. J. M., Bonilla-Escobar, F. J., Garcia-Perdomo, H. A., Petkov, M., Becerra, L., Borsook, D., & Linnman, C. (2014). Nocebo effect in randomized clinical trials of antidepressants in children and adolescents: Systematic review and meta-analysis. *Frontiers in Behavioral Neuroscience*, *8* (375), 1–12. https://doi.org/10.3389/fnbeh.2014.00375

Romanella, S. M., Mencarelli, L., Burke, M. J., Rossi, S., Kaptchuk, T. J., & Santarnecchi, E. (2023). Targeting neural correlates of placebo effects. *Cognitive Affective & Behavioral Neuroscience*, *23* (1), 217–236. https://doi.org/10.3758/s13415-022-01039-3

Rossettini, G., Camerone, E. M., Carlino, E., Benedetti, F., & Testa, M. (2020). Context matters: The psychoneurobiological determinants of placebo, nocebo and context-related effects in physiotherapy. *Archives of Physiotherapy*, *10* (1), 1–12. https://doi.org/10.1186/s40945-020-00082-y

Rossettini, G., Campaci, F., Bialosky, J., Huysmans, E., Vase, L., & Carlino, E. (2023). The biology of placebo and nocebo effects on experimental and chronic pain: State of the Art. *Journal of Clinical Medicine*, *12* (12), 4113. https://doi.org/10.3390/JCM12124113

Schedlowski, M., Enck, P., Rief, W., & Bingel, U. (2015). Neuro-bio-behavioral mechanisms of placebo and nocebo responses: Implications for clinical trials and clinical practice. *Pharmacological Reviews*, *67* (3), 697–730. https://doi.org/10.1124/pr.114.009423

Schwartz, N. A., Turturro, M. A., Istvan, D. J., & Larkin, G. L. (2000). Patients' perceptions of route of nonsteroidal anti-inflammatory drug administration and its effect on analgesia. *Academic Emergency Medicine*, *7* (8), 857–861. https://doi.org/10.1111/j.1553-2712.2000.tb02061.x

Scott, D. J., Stohler, C. S., Egnatuk, C. M., Wang, H., Koeppe, R. A., & Zubieta, J. K. (2008). Placebo and nocebo effects are defined by opposite opioid and dopaminergic responses. *Archives of General Psychiatry*, *65* (2), 220–231. https://doi.org/10.1001/archgenpsychiatry.2007.34

Sedano, R., Hogan, M., Nguyen, T. M., Chang, J., Zou, G. Y., MacDonald, J. K., Casteele, N. V., Hanzel, J., Crowley, E., Battat, R., Dulai, P. S., Singh, S., D'Haens, G., Sandborn, W., Feagan, B. G., Ma, C., & Jairath, V. (2022). Systematic review and meta-analysis: Clinical, endoscopic, histological and safety placebo rates in induction and maintenance trials of ulcerative colitis. *Journal of Crohn's & Colitis*, *16* (2), 224–243. https://doi.org/10.1093/ECCO-JCC/JJAB135

Shapiro, A. K., & Shapiro, E. (2000). *The powerful placebo: From ancient priest to modern physician*. JHU Press (ed.). https://doi.org/10.1136/bmj.316.7141.1396b

Siafis, S., Çlray, O., Schneider-Thoma, J., Bighelli, I., Krause, M., Rodolico, A., Ceraso, A., Deste, G., Huhn, M., Fraguas, D., Mavridis, D., Charman, T., Murphy, D. G., Parellada, M., Arango, C., & Leucht, S. (2020). Placebo response in pharmacological and dietary supplement trials of autism spectrum disorder (ASD): systematic review and meta-regression analysis. *Molecular Autism*, *11* (1), 1–19. https://doi.org/10.1186/s13229-020-00372-z

Siddiqi, S. H., Kording, K. P., Parvizi, J., & Fox, M. D. (2022). Causal mapping of human brain function. *Nature Reviews Neuroscience*, *23* (6), 361–375. https://doi.org/10.1038/s41583-022-00583-8

Silva, M. A., Duarte, G. S., Camara, R., Rodrigues, F. B., Fernandes, R. M., Abreu, D., Mestre, T., Costa, J., Trenkwalder, C., & Ferreira, J. J. (2017). Placebo and nocebo responses in restless legs syndrome: A systematic review and meta-analysis. *Neurology*, *88* (23), 2216–2224. https://doi.org/10.1212/WNL.0000000000004004

Skyt, I., Lunde, S. J., Baastrup, C., Svensson, P., Jensen, T. S., & Vase, L. (2020). Neurotransmitter systems involved in placebo and nocebo effects in healthy participants and patients with chronic pain: A systematic review. *Pain*, *161* (1), 11–23. https://doi.org/10.1097/j.pain.0000000000001682

Su, C., Lewis, J. D., Goldberg, B., Brensinger, C., & Lichtenstein, G. R. (2007). A meta-analysis of the placebo rates of remission and response in clinical trials of active ulcerative colitis. *Gastroenterology*, *126* (5), 1257–1269. https://doi.org/10.1053/j.gastro.2006.12.037

Su, C., Lichtenstein, G. R., Krok, K., Brensinger, C. M., & Lewis, J. D. (2004). A meta-analysis of the placebo rates of remission and response in clinical trials of active Crohn's disease. *Gastroenterology*, *126* (5), 1257–1269. https://doi.org/10.1053/j.gastro.2004.01.024

Swerts, D. B., Benedetti, F., & Prieto Peres, M. F. (2022). Different routes of administration in chronic migraine prevention lead to different placebo responses: A meta-analysis. *PAIN*, *163* (3), 415–424. https://doi.org/10.1097/j.pain.0000000000002365

Świder, K., & Bąbel, P. (2013). The effect of the sex of a model on nocebo hyperalgesia induced by social observational learning. *PAIN®*, *154* (8), 1312–1317. https://doi.org/10.1016/J.PAIN.2013.04.001

Ter Riet, G., De Craen, A. J. M., De Boer, A., & Kessels, A. G. H. (1998). Is placebo analgesia mediated by endogenous opioids? A systematic review. *Pain*, *76* (3), 273–275. https://doi.org/10.1016/S0304-3959(98)00057-8

Tricco, A. C., Lillie, E., Zarin, W., O'Brien, K. K., Colquhoun, H., Levac, D., Moher, D., Peters, M. D. J., Horsley, T., Weeks, L., Hempel, S., Akl, E. A., Chang, C., McGowan, J., Stewart, L., Hartling, L., Aldcroft, A., Wilson, M. G., Garritty, C., … Straus, S. E. (2018). PRISMA extension for scoping reviews (PRISMA-ScR): checklist and explanation. *Annals of Internal Medicine*, *169* (7), 467–473. https://doi.org/10.7326/M18-0850

Vambheim, S. M., & Flaten, M. A. (2017). A systematic review of sex differences in the placebo and the nocebo effect. *Journal of Pain Research*, *10*, 1831–1839. https://doi.org/10.2147/JPR.S134745

Vase, L., Riley, I. I. I., Price, J. L., & D, D. (2002). A comparison of placebo effects in clinical analgesic trials versus studies of placebo analgesia. *Pain*, *99* (3), 443–452. https://doi.org/10.1016/S0304-3959(02)00205-1

Vlaeyen, J. W., Wicksell, R. K., Simons, L. E., Gentili, C., De, T. K., Tate, R. L., … Onghena, P. (2020). From boulder to Stockholm in 70 years: Single case experimental designs in clinical research. *The Psychological Record*, *70* (4), 659–670. https://doi.org/10.1007/s40732-020-00402-5

Vollert, J., Cook, N. R., Kaptchuk, T. J., Sehra, S. T., Tobias, D. K., & Hall, K. T. (2020). Assessment of placebo response in objective and subjective outcome measures in rheumatoid arthritis clinical trials. *JAMA Network Open*, *3* (9), e2013196–e2013196. https://doi.org/10.1001/jamanetworkopen.2020.13196

von Wernsdorff, M., Loef, M., Tuschen-Caffier, B., & Schmidt, S. (2021). Effects of open-label placebos in clinical trials: A systematic review and meta-analysis. *Scientific Reports*, *11* (1), 1–15. https://doi.org/10.1038/s41598-021-83148-6

Wager, T. D., & Atlas, L. Y. (2015). The neuroscience of placebo effects: Connecting context, learning and health. *Nature Reviews Neuroscience*, *16* (7), 403–418. https://doi.org/10.1038/nrn3976

Wager, T. D., Rilling, J. K., Smith, E. E., Sokolik, A., Casey, K. L., Davidson, R. J., Kosslyn, S. M., Rose, R. M., & Cohen, J. D. (2004). Placebo-Induced changes in fMRI in the anticipation and experience of pain. *Science*, *303* (5661), 1162–1167. https://doi.org/10.1126/science.1093065

Wartolowska, K. A., Feakins, B. G., Collins, G. S., Cook, J., Judge, A., Rombach, I., Dean, B. J., Smith, J. A., & Carr, A. J. (2016). The magnitude and temporal changes of response in the placebo arm of surgical randomized controlled trials: A systematic review and meta-analysis. *Trials*, *17* (1), 589. https://doi.org/10.1186/s13063-016-1720-7

Wartolowska, K. A., Gerry, S., Feakins, B. G., Collins, G. S., Cook, J., Judge, A., & Carr, A. J. (2017). A meta-analysis of temporal changes of response in the placebo arm of surgical randomized controlled trials: An update. *Trials*, *18* (1), 323. https://doi.org/10.1186/s13063-017-2070-9

Weimer, K., Colloca, L., & Enck, P. (2015). Age and sex as moderators of the placebo response: An evaluation of systematic reviews and meta-analyses across medicine. *Gerontology*, *61* (2), 97–108. https://doi.org/10.1159/000365248

Welge, J. A., & Keck, P. E. (2003). Moderators of placebo response to antipsychotic treatment in patients with schizophrenia: A meta-regression. *Psychopharmacology*, *166* (1), 1–10. https://doi.org/10.1007/s00213-002-1299-4

Wilhelm, M., Winkler, A., Rief, W., & Doering, B. K. (2016). Effect of placebo groups on blood pressure in hypertension: A meta-analysis of beta-blocker trials. *Journal of the American Society of Hypertension*, *10* (12), 917–929. https://doi.org/10.1016/j.jash.2016.10.009

Yang, S., Gomeni, R., & Beerahee, M. (2014). Does short-term placebo response predict the long-term observation? Meta-analysis on forced expiratory volume in 1 s from asthma trials. *Journal of Clinical Pharmacology*, *54* (11), 1207–1213. https://doi.org/10.1002/jcph.329

Yeung, V., Sharpe, L., Glozier, N., Hackett, M. L., & Colagiuri, B. (2018). A systematic review and meta-analysis of placebo versus no treatment for insomnia symptoms. *Sleep Medicine Reviews*, *38*, 17–27. https://doi.org/10.1016/j.smrv.2017.03.006

Yildiz, A., Vieta, E., Tohen, M., & Baldessarini, R. J. (2011). Factors modifying drug and placebo responses in randomized trials for bipolar mania. *International Journal of Neuropsychopharmacology*, *14* (7), 863–875. https://doi.org/10.1017/S1461145710001641

Zhang, W., Robertson, J., Jones, A. C., Dieppe, P. A., & Doherty, M. (2008). The placebo effect and its determinants in osteoarthritis: Meta-analysis of randomised controlled trials. *Annals of the Rheumatic Diseases*, *67* (12), 1716–1723. https://doi.org/10.1136/ard.2008.092015

Zubieta, J. K., Bueller, J. A., Jackson, L. R., Scott, D. J., Xu, Y., Koeppe, R. A., Nichols, T. E., & Stohler, C. S. (2005). Placebo effects mediated by endogenous opioid activity on μ-opioid receptors. *Journal of Neuroscience*, *25* (34), 7754–7762. https://doi.org/10.1523/JNEUROSCI.0439-05.2005

Zunhammer, M., Spisák, T., Wager, T. D., Bingel, U., Atlas, L., Benedetti, F., Büchel, C., Choi, J. C., Colloca, L., Duzzi, D., Eippert, F., Ellingsen, D. M., Elsenbruch, S., Geuter, S., Kaptchuk, T. J., Kessner, S. S., Kirsch, I., Kong, J., Lamm, C., … Zeidan, F. (2021). Meta-analysis of neural systems underlying placebo analgesia from individual participant fMRI data. *Nature Communications*, *12* (1), 1–11. https://doi.org/10.1038/s41467-021-21179-3