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Placebo effects in osteoarthritis: implications for treatment and drug development

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Abstract

Osteoarthritis (OA) is the most common form of arthritis worldwide, affecting ~500 million people, yet there are no effective treatments to halt its progression. Without any structure-modifying agents, management of OA focuses on ameliorating pain and improving function. Treatment approaches typically have modest efficacy, and many patients have contraindications to recommended pharmacological treatments. Drug development for OA is hindered by the gradual and progressive nature of the disease and the targeting of established disease in clinical trials. Additionally, new medications for OA cannot receive regulatory approval without demonstrating improvements in both structure (pathological features of OA) and symptoms (reduced pain and/or improved function). In clinical trials, people with OA show high 'placebo responses', which hamper the ability to identify new effective treatments. Placebo responses refer to the individual variability in response to placebos given in the context of clinical trials and other settings. Placebo effects refer specifically to short-lasting improvements in symptoms that occur because of physiological changes. To mitigate the effects of the placebo phenomenon, we must first understand what it is, how it manifests, how to identify placebo responders in OA trials and how these insights can be used to improve clinical trials in OA. Leveraging placebo responses and effects in clinical practice might provide additional avenues to augment symptom management of OA.

Introduction

Osteoarthritis (OA), a disease of diarthrodial joints, affects >500 million adults worldwide[1,2]. Pain and functional limitations are the most common disease manifestations,

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contributing substantially to disability[3]. Despite this public health burden, no treatments are available to prevent disease progression. Management focuses on symptom relief, though recommended treatments have modest efficacy, and many patients have contraindications for mainstay pharmacological treatments such as NSAIDs. With inadequate management options, knee and hip replacement surgeries, which are reserved for end-stage disease, are increasingly used[4], and opioids are frequently prescribed for OA despite not being recommended by treatment guidelines[5]. Thus, an unmet need exists to identify safe and effective management options, particularly given the rising prevalence of OA in the setting of an aging population and the obesity epidemic.

Many promising agents have been developed and tested for efficacy in OA, particularly of the knee, which is the most common symptomatic joint, but they have largely failed in clinical trials[6–9]. Drugs cannot receive regulatory approval as disease modifiers without demonstrating improvements in both structure and symptoms. However, studying the effects of a structure-modifying intervention in OA is challenging because of the slow, progressive nature of the disease. Such trials require large sample sizes and long follow-up[10]. Although some trials have demonstrated potential structure modification, they have been hampered by a lack of symptomatic benefits[11].

The placebo phenomenon is a broad concept that refers to the observation that a patient's symptoms can improve after receiving an intervention, even if the intervention itself is inactive or has no specific therapeutic effect. This phenomenon can occur in different settings, such as clinical trials, medical practice and everyday life, and it includes placebo effects and placebo responses. Placebo effects are the improvements in symptoms that occur because of physiological changes. These effects are typically attributed to patients' expectancy that the treatments will be effective, previously learned therapeutic experiences, benefits observed in others and the patient–provider interaction that can in turn activate endogenous brain mechanisms and produce measurable physiological and biological changes. Placebo responses refer to the individual variability in response to placebos given in the context of clinical trials and other clinical settings. Placebo responses are related to factors such as the nature of the illness, bias, co-interventions and the characteristics of the treatment itself. In this Review, we discuss the placebo phenomenon and how it influences drug development and therapy in OA. Trials in OA are recognized to have high placebo responses (with spontaneous improvements resulting from natural disease fluctuations that are not attributable to placebo effects), making it difficult to demonstrate symptom-modifying efficacy[12,13]. Even exercise, which is considered first-line OA management, has recently been questioned as potentially being no better than placebo[14,15]. The need to identify effective therapies in OA necessitates understanding the role of the placebo phenomenon in clinical trials. To do so, we must first understand placebo effects and placebo responses, their manifestation, and identification of placebo responders. Notably, placebo effects have implications for symptom management and care. We propose that leveraging the placebo phenomenon in drug development and ultimately in clinical practice can provide additional options to augment OA symptom management. Future efforts should be made to disentangle the role of nocebo effects in OA drug development and clinical practice (Box 1).

Placebo effects: physiological mechanisms

Linked to psychobiological changes, placebo effects refer to beneficial effects produced by a placebo drug or treatment or a manipulation of the participant's belief, which cannot be attributed to the properties of the placebo or manipulation itself. Rather, placebo effects are results of the cascade of neurobiological changes related to expectancies, prior therapeutic experiences, observation of benefits in others, contextual and treatment cues, and the overall interpersonal interactions between the patient and the heath care provider[16]. The inclusion of a no-intervention arm and possibly a measurement of expectations are critical study design elements that can dissociate placebo effects from placebo responses and related potential confounding factors. By having a `no-treatment group` or non-intervention group, researchers can compare the observed changes in this group with those in the placebo group. If the placebo group shows significantly greater improvements than the no-treatment group, it suggests that the placebo treatment itself (with its psychological and contextual factors) has contributed to the observed changes. By contrast, if there are no significant differences in the observed changes between the placebo group and the no-treatment group, it suggests that the observed improvements are more likely attributable to non-specific factors rather than to placebo effects themselves.

Biological and learning mechanisms involved in placebo effects

Placebo effects engage several neurobiological and physiological mechanisms, including the endogenous opioid, serotonin, β-adrenergic, dopamine, endocannabinoid, oxytocin and vasopressin systems, as well as modulation of peripheral cytokines[16–18]. Mechanisms of placebo effects depend on the target system and illness.

Placebo hypoalgesia, the reduction of pain in response to placebos[16], is a form of endogenous pain modulation that depends on the activation of descending neural pathways, which inhibits pain signalling[19,20].

Classic conditioning-mediated placebo effects can induce immune responses[21,22] and affect disease progression, as demonstrated in a rat model of rheumatoid arthritis (RA)[23]. In this model, a saccharine-flavoured solution was paired with the immunosuppressant cyclophosphamide in rats, and after several paired administrations, the conditioned stimulus (saccharine solution alone) caused immunosuppression, producing a placebo-like, measurable, physiological effect[24].

Placebo effects mediated by classic conditioning processes are also observed in clinical settings. For example, in one study, children received chemotherapy paired with taste and smell stimuli, and a 'chemotherapy-like treatment effect' was achieved using taste and smell stimuli alone in half of the monthly chemotherapy sessions[25]. The term 'chemotherapy-like treatment effects' refers to observed outcomes or responses that resemble the effects typically associated with chemotherapy. These effects can include improvements in symptom relief, changes in physiological markers, or other relevant indicators that are commonly associated with chemotherapy treatment[25]. In another study, patients receiving cyclophosphamide for multiple sclerosis were conditioned with an anise-flavoured syrup and displayed conditioned immunosuppression during a test session, as evidenced by decreased

peripheral leukocyte counts[26]. Similarly, repeated Pavlovian pairings between cyclosporin A and a flavoured drink can produce conditioned immunosuppression, as assessed by the expression of *IL2* and *IFNG* mRNAs, in vitro release of IL-2 and IFNγ and lymphocyte proliferation[27].

These findings indicate that conditioned physiological responses can contribute to placebo effects in humans and can be deliberately used in pain and immune pharmacotherapy with potential clinical implications for structure-modifying interventions in patients with OA (Box 2).

The role of expectancies and expectations

Expectancies, or subjective predictions of future events, can trigger neural responses[28], and could contribute to improvement of clinical outcomes[29–31]. As an illustrative example, honeybees that are exposed to a frequent rewarding system develop expectancies in anticipation of upcoming rewards[32]. These expectancies influence their behaviour later on, even when there are no immediate rewards. It is plausible to think that as we move up the evolutionary scale, conscious cognitive abilities have a greater role in shaping expectations[30]. Expectancies can be unconscious, and consequently are difficult to measure in clinical trials and practices. In fact, there is some overlap between conscious and unconscious processes. By contrast, expectations (which are by definition conscious) can be measured at baseline before a treatment is administered (when establishing patient consent), during the treatment administrations and at the follow-ups. Quantitative measures of expectation can be associated with placebo effects but do not necessarily mediate these effects[33] because placebo effects can occur without any expectation of benefits.

In clinical settings, expectations are affected by the way in which a medication is described, or ‘framed’. For example, in postoperative settings, morphine administered along with the statement “the treatment that you are about to receive is potent in relieving your pain” induces a stronger analgesic effect than covert administration in which the patient is unaware of the timing of morphine administration[34]. In this situation, potential awareness of the upcoming treatment administration (resulting in treatment or stimulus expectancies) and the information related to the therapeutic effect (giving outcome or response expectancies) conflate, enhancing the overall outcome.

The possibility that expectations influence response to treatment in OA trials was investigated in a randomized controlled trial (RCT) in which participants were randomized to genuine or to sham acupuncture, and within each group, further randomized to a communication style designed to shape high or neutral expectations[35]. No difference was observed in pain outcomes between genuine and sham acupuncture groups, but independent of treatment assignment, the high-expectation communication group had better outcomes than the neutral-expectation group.

At the neural level, several studies have addressed the topic of expectancies and outcomes in OA. Using functional MRI, the influence of expectancy on analgesia was investigated in adults with OA who were treated with genuine or with sham electroacupuncture[36]. Expectancy was manipulated by the use of verbal suggestion that acupuncture would

diminish heat pain and by surreptitiously lowering the temperature of a noxious heat stimulus applied after an initial heat stimulus and electroacupuncture. Expectancy influenced both genuine and sham acupuncture treatment responses. However, brain activity associated with genuine and sham acupuncture treatment had specific patterns of blood oxygenation level-dependent activity in the lateral prefrontal cortex, suggesting that different brain mechanisms mediate responses to these placebo and active treatments[36].

Whether boosting patients' expectations could improve treatment outcomes was investigated in patients with OA who were randomly assigned to 'boosted' acupuncture (with an expectation manipulation), 'standard' acupuncture or treatment as usual (the 'standard' pathway but without acupuncture); the study consisted of 6–10 sessions per patient[37]. Brain imaging scans were acquired during the first and sixth treatment sessions. The boosted acupuncture group showed greater pain reduction than the standard acupuncture and treatment-as-usual groups. Functional connectivity of nucleus accumbens with medial prefrontal cortex/rostral anterior cingulate cortex and dorsolateral prefrontal cortex was higher with boosted acupuncture than with standard acupuncture after multiple treatments. Additionally, expectation ratings after the first treatment session were associated with decreased post-treatment OA pain and increased functional connectivity[37].

Introducing proxies of expectations is a useful way to control for the role of expectations in treatment outcomes and, to some extent, placebo responses[38]. Various scales have been suggested to measure expectations[39], including validated questionnaires[39–42] and visual analogue scales[33]. These scales can be framed to assess anticipated outcomes, the desire for benefits, allocation guessing and perception of benefits, as well as the patient's direct perceived benefits (such as perceived placebo effects).

Implementing measures to mitigate potential reporting bias and exploring strategies to enhance blinding and to minimize the effects of patient and assessor expectations could contribute to attainment of a more nuanced understanding of the underlying mechanisms by which these factors influence study outcomes. Careful assessment of expectations could help to discriminate between changes resulting from placebo effects and those associated with positive `Hawthorne effects`, which are described later in the Review.

How to identify placebo responders: from brain signatures to sociodemographic factors

An important goal is to phenotype individuals who are placebo responders, and to better understand clinically measurable factors that influence placebo effects biologically[43]. Brain signatures and genetic and sociodemographic phenotypes can identify placebo responders.

In a study involving brain imaging, participants with chronic knee OA engaged in two clinical trials: trial 1 was a 2-week single-blinded study in which the 17 participants all received placebo pills, and trial 2 was a 3-month double-blinded randomized study in which 20 participants received placebo pills and 19 received duloxetine[44]. All participants underwent baseline and follow-up resting-state functional MRI. A separate 'no-treatment' `natural history` group ($n = 42$) of people with knee OA was also included. In both trials, ~50% of participants showed placebo analgesia, and placebo responders were best identified by right midfrontal gyrus connectivity. Subtraction of the linearly modelled

placebo response from the duloxetine response demonstrated that the right parahippocampal gyrus connectivity predicted the drug responses.

A biosignature consisting of dorsolateral prefrontal cortex-precentral gyrus functional connectivity was investigated for classification of individuals with chronic low back pain into placebo responders and non-responders, with the goal of dissociating the placebo and active-treatment responses[45] (Fig. 1). Participants were randomized to no treatment, placebo or naproxen for 6 weeks after 3 weeks of baseline pre-treatment and followed by 3 weeks of post-treatment monitoring. The biosignature separated placebo responses and naproxen responses, indicating that at least for these trials, the two effects were additive.

Imaging studies have correlated phenotypic variation with brain structure and function. A recent taskforce outlined the potential of using brain imaging for the prediction of treatment outcome in patients with chronic pain[46]. However, challenges remain in relation to generalizability, reproducibility, specificity, validity and interpretability[43].

Studies in both healthy controls and participants with different chronic pain conditions have suggested that placebo effects have genetic and/or genomic components[47,48]. Genetic profiling might therefore contribute to the identification of placebo responders.

In a study comparing patients with chronic pain from temporomandibular disorder and healthy individuals, placebo effects in response to painful thermal stimuli were observed in both groups, with placebo response rates of 53.4% and 67.8%, respectively[33]. Placebo effects in patients with temporomandibular disorder do not extinguish over time and depend on prior therapeutic experience[49]. These effects are predicted by learning patterns when latent classes are used to identify underlying subgroups within a larger population based on their response patterns[50], and are affected by race (with larger placebo effects occurring when participants and experimenters are of the same race)[51] and sex (with larger placebo effects in women than in men)[52,53]. Placebo mechanisms in healthy individuals differ from those in patients with temporomandibular disorder[54]. The psychological characteristics of lower emotional distress, lower pain-related fear and less catastro-phizing are associated with greater placebo effects[54–56]. Therefore, participants with emotional distress and maladaptive cognitive pain appraisals benefit less from placebo effects. The weaker placebo effect in these participants may account for their poorer treatment response (presumably, because they cannot activate a placebo effect to augment treatment effects).

An example of predictive modelling of placebo responses in OA trials

Data from two phase III RCTs (NCT02697773 and NCT02709486) in OA of subcutaneous tanezumab (an antibody targeting nerve growth factor that is no longer in development) were analysed to assess patient-related factors predicting treatment and placebo responses[57–60]. Factors such as baseline pain variability, use of rescue medication and excessive variability of pain ratings were investigated to account for treatment-effect heterogeneity. The two phase III RCTs included participants with moderate-to-severe OA who were randomly assigned to either subcutaneous placebo (n = 514) or tanezumab (n = 514). Secondary analyses were performed using machine-learning approaches (such as gradient-boosted regression trees and Virtual Twins models) to identify factors that predicted the pain scores

of the Western Ontario and McMaster Universities Osteoarthritis Index. The relationship between each variable and the response to placebo or tanezumab within the models was also assessed, and subgroups with differential reactions to active treatment and placebo were determined. The results were that baseline pain severity and Kellgren–Lawrence grade of radiographic OA severity were positively associated with placebo responses. These characteristics suggest heightened expectations and expectancies that a novel treatment might provide relief in patients with severe disease. Longer OA duration and previous medication failures predicted treatment responses. One possibility is that a combination of factors predicting placebo and treatment responses determine the overall treatment efficacy. Whether factors identified in one study to predict placebo or treatment responses would also predict treatment outcomes in other studies is not yet known.

Variables related to the patient, such as sex, race, concomitant medical conditions and medications, as well as their individual expectations and prior experiences with therapy, can influence the response in both treatment and placebo groups[17,33,61,62]. The ability to identify patients based on their differential responses to treatment and placebo could improve clinical trial designs, assay sensitivity and outcomes, and ultimately contribute to the development of precision medicine for the treatment of pain in OA[63].

Ideally, an extension of this approach to OA (and other conditions) will leverage discovery of clinical phenotypes to improve trial designs, including consideration of the appropriateness of using the identified factors to randomize participants with the target phenotypes equally across groups and/or restrict them when a new clinical trial design is developed. Large datasets treated with appropriate statistical, machine learning and/or artificial intelligence approaches could help to identify clusters of features that can be used to guide treatment choices, which in turn will help to move OA management towards precision medicine. In addition to analyses of patient data using machine learning and artificial intelligence approaches, similar methods could be employed to identify characteristics of investigators that are associated with greater placebo responses. These characteristics might include the investigators' cultural backgrounds, personality traits and their knowledge and beliefs about the verum and placebo. This approach could help to elucidate the complex interactions between investigator characteristics, patient expectations and treatment outcomes, contributing to a deeper understanding of the placebo phenomenon in clinical trials.

Placebo responses in clinical trials: in search of the optimal study design

Understanding placebo responses to improve clinical trials is important, particularly in a disease such as OA in which long trial durations are often necessary. The placebo response in RCTs is generally recognized to be a factor that must be accounted for, either by trying to minimize its presence, or by ensuring an adequate sample size to overcome it. Large placebo responses can decrease one's ability to distinguish treatment effects, thereby potentially keeping effective therapies from being approved by regulatory agencies.

From confounding factors to randomization

Frequently, the clinical response observed in the placebo group is inaccurately attributed to placebo effects. To identify placebo responses, it is crucial to conduct an adequate evaluation of factors that could be confounders[64,65]. These confounding factors include (but are not limited to) natural history, `regression to the mean`, bias, measurement errors (false-positive and false-negative errors) and even unidentified co-interventions[66] (Fig. 2). For example, flares in OA are frequent, and the challenge lies in distinguishing the genuine effects of treatment (including placebo effects) from the influence of flares and regression to the mean. Typically, participants are enrolled in trials during a flare to meet inclusion criteria related to pain severity. As a result, a substantial portion of the observed improvement at trial end points (especially in trials lasting for months) is often attributable more to regression to the mean than to specific placebo effects. Careful study design, statistical analysis and appropriate `control groups` can help researchers to accurately interpret treatment responses and discern the actual contributions of placebo effects in the context of OA clinical trials.

The Hawthorne effect – that patients can experience therapeutic benefits simply from being included in a clinical trial – is another factor to consider[67–69]. Hawthorne effects refer to the phenomenon whereby individuals modify their behaviours or responses in research or clinical settings because of the awareness of being observed or studied. In the context of clinical trials, patients might alter their symptom expression to align with what they perceive as the expectations of the investigators, or to please their physicians[70]. Additionally, social interaction among participants in a trial could potentially contribute to alterations in outcome measures[71]. This effect is attributed to the desire to comply with perceived expectations, or to the belief that positive responses will lead to better outcomes[69]. The issue of participants' willingness to please assessors and its potential influence on observed outcomes warrants further consideration. For example, improvements observed in clinical trials that use subjective assessment tools can sometimes disappear after the trials end[72]. For example, in a study of participants with RA, almost half of the improvement measured using the subjective Health Assessment Questionnaire score vanished in a non-sponsored follow-up study conducted by different investigators, despite treatments remaining unchanged and the Health Assessment Questionnaire score remaining stable during the trial[72]. A substantial proportion of improvements in pain, patient global assessment and fatigue also disappeared in the follow-up study. These findings highlight the influence of investigators' expectations on participants' responses and the participants' inclination to 'reward' their supportive investigators. Finally, the notion that positive Hawthorne effects are merely psychological in nature is being challenged by results demonstrating reduced pain intensity and activation of underlying brain processes during patient–clinician interactions[73]. Additional functional MRI studies and other research is necessary to disentangle the contributions of placebo effects and Hawthorne effects to subjective scores, such as pain assessments. Furthermore, understanding the effects of investigator and assessor beliefs and expectations on treatment outcomes should be a focus of further investigation, especially in the context of individual variability and multicentre trials.

RCTs that only include a new-treatment group, an active-control group and a placebo group but that lack a no-treatment control group, might capture various effects that can potentially obscure real outcomes[66]. An example of a no-treatment control group is the wait-list group of participants who receive delayed treatment or intervention after a waiting period. The wait-list group serves as a comparison group to assess the effectiveness of a delayed intervention or treatment by comparing its outcomes to those of patients who received the intervention immediately. This strategy is often used in OA exercise trials where blinding is challenging. When a placebo comparator or a wait-list group is not possible, such as in circumstances in which it is unethical to use one or when a placebo is not readily available, RCTs can compare a new treatment with the standard-of-care treatment (the active control group). Thus, to accurately measure placebo effects, it is essential to include an untreated control group (the standard-of-care treatment group) in clinical trials to identify other non-specific effects[74].

The use of wait-list groups as controls in RCTs is not without its limitations. Participants in these groups are often aware of their exclusion from the study, which can introduce biases. Hawthorne effects, both positive (such as limiting pain complaints in response to assessor kindness) and negative (such as exaggerating assessments to align with perceived investigator expectations or to express frustration), can influence outcomes.

The benefit of randomization in a trial is related to the balancing of both known and unknown confounders across trial treatment groups, so that any differences in outcome between the groups can be ascribed to the intervention rather than to extraneous factors. Furthermore, there are many factors beyond the intervention that can lead to improvement, thus necessitating a comparator group, which is customarily a placebo when ethically feasible. The difference in improvement between the intervention group and the placebo group is attributed to the benefits of the intervention. This approach presupposes that the full benefit of the intervention, which reflects the specific biological effects of the intervention plus the many factors involved in the placebo responses that can lead to improvement, is not as important as the specific component directly attributable to the biological mechanism of the intervention.

Study designs

Various clinical trial designs have been used for the separation of placebo effects from treatment effects[17,75]. The placebo-controlled design is commonly used, but other designs such as the balanced-placebo design[76], double-blind versus deceptive design[77], open–hidden treatment administration[34,78,79], open-label placebo design[80,81], dose-extending placebo design[82], free-choice design[83], sequential parallel comparison[84] and enriched enrolment with randomized withdrawal design[85] have been used in various settings.

Balanced placebo.—The balanced-placebo design was formulated in 1962 (ref. 76) and is a research method used for the investigation of the psychological effects of a drug by manipulating participants' expectations of receiving the drug. In this design, participants are randomly assigned to one of four groups: those who receive the actual drug and are told

that they are receiving it (true-drug group), those who receive a placebo and are told that they are receiving the drug (placebo group), those who receive the actual drug but are told that they are receiving a placebo (hidden-drug group), and those who receive a placebo and are told that they are receiving a placebo (control group). By comparing the responses of these groups, researchers can determine the extent to which expectations of receiving a drug influence the reported effects of the drug. The design helps to control for placebo effects and provides valuable information on the pharmacological and psychological effects of a drug. In a hypothetical OA trial of a structure-modifying drug, this design would enable the 'true' treatment effect to be determined by comparing the relative 2 × 2 differences in objective and subjective outcomes (Fig. 3). For example, the differences in outcomes between the true-drug group and the placebo group provide insights into the true treatment effect while accounting for expectancies. Comparison of the hidden-drug group and the control group provides insights regarding synergistic and additive treatment and placebo effects.

The balanced-placebo design enables isolation of treatment efficacy under the reduced (treatment given as a placebo) and augmented (treatment given as treatment) expectation effects on symptom and structure modifications. An authorized deception[86] in consenting prospective study participants would enable implementation of this design in real-world settings. Currently, it is not known whether regulatory agencies would accept such a design for a clinical trial. It would be interesting to establish whether, if an OA trial has demonstrated some structural benefits but no symptomatic benefits, the balanced-placebo design might enable identification of symptomatic treatment efficacy.

Double-blind versus deceptive.—The double-blind-versus-deceptive design compares administration of an active drug or placebo in a double-blind setting to deceptive administration of the same drug. For example, in a study in which patients received a basal saline infusion and were told that it could be either a placebo or a painkiller (double-blind administration), or they were told that it was a potent painkiller (deceptive administration), the subsequent requirement for opioids was lower in the double-blind group than in patients given no information about the basal infusion, and was lower still in the deceptive-administration group[87], emphasizing the importance of expectancy in treatment response.

Double balanced placebo.—The balanced-placebo design and double-blind-versus-deceptive design both have their merits but one limitation is that some investigators might be aware of the treatment given, which would compromise the benefits of double-blinding. More sophisticated designs can be imagined, such as the double balanced-placebo design that would involve additionally manipulating the investigator's knowledge of the drug given, to better assess the relative effects of patient expectations and investigator expectations on the study outcomes. Implementing a double balanced-placebo design could provide valuable insights into understanding the influence of different expectations on treatment outcomes, while addressing the limitation of investigator awareness.

Overt–covert.—An overt–covert (also called open-hidden) treatment administration procedure can separate active treatment from psychosocial effects without any placebo

treatment[34,78,79]. For the covert administration, the onset of delivery of the treatment remains unknown, but to minimize deception, patients know that they are being treated[88].

Open label.—Open-label-placebo designs involve the use of adjuvant placebos given along with standard treatments[89]. This design has shown that even when patients are informed that they are receiving a placebo rather than an active treatment, they still experience improvements in their symptoms. Unlike traditional designs, in which the patient is not aware that they are receiving a placebo, open-label placebos are administered with full disclosure to the patient.

Free choice.—Another emerging methodology is the free-choice design[83], in which participants are typically presented with a range of alternatives or stimuli and are given the autonomy to select the option that best aligns with their preferences or interests. The free-choice design has several key aspects. The first involves autonomy and freedom, as participants have the freedom to select their preferred option, enabling researchers to study the genuine choices made in accordance with individual motivations and preferences. The second is the naturalistic setting, as free-choice designs create an environment that simulates the conditions individuals encounter when making choices in their daily lives. The third aspect is that of individual differences, as free-choice designs acknowledge and capture the individual differences in decision-making processes and preferences. However, a problem with this design is the lack of random assignment to the experimental conditions. Despite this limitation, this design enables participants to freely choose, so that researchers can observe variations in choices and investigate the factors that influence decision outcomes.

Replication and assay sensitivity

Some 60–90% of the results of published clinical-research studies cannot be replicated[90]. In a meta-analysis across all scientific research areas to identify factors associated with bias and lack of replicability, small-study effects, publication bias and citation bias were the most common issues[91]. Small-study effects, in which smaller studies report larger effect sizes, were the most notable source of bias. However, ignoring the impact of placebo responses and effects can also contribute to replication failure.

The ‘decline effect’ is a phenomenon in which initial studies tend to overestimate the magnitude of a particular psychological or physiological effect compared with later studies. This decline in effect size could be the result of various factors, including regression to the mean, natural history, quality of blinding and placebo effects[92]. A decline in effect is often noted with respect to promising results from phase II trials that fail to replicate in phase III trials. A recent evaluation illustrated that 55% of phase III trials failed because of a lack of efficacy, and all of these trials were presumably based on promising efficacy data at earlier phases[93].

Placebo responses decrease the ability of clinical trials to detect true treatment effects. The development of novel therapeutics requires study designs that have sufficient assay sensitivity and reproducibility to detect genuine differences between the study treatments and placebo across multiple studies. As indicated previously, placebo responses can be substantial in OA trials. A meta-analysis reported that the effect size for placebo effects

for pain outcomes was 0.51 (95% CI 0.46–0.55), which is better than many standard OA treatments[13]. Additionally, the effect size for no treatment was 0.03 (95% CI −0.13 to 0.18), providing an example where natural history gives a useful comparison with placebo and illustrates the size of placebo effects.

Additivity versus synergism

The gold standard to prove efficacy often assumes additivity, so that the effect of a treatment is the result of subtraction of the effect observed in the placebo group from the effect observed in the active-treatment group[94]. Additivity has been extensively discussed in relation to placebo analgesia[95], and additive[96] and synergistic effects have been documented[95]. Several assumptions about the additivity of placebo effects and their components are challenged by results from many studies[17,64,65]. First, it assumes that a simple two-group design with a single placebo comparison group is sufficient to capture placebo effects and their interactions with the active treatment, and therefore is sufficient to determine that the active treatment effect is real. We now know that placebo effects consist of multiple dissociable mechanisms, so a simple additive notion to explain treatment effect is probably not accurate[16].

Another challenge in OA trials is the concern that placebo effects are greater for subjective than for objective outcomes[97]. Several studies have shown discordance between the observation of structural or biochemical improvement and a lack of effect on subjective pain outcomes, raising concerns about placebo responses in subjective outcomes in OA obscuring real structural or biochemical treatment effects[7,11]. In further elucidating the conundrum of objective versus subjective outcome improvements, it might be helpful to consider a placebo study that compared the effects of a bronchodilator, two placebo interventions, and no intervention on outcomes in patients with asthma[98]. The results showed that albuterol increased lung function compared with the placebo interventions or no intervention. However, patient self-reported improvement ratings did not differ between albuterol and the placebo interventions, and all three interventions resulted in greater subjective improvement than in the no-intervention arm. The conclusion was that placebo effects can be clinically meaningful in patients with asthma, but patient self-reported outcomes can be unreliable, and an assessment of the untreated response might be essential in evaluating patient-reported outcomes[98]. By contrast, an evaluation of five RCTs in RA called into question the meaningful difference in placebo responses between subjective and objective outcomes[97]. It should be noted, however, that it is challenging to address the potential for regression to the mean for some objective outcomes such as inflammatory markers that might be elevated in the midst of a flare when participants are more likely to enter a trial.

Other factors to consider in study design and analysis include differences in outcome perception between patients and caregivers (and clinicians), and the choice of outcomes, such as using pain disability versus pain intensity[17]. Variation in patients' responses to treatment, which is also referred to as treatment-effect heterogeneity, could contribute to differences in treatment response[99]. In particular, baseline pain variability and excessive variability of pain ratings have been associated with treatment-effect heterogeneity[100,101].

Screening

Screening out placebo responders in OA clinical trials might increase the opportunity to detect treatment effects[102]. The assumption is that removing placebo responders could help to maximize the overall effect of the active treatment. However, excluding placebo responders from clinical trials can be detrimental, because placebo responders often respond to treatments. It might be assumed that placebo responses are reproducible, and it is clear that some people respond to placebos over time[103], whereas others do not. However, whether placebo responsivity is reproducible[103] (that is, whether it is a state or a trait) across contexts is not known[104]. Measurements of expectations can help to predict changes in outcomes, but not necessarily to identify placebo responders and non-responders.

Blinding

Examination of blinding strategies, including the assessment of unblinding during the trial and its potential effects, enhances study robustness and strengthens the validity of the findings. Regularly checking participants' beliefs regarding the treatments they are receiving (verum versus placebo) during the trial can help to identify and correct any unblinding bias that can occur, which becomes especially important for injectable OA treatments such as hyaluronic acid, where the viscosity of the verum can potentially reveal its identity, or for platelet-rich plasma treatments in regions where local regulations require preparation in plain view of the patient. The concept of blinding in trials is often disputed, and concealment is frequently imperfect[105]. Inadequate or unclear allocation concealment can lead to exaggerated effect estimates in trials with subjective outcomes, such as pain[106]. Last, but not least, the importance of information leaflets and their clarity in clinical trials should be considered.

Commercial leaflets

Commercial leaflets often fail to acknowledge the possibility that a drug or procedure might induce improvement through various placebo phenomena. Although the placebo phenomenon is typically briefly described in the information sheets provided to patients before entering a trial, it would be valuable to assess through short questionnaires what participants enrolled in OA trials truly understood after reading this information. Commercial leaflets are also influenced by cultural factors, which contribute to the variability in placebo responses observed in RCTs of pharmacological treatments, as demonstrated for ulcers, hypertension and other conditions[107]. By examining participants' comprehension of placebo-related information (including sharing clinical notes)[108] researchers can gain insights into how effectively this important aspect is conveyed and whether there is room for improvement in enhancing patient understanding and informed consent.

Geographic and cultural aspects

Geographic and cultural aspects that contribute to variability in placebo responses include social, environmental and lifestyle factors that can influence individuals' expectations and perceptions of treatment. Results from a three-group study of acupuncture for xerostomia (dry mouth) among patients with head and neck cancer illustrate the effect of culture and

context. The study compared sham acupuncture (wrong body points), real acupuncture (correct body points) and standard therapy without acupuncture in centres in China and the USA[109]. The effectiveness of sham acupuncture differed between the USA and China. Thus, context (in this case, location) trumped the treatment effects in a direct way. Guidelines would have approved acupuncture based on the US results, but not the Chinese results[110]. Various features of treatments, including cost (more expensive treatments are associated with greater placebo effects)[111,112], generic versus branded labelling[113] and administration route (placebo tablets versus injection)[114] affect placebo responsivity. In OA trials, more-invasive placebos, such as intra-articular injections (and also topical treatments), are associated with greater placebo responses than oral placebos[12,13].

In summary, to confirm the presence of placebo effects, it is essential to demonstrate a distinction between the natural history experienced in the no-treatment group, which reflects spontaneous changes in symptoms, and the placebo group. Many studies have investigated the role of patient characteristics and trial design factors that might affect patient response to placebos or treatments.

Implications for clinical care

An unmet need exists for effective OA therapies. We believe that one way to remedy this situation is to leverage placebo effects. One could envision that, in the future, treatment plans could incorporate placebo-related procedures (such as open-label or dose-extending designs) as well as strategies to shape expectations of benefit and patient–provider communication and interactions. Precision medicine could help by incorporating biological and clinical phenotypes so that therapeutic strategies are guided by individuals' treatment-response and placebo-response profiles (Fig. 4).

Open-label placebos

Clinicians are often concerned with the moral and ethical appropriateness of attempting to leverage placebo effects as potentially being dishonest about the 'true' efficacy[115]. In this regard, the use of the open-label placebo procedure merits consideration and further investigation in OA. This design has been used in proof-of concept trials for irritable bowel syndrome in adults[81,116] and children[117], and for chronic low back pain[118,119], depression[120], rhinitis[121], cancer-related fatigue[122] and menopausal hot flushes[123].

Criticisms of the open-label placebo approach relate to the clinical implications (such as the consequences of prescribing placebos), recruitment biases, blinding and randomization. However, by eliminating the ethical dilemma of deception, open-label placebos can potentially be used for the mitigation of chronic pain. Open-label placebos can improve knee pain in older adults with symptomatic knee OA[124], but they do not affect functional limitation or mobility of the knee. Patients with severe disease might have heightened expectancies of benefit because of the content of verbal suggestions. However, it seems that the specific content of the verbal suggestion does not substantially influence the effectiveness of open-label placebos. Overall, open-label placebo administration can be considered as a supportive analgesic treatment option for symptomatic knee OA in elderly patients, but further research is needed to explore the potential benefits and limitations

of this approach. It is also worth noting that open-label placebo treatments should not be viewed as a replacement for other conventional treatments or interventions for knee OA, but rather as an adjunctive therapy that can complement other treatments.

Dose-extending placebos

Dose-extending placebo procedures can be used for the maintenance of clinical therapeutic responses[82]. In this approach, a cue paired repetitively with a given pharmacological treatment induces a treatment-like response that maintains the therapeutic effect with a sub-clinical dose or without the active treatment[125–127]. By this method, the placebo effect can decrease the total dose of active medications required for a clinical response, including opioids for pain following spinal cord injury[126], stimulants for attention-deficit hyperactivity disorder[127], glucocorticoids for psoriasis[125], zolpidem for insomnia[128], desloratadine for allergic rhinitis[129] and immunosuppressive drugs following renal transplantation[130].

This area of research harnesses placebos to improve therapeutic outcomes using learning-based approaches that elicit behavioural and physiological responses resembling those produced by active drugs[131–133]. Results indicate that placebos associated with repeated administration of active treatments, such as morphine, can acquire drug-like properties, such as pain reduction, in both humans[134,135] and animals[136]. Furthermore, the effects achieved by this method are more pronounced than those achieved by administering placebos alone[135,137–140]. If placebos administered in a learning-based manner can enhance and replicate the actions of active drugs, they could be employed to regulate pain and other OA symptoms, potentially minimizing the adverse effects and drawbacks associated with the continued use of active drugs. Importantly, a patient's pre-authorized use of placebos avoids ethical challenges linked to deception and aligns with professional norms of disclosure and informed consent. When robust evidence indicates therapeutic benefits comparable with standard treatment, the consideration of introducing pre-authorized, dose-extending placebo use into clinical practice becomes warranted.

Preoperative opioid utilization in patients undergoing joint-replacement surgery is linked to unfavourable postoperative consequences, such as increased risks of surgical-site and periprosthetic infections, higher rates of revision surgery, reduced improvement in pain and function, persistent opioid use after discharge, longer hospital stays and elevated healthcare costs[141–144]. The high rates of joint-replacement surgeries in OA, along with the role of preoperative opioid use, makes this area an intriguing one for the optimization of dose-extending placebo effects.

Exploring the preoperative rationalization of opioids by leveraging placebo analgesic mechanisms, whether through open-label placebo, dose-extension placebo or other designs, has great clinical potential. Promoting and researching such strategies could have meaningful implications for the improvement of patient outcomes, reduction of healthcare costs and addressing the issues associated with opioid use in the context of OA-related joint-replacement surgeries.

Leveraging placebo effects therapeutically without any placebos

The use of drugs or procedures primarily based on their placebo effects, especially when they have adverse effects and high costs, raises its own ethical concerns. Pharmaceutical companies and healthcare providers might benefit from the placebo use more than the patients themselves. Patients might then be exposed to ineffective, costly and potentially risky therapies or procedures, diverting medical resources and funding from other needed areas. Furthermore, it is likely that resources are unnecessarily expended because of under-recognition of the fact that improvements that are attributed to drug therapies might actually result from regression to the mean. If improvements are mistakenly attributed to the drug's effectiveness without considering regression to the mean, it can lead to unnecessary use of the drug in cases where natural variations would have resulted in improvement regardless of the treatment, leading to the overuse of certain medications and unnecessary resource expenditure. These concerns and others suggest that it would be unethical to endorse the use of active drugs that work as placebos and that are not cost free.

One way to leverage placebo effects without giving placebos is to discuss therapeutic options in a positive manner, which can improve treatment outcomes. For example, in an RCT of acupuncture in which participants were randomized to a high-expectation or a neutral-expectation communication style, the high-expectation groups had better treatment outcomes[35]. It is likely that a combination of factors associated with placebo responses (and placebo effects) could result in improved treatment outcomes. Thus, one way to leverage placebo effects is to augment the therapeutic alliance between healthcare providers and patients to support positive patient expectations of improvement. The observation of improvement following opioid intake provides an example of the role of expectations and placebo effects and/or responses. Particularly in patients with chronic conditions such as OA, a substantial portion of the overall effect of opioids can be attributed to expectations and placebo effects and/or responses. This observation highlights the potential role of patients' expectations, conditioning and the contextual factors surrounding opioid administration in influencing treatment outcomes. Furthermore, the limited availability of double-blind, placebo-controlled trials examining the short-term and long-term efficacy of opioids in OA emphasizes the need for more rigorous research in this area to better understand the specific contributions of opioids and placebo effects in managing OA-related symptoms.

Regardless of the potential to leverage various placebo strategies in clinical practice, discussion of the risks and benefits and understanding of placebo mechanisms are important aspects of informed consent[145,146] and shared decision-making[147]. For such healthcare provider–patient relationships, communication style and framing effects[148] are important. A clinician who conveys too much negativity about the potential for a therapy to provide benefit, or who is too cautious regarding the patients' concerns about overstating benefits or underplaying risks, can negatively influence the eventual perceived treatment benefits.

Some of these ethical and clinical considerations are also culturally influenced. In some regions and cultures, simply making a recommendation to a patient as to what to do would be considered paternalistic as patient autonomy is deemed a high priority[149]. Other related factors in patient–clinician communication include patient (and clinician) expectations, coping skills and perception of pain severity. Alignment of the expectations of patients

and health providers with realistic and achievable benefits is also important. For example, zero pain is often not a realistic goal for people with knee OA, whereas improvement in physical functioning would be more realistic and lead to improved quality of life with reduced treatment burden.

Given these considerations, shaping patients' expectations, teaching clinicians how to communicate with patients in a positive manner and studying the potential use of open-label and dose-extension placebos in OA can help to improve treatment outcomes in clinical trials and in practice. At the same time, the OA research community must continue to address the heterogeneity of study participants enrolled into RCTs with targeted phenotyping to match the right treatment to the right patient, and it must improve measurement of relevant outcomes (by improving assay sensitivity) to enhance the ability to detect treatment signals.

Conclusions

OA has a substantial public-health burden, as no proven disease-modifying therapies are yet available, and symptomatic treatment options are limited. Effective and safe management options for OA represent a major unmet need. Identification of placebo responders and incorporation of an understanding of the placebo phenomenon into the design of RCTs in OA can provide an opportunity for improved detection of treatment effects. Leveraging placebo effects in the clinical management of OA can also offer adjunctive treatment options to improve symptoms and quality of life in people with OA.

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Glossary

Active-control group
The group assigned to receive a treatment that is known to have physiological effects

Balanced-placebo
The balanced-placebo design refers to a research methodology used in placebo-controlled studies to differentiate between the pharmacological effects of a treatment and the psychological effects of believing that one is receiving the treatment. In this design, participants are divided into groups, and each group receives a combination of active treatment, placebo and information about which they have received

Bias
Bias in research refers to an aspect of the study design, data collection or analysis of data that can lead to incorrect interpretation and/or conclusions about the results of a study

Control groups
The groups assigned to receive either no treatment or a placebo, enabling comparison to determine the effectiveness of the experimental treatment

Dose-extending placebo
A classic conditioning placebo-related procedure used to extend the effect of the active treatment. After repeated pairing of the active full-dose treatment with a conditioning stimulus, exposure to the conditioned stimulus, either alone or together with a lower dose of the active treatment, mimics the therapeutic effect of the active treatment or extends its effect

Double-blind versus deceptive
Comparison between a double-blind and a deceptive design. In the double-blind design neither the participants nor the researchers administering the treatments know who is receiving the active treatment and who is receiving the placebo. This helps to reduce bias and ensures objective evaluation of the treatment's effects. The deceptive design in the context of clinical trials or experiments refers to intentionally misleading participants or withholding information about the nature of the treatment or intervention that they are receiving

Expectancy
Implicit expectancies are those that are present without full awareness or conscious intent. As opposed to expectations, expectancies are difficult to formally measure and quantify

Expectations
Expectations refer to the belief or anticipation that a certain outcome will occur, which can be both conscious and unconscious. Expectations can be measured using validated scales and questionnaires to assess how strongly participants expect a certain outcome to occur in clinical trials and other studies

Hawthorne effects
Hawthorne effects refer to the phenomenon whereby individuals modify their behaviours or responses in research or clinical settings because of the awareness of being observed or studied

Natural history
The natural history of a condition refers to the expected course and outcome of a particular medical condition in the absence of any intervention or treatment

No-treatment group
The group randomly assigned to receive no treatment who provide information about the natural history of the condition in the absence of the intervention

Open-hidden treatment
A research design where some participants are aware of the treatment they are receiving (open treatment), whereas others are unaware or are kept in the dark about the nature of their treatment or the time of administration (hidden treatment). This design enables the investigation of how participants' knowledge or lack thereof about their treatment influences treatment outcomes and placebo responses.

Open-label placebo

An adjuvant treatment given along with the treatment-as-usual to elicit placebo effects. Participants and researchers are aware that the treatment being given is a placebo and not an active treatment

Placebo
A substance or treatment that is physically inert and has no therapeutic effect on a person's health condition. Non-physical placebos do not involve any tangible substances and encompass a wide range of interventions, such as sham procedures, psychological interventions and imagined treatments

Placebo effects
Placebo effects refer specifically to short-lasting improvements in symptoms that occur because of physiological changes

Placebo responses
Placebo responses refer to the individual variability in response to placebos given in the context of clinical trials and other settings

Regression to the mean
The phenomenon where extreme results obtained by chance after a first measurement tend to move closer to the mean on repeated measurements, often seen when patients with high-activity disease flares are enrolled in trials and experience reduction of disease activity that is falsely attributed to the treatment

References

1. Long H et al. Prevalence trends of site-specific osteoarthritis from 1990 to 2019: findings from the Global Burden of Disease Study 2019. Arthritis Rheumatol. 74, 1172–1183 (2022). [PubMed: 35233975]
2. Hunter DJ & Bierma-Zeinstra S Osteoarthritis. Lancet 393, 1745–1759 (2019). [PubMed: 31034380]
3. Sebbag E et al. The world-wide burden of musculoskeletal diseases: a systematic analysis of the World Health Organization burden of diseases database. Ann. Rheum. Dis 78, 844–848 (2019). [PubMed: 30987966]
4. Singh JA, Yu S, Chen L & Cleveland JD Rates of total joint replacement in the United States: future projections to 2020–2040 using the national inpatient sample. J. Rheumatol 46, 1134–1140 (2019). [PubMed: 30988126]
5. Stokes A, Berry KM, Hempstead K, Lundberg DJ & Neogi T Trends in prescription analgesic use among adults with musculoskeletal conditions in the united states, 1999–2016. JAMA Netw. Open 2, e1917228 (2019). [PubMed: 31825504]
6. Hellio le Graverand MP et al. A 2-year randomised, double-blind, placebo-controlled, multicentre study of oral selective iNOS inhibitor, cindunistat (SD-6010), in patients with symptomatic osteoarthritis of the knee. Ann. Rheum. Dis 72, 187–195 (2013). [PubMed: 23144445]
7. Bingham CO III et al. Risedronate decreases biochemical markers of cartilage degradation but does not decrease symptoms or slow radiographic progression in patients with medial compartment osteoarthritis of the knee: results of the two-year multinational knee osteoarthritis structural arthritis study. Arthritis Rheum. 54, 3494–3507 (2006). [PubMed: 17075851]
8. Karsdal MA et al. Treatment of symptomatic knee osteoarthritis with oral salmon calcitonin: results from two phase 3 trials. Osteoarthritis Cartilage 23, 532–543 (2015). [PubMed: 25582279]
9. Conaghan PG et al. Disease-modifying effects of a novel cathepsin K inhibitor in osteoarthritis: a randomized controlled trial. Ann. Intern. Med 172, 86–95 (2020). [PubMed: 31887743]

10. Kraus VB et al. Proposed study designs for approval based on a surrogate endpoint and a post-marketing confirmatory study under FDA's accelerated approval regulations for disease modifying osteoarthritis drugs. Osteoarthritis Cartilage 27, 571–579 (2019). [PubMed: 30465809]
11. Hochberg MC et al. Effect of intra-articular sprifermin vs placebo on femorotibial joint cartilage thickness in patients with osteoarthritis: the FORWARD randomized clinical trial. J. Am. Med. Assoc 322, 1360–1370 (2019).
12. Bannuru RR et al. Effectiveness and implications of alternative placebo treatments: a systematic review and network meta-analysis of osteoarthritis trials. Ann. Intern. Med 163, 365–372 (2015). [PubMed: 26215539]
13. Zhang W, Robertson J, Jones AC, Dieppe PA & Doherty M The placebo effect and its determinants in osteoarthritis: meta-analysis of randomised controlled trials. Ann. Rheum. Dis 67, 1716–1723 (2008). [PubMed: 18541604]
14. Henriksen M et al. Exercise and education vs intra-articular saline for knee osteoarthritis: a 1-year follow-up of a randomized trial. Osteoarthritis Cartilage 31, 627–635 (2023). [PubMed: 36657659]
15. Englund M & Turkiewicz A The emperor's new clothes. Osteoarthritis Cartilage 31, 549–551 (2023). [PubMed: 36764354]
16. Colloca L The placebo effect in pain therapies. Annu. Rev. Pharmacol. Toxicol 59, 191–211 (2019). [PubMed: 30216744]
17. Colloca L & Barsky AJ Placebo and nocebo effects. N. Engl. J. Med 382, 554–561 (2020). [PubMed: 32023375]
18. Benedetti F, Frisaldi E & Shaibani A Thirty years of neuroscientific investigation of placebo and nocebo: the interesting, the good, and the bad. Annu. Rev. Pharmacol. Toxicol 62, 323–340 (2022). [PubMed: 34460317]
19. Benedetti F Placebo effects: from the neurobiological paradigm to translational implications. Neuron 84, 623–637 (2014). [PubMed: 25442940]
20. Benedetti F, Mayberg HS, Wager TD, Stohler CS & Zubieta JK Neurobiological mechanisms of the placebo effect. J. Neurosci 25, 10390–10402 (2005). [PubMed: 16280578]
21. Wendt L, Albring A & Schedlowski M Learned placebo responses in neuroendocrine and immune functions. Handb. Exp. Pharmacol 225, 159–181 (2014). [PubMed: 25304532]
22. Hadamitzky M, Sondermann W, Benson S & Schedlowski M Placebo effects in the immune system. Int. Rev. Neurobiol 138, 39–59 (2018). [PubMed: 29681334]
23. Luckemann L, Stangl H, Straub RH, Schedlowski M & Hadamitzky M Learned immunosuppressive placebo response attenuates disease progression in a rodent model of rheumatoid arthritis. Arthritis Rheumatol. 72, 588–597 (2020). [PubMed: 31509354]
24. Ader R & Cohen N Behaviorally conditioned immunosuppression. Psychosom. Med 37, 333–340 (1975). [PubMed: 1162023]
25. Olness K & Ader R Conditioning as an adjunct in the pharmacotherapy of lupus erythematosus. J. Dev. Behav. Pediatr 13, 124–125 (1992). [PubMed: 1577957]
26. Giang DW et al. Conditioning of cyclophosphamide-induced leukopenia in humans. J. Neuropsychiatry Clin. Neurosci 8, 194–201 (1996). [PubMed: 9081556]
27. Goebel MU et al. Behavioral conditioning of immunosuppression is possible in humans. FASEB J. 16, 1869–1873 (2002). [PubMed: 12468450]
28. Colloca L Placebo, nocebo, and learning mechanisms. Handb. Exp. Pharmacol 225, 17–35 (2014). [PubMed: 25304524]
29. Colloca L & Miller FG How placebo responses are formed: a learning perspective. Phil. Trans. R. Soc. B 366, 1859–1869 (2011). [PubMed: 21576143]
30. Colloca L & Miller FG Role of expectations in health. Curr. Opin. Psychiatry 24, 149–155 (2011). [PubMed: 21248640]
31. Langford DJ et al. Expectations for improvement: a neglected but potentially important covariate or moderator for chronic pain clinical trials. J. Pain 24, 575–581 (2022). [PubMed: 36577461]
32. Gil M, Menzel R & De Marco RJ Does an insect's unconditioned response to sucrose reveal expectations of reward? PLoS ONE 3, e2810 (2008). [PubMed: 18665249]

33. Colloca L et al. Prior therapeutic experiences, not expectation ratings, predict placebo effects: an experimental study in chronic pain and healthy participants. Psychother. Psychosom 89, 371–378 (2020). [PubMed: 32492688]
34. Colloca L, Lopiano L, Lanotte M & Benedetti F Overt versus covert treatment for pain, anxiety, and Parkinson's disease. Lancet Neurol. 3, 679–684 (2004). [PubMed: 15488461]
35. Suarez-Almazor M et al. A randomized controlled trial of acupuncture for osteoarthritis of the knee: effects of provider communication style. Arthritis Rheum. 56, S315 (2007).
36. Gollub RL et al. A functional neuroimaging study of expectancy effects on pain response in patients with knee osteoarthritis. J. Pain 19, 515–527 (2018). [PubMed: 29325883]
37. Kong J et al. Enhancing treatment of osteoarthritis knee pain by boosting expectancy: a functional neuroimaging study. Neuroimage Clin. 18, 325–334 (2018). [PubMed: 29868449]
38. Rosenkjaer S, Lunde SJ, Kirsch I & Vase L Expectations: how and when do they contribute to placebo analgesia. Front. Psychiatry 13, 817179 (2022). [PubMed: 36147975]
39. Younger J, Gandhi V, Hubbard E & Mackey S Development of the Stanford Expectations of Treatment Scale (SETS): a tool for measuring patient outcome expectancy in clinical trials. Clin. Trials 9, 767–776 (2012). [PubMed: 23169874]
40. Ferkin AC et al. A psychometric evaluation of the Stanford Expectations of Treatment Scale (SETS) in the context of a smoking cessation trial. Nicotine Tob. Res 24, 1914–1920 (2022). [PubMed: 35906990]
41. Shedden-Mora MC et al. The treatment expectation questionnaire (TEX-Q): validation of a generic multidimensional scale measuring patients' treatment expectations. PLoS ONE 18, e0280472 (2023). [PubMed: 36689398]
42. Alberts J et al. Development of the generic, multidimensional treatment expectation questionnaire (TEX-Q) through systematic literature review, expert surveys and qualitative interviews. BMJ Open 10, e036169 (2020).
43. Spisak T, Bingel U & Wager TD Multivariate BWAS can be replicable with moderate sample sizes. Nature 615, E4–E7 (2023). [PubMed: 36890392]
44. Tetreault P et al. Brain connectivity predicts placebo response across chronic pain clinical trials. PLoS Biol. 14, e1002570 (2016). [PubMed: 27788130]
45. Vachon-Presseau E et al. Validating a biosignature-predicting placebo pill response in chronic pain in the settings of a randomized controlled trial. Pain 163, 910–922 (2022). [PubMed: 34433773]
46. Davis KD et al. Brain imaging tests for chronic pain: medical, legal and ethical issues and recommendations. Nat. Rev. Neurol 13, 624–638 (2017). [PubMed: 28884750]
47. Colagiuri B, Schenk LA, Kessler MD, Dorsey SG & Colloca L The placebo effect: from concepts to genes. Neuroscience 307, 171–190 (2015). [PubMed: 26272535]
48. Hall KT, Loscalzo J & Kaptchuk TJ Genetics and the placebo effect: the placebome. Trends Mol. Med 21, 285–294 (2015). [PubMed: 25883069]
49. Eippert F, Finsterbusch J, Bingel U & Buchel C Direct evidence for spinal cord involvement in placebo analgesia. Science 326, 404 (2009). [PubMed: 19833962]
50. Wang Y et al. Modeling learning patterns to predict placebo analgesic effects in healthy and chronic orofacial pain participants. Front. Psychiatry 11, 39 (2020). [PubMed: 32116854]
51. Colloca L, Thomas S, Yin M, Haycock NR & Wang Y Pain experience and mood disorders during the lockdown of the COVID-19 pandemic in the United States: an opportunistic study. Pain Rep. 6, e958 (2021). [PubMed: 34589641]
52. Shafir R, Olson E & Colloca L The neglect of sex: a call to action for including sex as a biological variable in placebo and nocebo research. Contemp. Clin. Trials 116, 106734 (2022). [PubMed: 35306216]
53. Olson EM et al. Effects of sex on placebo effects in chronic pain participants: a cross-sectional study. Pain 162, 531–542 (2021). [PubMed: 32826757]
54. Wang Y, Chan E, Dorsey SG, Campbell CM & Colloca L Who are the placebo responders? A cross-sectional cohort study for psychological determinants. Pain 163, 1078–1090 (2022). [PubMed: 34740998]

55. Sanislow CA et al. Developing constructs for psychopathology research: research domain criteria. J. Abnorm. Psychol 119, 631–639 (2010). [PubMed: 20939653]
56. Insel T et al. Research domain criteria (RDoC): toward a new classification framework for research on mental disorders. Am. J. Psychiatry 167, 748–751 (2010). [PubMed: 20595427]
57. Dworkin RH et al. Meta-analysis of assay sensitivity and study features in clinical trials of pharmacologic treatments for osteoarthritis pain. Arthritis Rheumatol. 66, 3327–3336 (2014). [PubMed: 25186636]
58. Finnerup NB et al. Neuropathic pain clinical trials: factors associated with decreases in estimated drug efficacy. Pain 159, 2339–2346 (2018). [PubMed: 30015707]
59. Farrar JT et al. Effect of variability in the 7-day baseline pain diary on the assay sensitivity of neuropathic pain randomized clinical trials: an ACTTION study. Pain 155, 1622–1631 (2014). [PubMed: 24831421]
60. Treister R, Honigman L, Lawal OD, Lanier RK & Katz NP A deeper look at pain variability and its relationship with the placebo response: results from a randomized, double-blind, placebo-controlled clinical trial of naproxen in osteoarthritis of the knee. Pain 160, 1522–1528 (2019). [PubMed: 30817436]
61. Okusogu C et al. Placebo hypoalgesia: racial differences. Pain 161, 1872–1883 (2020). [PubMed: 32701846]
62. Olson EM et al. Effects of sex on placebo effects in chronic pain participants: a cross-sectional study. Pain 162, 531–542 (2020).
63. Dworkin RH & Edwards RR Phenotypes and treatment response: it's difficult to make predictions, especially about the future. Pain 158, 187–189 (2017). [PubMed: 28092645]
64. Hohenschurz-Schmidt D, Draper-Rodi J & Vase L Dissimilar control interventions in clinical trials undermine interpretability. JAMA Psychiatry 79, 271–272 (2022). [PubMed: 35044434]
65. Hohenschurz-Schmidt D et al. Blinding and sham control methods in trials of physical, psychological, and self-management interventions for pain (article II): a meta-analysis relating methods to trial results. Pain 164, 509–533 (2022). [PubMed: 36271798]
66. Colloca L, Benedetti F & Porro CA Experimental designs and brain mapping approaches for studying the placebo analgesic effect. Eur. J. Appl. Physiol 102, 371–380 (2008). [PubMed: 17960416]
67. Parsons HM What happened at Hawthorne?: new evidence suggests the Hawthorne effect resulted from operant reinforcement contingencies. Science 183, 922–932 (1974). [PubMed: 17756742]
68. Ulmer FC The Hawthorne effect. Educ. Dir. Dent. Aux 1, 28 (1976).
69. Benedetti F, Carlino E & Piedimonte A Increasing uncertainty in CNS clinical trials: the role of placebo, nocebo, and Hawthorne effects. Lancet Neurol. 15, 736–747 (2016). [PubMed: 27106073]
70. Berthelot JM, Le Goff B & Maugars Y The Hawthorne effect: stronger than the placebo effect. Jt. Bone Spine 78, 335–336 (2011).
71. Colloca L & Benedetti F Placebo analgesia induced by social observational learning. Pain 144, 28–34 (2009). [PubMed: 19278785]
72. Wolfe F & Michaud K The Hawthorne effect, sponsored trials, and the overestimation of treatment effectiveness. J. Rheumatol 37, 2216–2220 (2010). [PubMed: 20843902]
73. Ellingsen DM et al. Brain-to-brain mechanisms underlying pain empathy and social modulation of pain in the patient-clinician interaction. Proc. Natl Acad. Sci. USA 120, e2212910120 (2023). [PubMed: 37339198]
74. Ernst E & Resch KL Concept of true and perceived placebo effects. Br. Med. J 311, 551–553 (1995). [PubMed: 7663213]
75. Colloca L & Benedetti F Placebos and painkillers: is mind as real as matter? Nat. Rev. Neurosci 6, 545–552 (2005). [PubMed: 15995725]
76. Ross S, Krugman AD, Lyerly SB, Clyde J,D. Drugs and placebos: a model design. Psychol. Rep 10, 383–392 (1962).
77. Kirsch I & Weixel LJ Double-blind versus deceptive administration of a placebo. Behav. Neurosci 102, 319–323 (1988). [PubMed: 3365327]

78. Benedetti F et al. Open versus hidden medical treatments: the patient's knowledge about a therapy affects the therapy outcome. Prev. Treat 6, 1a (2003).
79. Benedetti F et al. Autonomic and emotional responses to open and hidden stimulations of the human subthalamic region. Brain Res. Bull 63, 203–211 (2004). [PubMed: 15145139]
80. Park LC & Covi L Nonblind placebo trial: an exploration of neurotic patients' responses to placebo when its inert content is disclosed. Arch. Gen. Psychiatry 12, 36–45 (1965). [PubMed: 14258363]
81. Kaptchuk TJ et al. Placebos without deception: a randomized controlled trial in irritable bowel syndrome. PLoS ONE 5, e15591 (2010). [PubMed: 21203519]
82. Colloca L, Enck P & DeGrazia D Relieving pain using dose-extending placebos: a scoping review. Pain 157, 1590–1598 (2016). [PubMed: 27023425]
83. Enck P, Grundy D & Klosterhalfen S A novel placebo-controlled clinical study design without ethical concerns — the free choice paradigm. Med. Hypotheses 79, 880–882 (2012). [PubMed: 23089197]
84. Fava M, Evins AE, Dorer DJ & Schoenfeld DA The problem of the placebo response in clinical trials for psychiatric disorders: culprits, possible remedies, and a novel study design approach. Psychother. Psychosom 72, 115–127 (2003). [PubMed: 12707478]
85. Staud R & Price DD Role of placebo factors in clinical trials with special focus on enrichment designs. Pain 139, 479–480 (2008). [PubMed: 19838289]
86. Wendler D & Miller FG Deception in the pursuit of science. Arch. Intern. Med 164, 597–600 (2004). [PubMed: 15037487]
87. Pollo A et al. Response expectancies in placebo analgesia and their clinical relevance. Pain 93, 77–84 (2001). [PubMed: 11406341]
88. Colloca L et al. Veteran engagement in opioid tapering research: a mission to optimize pain management. Pain Rep. 6, e932 (2021). [PubMed: 34104838]
89. Park L & TRIAL C. L. N. P. An exploration of neurotic patients'responses to placebo when its inert content is disclosed. Arch. Gen. Psychiatry 12, 36–45 (1965). [PubMed: 14258363]
90. Young NS, Ioannidis JP & Al-Ubaydli O Why current publication practices may distort science. PLoS Med. 5, e201 (2008). [PubMed: 18844432]
91. Fanelli D, Costas R & Ioannidis JP Meta-assessment of bias in science. Proc. Natl Acad. Sci. USA 114, 3714–3719 (2017). [PubMed: 28320937]
92. Schooler J Unpublished results hide the decline effect. Nature 470, 437–437 (2011). [PubMed: 21350443]
93. Harrison RK Phase II and phase III failures: 2013–2015. Nat. Rev. Drug Discov 15, 817–818 (2016). [PubMed: 27811931]
94. Scott AJ, Sharpe L, Quinn V & Colagiuri B Association of single-blind placebo run-in periods with the placebo response in randomized clinical trials of antidepressants: a systematic review and meta-analysis. JAMA Psychiatry 79, 42–49 (2022). [PubMed: 34757405]
95. Coleshill MJ, Sharpe L, Colloca L, Zachariae R & Colagiuri B Placebo and active treatment additivity in placebo analgesia: research to date and future directions. Int. Rev. Neurobiol 139, 407–441 (2018). [PubMed: 30146056]
96. Colagiuri B Participant expectancies in double-blind randomized placebo-controlled trials: potential limitations to trial validity. Clin. Trials 7, 246–255 (2010). [PubMed: 20421243]
97. Vollert J et al. Assessment of placebo response in objective and subjective outcome measures in rheumatoid arthritis clinical trials. JAMA Netw. Open 3, e2013196 (2020). [PubMed: 32936297]
98. Wechsler ME et al. Active albuterol or placebo, sham acupuncture, or no intervention in asthma. N. Engl. J. Med 365, 119–126 (2011). [PubMed: 21751905]
99. Kent DM et al. The predictive approaches to treatment effect heterogeneity (PATH) statement. Ann. Intern. Med 172, 35–45 (2020). [PubMed: 31711134]
100. Schnitzer TJ et al. Effect of tanezumab on joint pain, physical function, and patient global assessment of osteoarthritis among patients with osteoarthritis of the hip or knee: a randomized clinical trial. J. Am. Med. Assoc 322, 37–48 (2019).

101. Berenbaum F et al. Subcutaneous tanezumab for osteoarthritis of the hip or knee: efficacy and safety results from a 24-week randomised phase Ill study with a 24-week follow-up period. Ann. Rheum. Dis 79, 800–810 (2020). [PubMed: 32234715]
102. Vase L, Amanzio M & Price DD Nocebo vs. placebo: the challenges of trial design in analgesia research. Clin. Pharmacol. Ther 97, 143–150 (2015). [PubMed: 25670519]
103. Morton DL, Watson A, El-Deredy W & Jones AK Reproducibility of placebo analgesia: effect of dispositional optimism. Pain 146, 194–198 (2009). [PubMed: 19692178]
104. Vase L et al. Predictors of the placebo analgesia response in randomized controlled trials of chronic pain: a meta-analysis of the individual data from nine industrially sponsored trials. Pain 156, 1795–1802 (2015). [PubMed: 25955965]
105. Lang TA & Stroup DF Who knew? The misleading specificity of “double-blind” and what to do about it. Trials 21, 697 (2020). [PubMed: 32758278]
106. Wood L et al. Empirical evidence of bias in treatment effect estimates in controlled trials with different interventions and outcomes: meta-epidemiological study. Br. Med. J 336, 601–605 (2008). [PubMed: 18316340]
107. Moerman DE Cultural variations in the placebo effect: ulcers, anxiety, and blood pressure. Med. Anthropol. Q 14, 51–72 (2000). [PubMed: 10812563]
108. Blease CR et al. Sharing clinical notes, and placebo and nocebo effects: can documentation affect patient health? J. Health Psychol 27, 135–146 (2022). [PubMed: 32772861]
109. Garcia MK et al. Effect of true and sham acupuncture on radiation-induced xerostomia among patients with head and neck cancer: a randomized clinical trial. JAMA Netw. Open 2, e1916910 (2019). [PubMed: 31808921]
110. Karst M & Li C Acupuncture—a question of culture. JAMA Netw. Open 2, e1916929 (2019). [PubMed: 31808917]
111. Waber RL, Shiv B, Carmon Z & Ariely D Commercial features of placebo and therapeutic efficacy. J. Am. Med. Assoc 299, 1016–1017 (2008).
112. Kam-Hansen S et al. Altered placebo and drug labeling changes the outcome of episodic migraine attacks. Sci. Transl Med 6, 218ra215 (2014).
113. Faasse K, Martin LR, Grey A, Gamble G & Petrie KJ Impact of brand or generic labeling on medication effectiveness and side effects. Health Psychol. 35, 187–190 (2016). [PubMed: 26462056]
114. Meissner K et al. Differential effectiveness of placebo treatments: a systematic review of migraine prophylaxis. JAMA Intern. Med 173, 1941–1951 (2013). [PubMed: 24126676]
115. Blease C, Colloca L & Kaptchuk TJ Are open-label placebos ethical? Informed consent and ethical equivocations. Bioethics 30, 407–414 (2016). [PubMed: 26840547]
116. Lembo A et al. Open-label placebo vs double-blind placebo for irritable bowel syndrome: a randomized clinical trial. Pain 162, 2428–2435 (2021). [PubMed: 33605656]
117. Nurko S et al. Effect of open-label placebo on children and adolescents with functional abdominal pain or irritable bowel syndrome: a randomized clinical trial. JAMA Pediatrics 176, 349–356 (2022). [PubMed: 35099543]
118. Carvalho C et al. Open-label placebo treatment in chronic low back pain: a randomized controlled trial. Pain 157, 2766–2772 (2016). [PubMed: 27755279]
119. Carvalho C et al. Open-label placebo for chronic low back pain: a 5-year follow-up. Pain 162, 1521–1527 (2021). [PubMed: 33259459]
120. Kelley JM, Kaptchuk TJ, Cusin C, Lipkin S & Fava M Open-label placebo for major depressive disorder: a pilot randomized controlled trial. Psychother. Psychosom 81, 312–314 (2012). [PubMed: 22854752]
121. Schaefer M, Harke R & Denke C Open-label placebos improve symptoms in allergic rhinitis: a randomized controlled trial. Psychother. Psychosom 85, 373–374 (2016). [PubMed: 27744433]
122. Hoenemeyer TW, Kaptchuk TJ, Mehta TS & Fontaine KR Open-label placebo treatment for cancer-related fatigue: a randomized-controlled clinical trial. Sci. Rep 8, 2784 (2018). [PubMed: 29426869]

123. Pan Y et al. Open-label placebos for menopausal hot flushes: a randomized controlled trial. Sci. Rep 10, 20090 (2020). [PubMed: 33208855]

124. Olliges E et al. Open-label placebo administration decreases pain in elderly patients with symptomatic knee osteoarthritis — a randomized controlled trial. Front. Psychiatry 13, 853497 (2022). [PubMed: 35599777]

125. Ader R et al. Conditioned pharmacotherapeutic effects: a preliminary study. Psychosom. Med 72, 192–197 (2010). [PubMed: 20028830]

126. Morales-Quezada L et al. Conditioning open-label placebo: a pilot pharmacobehavioral approach for opioid dose reduction and pain control. Pain Rep. 5, e828 (2020). [PubMed: 32766465]

127. Sandler AD & Bodfish JW Open-label use of placebos in the treatment of ADHD: a pilot study. Child Care Health Dev. 34, 104–110 (2008). [PubMed: 18171451]

128. Perlis M et al. Durability of treatment response to zolpidem with three different maintenance regimens: a preliminary study. Sleep Med. 16, 1160–1168 (2015). [PubMed: 26298795]

129. Goebel MU, Meykadeh N, Kou W, Schedlowski M & Hengge UR Behavioral conditioning of antihistamine effects in patients with allergic rhinitis. Psychother. Psychosom 77, 227–234 (2008). [PubMed: 18418029]

130. Kirchhof J et al. Learned immunosuppressive placebo responses in renal transplant patients. Proc. Natl Acad. Sci. USA 115, 4223–4227 (2018). [PubMed: 29610294]

131. Colloca L & Miller FG Harnessing the placebo effect: the need for translational research. Phil. Trans. R. Soc. B 366, 1922–1930 (2011). [PubMed: 21576150]

132. Doering BK & Rief W Utilizing placebo mechanisms for dose reduction in pharmacotherapy. Trends Pharmacol. Sci 33, 165–172 (2012). [PubMed: 22284159]

133. Enck P, Bingel U, Schedlowski M & Rief W The placebo response in medicine: minimize, maximize or personalize? Nat. Rev. Drug Discov 12, 191–204 (2013). [PubMed: 23449306]

134. Benedetti F, Pollo A & Colloca L Opioid-mediated placebo responses boost pain endurance and physical performance: is it doping in sport competitions. J. Neurosci 27, 11934–11939 (2007). [PubMed: 17978033]

135. Amanzio M & Benedetti F Neuropharmacological dissection of placebo analgesia: expectation-activated opioid systems versus conditioning-activated specific subsystems. J. Neurosci 19, 484–494 (1999). [PubMed: 9870976]

136. Guo JY, Wang JY & Luo F Dissection of placebo analgesia in mice: the conditions for activation of opioid and non-opioid systems. J. Psychopharmacol 24, 1561–1567 (2010). [PubMed: 19395430]

137. Colloca L & Benedetti F How prior experience shapes placebo analgesia. Pain 124, 126–133 (2006). [PubMed: 16701952]

138. Fiorio M et al. Enhancing non-noxious perception: behavioural and neurophysiological correlates of a placebo-like manipulation. Neuroscience 217, 96–104 (2012). [PubMed: 22569155]

139. Fiorio M, Recchia S, Corra F & Tinazzi M Behavioural and neurophysiological investigation of the influence of verbal suggestion on tactile perception. Neuroscience 258, 332–339 (2014). [PubMed: 24291728]

140. Klinger R, Soost S, Flor H & Worm M Classical conditioning and expectancy in placebo hypoalgesia: a randomized controlled study in patients with atopic dermatitis and persons with healthy skin. Pain 128, 31–39 (2007). [PubMed: 17030095]

141. Adie S, Harris I, Chuan A, Lewis P & Naylor JM Selecting and optimising patients for total knee arthroplasty. Med. J. Aust 210, 135–141 (2019). [PubMed: 30656689]

142. Quinlan J, Levy N, Lobo DN & Macintyre PE Preoperative opioid use: a modifiable risk factor for poor postoperative outcomes. Br. J. Anaesth 127, 327–331 (2021). [PubMed: 34090682]

143. Ravi B et al. Patterns of pre-operative opioid use affect the risk for complications after total joint replacement. Sci. Rep 11, 22124 (2021). [PubMed: 34764305]

144. Shadbolt C et al. Opioid use and total joint replacement. Curr. Rheumatol. Rep 22, 58 (2020). [PubMed: 32808102]

145. Colloca L Informed consent: hints from placebo and nocebo research. Am. J. Bioeth 15, 17–19 (2015).

146. Miller FG & Colloca L The placebo phenomenon and medical ethics: rethinking the relationship between informed consent and risk-benefit assessment. Theor. Med. Bioeth 32, 229–243 (2011). [PubMed: 21479794]

147. Brody H, Colloca L & Miller FG The placebo phenomenon: implications for the ethics of shared decision-making. J. Gen. Intern. Med 27, 739–742 (2012). [PubMed: 22258918]

148. Barnes K et al. Can positive framing reduce nocebo side effects? Current evidence and recommendation for future research. Front. Pharmacol 10, 167 (2019). [PubMed: 30894815]

149. Brody H & Colloca L Patient autonomy and provider beneficence are compatible. Hastings Cent. Rep 43, 6 (2013).

Key points

- An understanding of placebo mechanisms and their role in clinical trials is important to facilitate the development of new treatments for osteoarthritis.
- Valuable insights on study designs and potential pitfalls for future clinical trials can aid researchers in improving research methodologies across different health conditions.
- Recognizing the clinical implications and potential benefits of harnessing placebo effects can lead to more effective treatment approaches in the management of diverse medical conditions.
- Examining opioid reduction in patients undergoing joint-replacement surgery for conditions other than osteoarthritis and its effect on outcomes offers important insights for optimizing postsurgical care in different health contexts.

Box 1

Knowledge gaps and future directions

Mechanistic research

- Discovering biomarkers (including systemic, imaging and 'omics' markers) of placebo effects in patients with osteoarthritis (OA)
- Understanding how clinical symptoms and disease-related features of OA are associated with placebo effects
- Elucidating the influence of placebo effects on determination of OA outcomes such as long-term pain trajectories
- Developing OA models in rodents to study placebo effects

Clinical trials

- Improving measurements of OA symptoms and structural outcomes
- Measuring patients' and clinicians' expectations by implementing standardized tools
- Implementing study designs in OA clinical trials that better dissociate placebo from treatment effects
- Developing predictive models (for example, using machine learning and artificial intelligence) to phenotype patients who are placebo responders and non-responders and patients who benefit least or most from active and placebo treatments
- Avoiding exclusion of placebo responders from clinical trials to optimize drug validation and generalization

Clinical practice

- Developing educational programmes to educate providers about the nature of placebo
- Evaluating and implementing dose-extending placebo designs to mimic the action of drugs used in OA treatment
- Evaluating and implementing open-label placebos as adjuvant treatments to OA medications
- Educating clinicians about placebo effects and responses, to train them in strategies to achieve supportive and positive communication with their patients

Box 2

Mechanisms of placebo effects

Placebo effects refer to beneficial effects produced by a placebo or treatment or a manipulation of a participant's belief, which cannot be attributed to the pharmacological effects of the treatment.

Expectancy, prior therapeutic experiences, observation of benefits in others, contextual and treatment cues, and the overall patient–clinical interactions trigger placebo responses. The mere act of taking a treatment can engage various neurobiological and physiological mechanisms, including activation of the opioid, serotonin, noradrenaline, endocannabinoid, oxytocin, arginine vasopressin and dopamine systems, as well as modulation of cytokines.

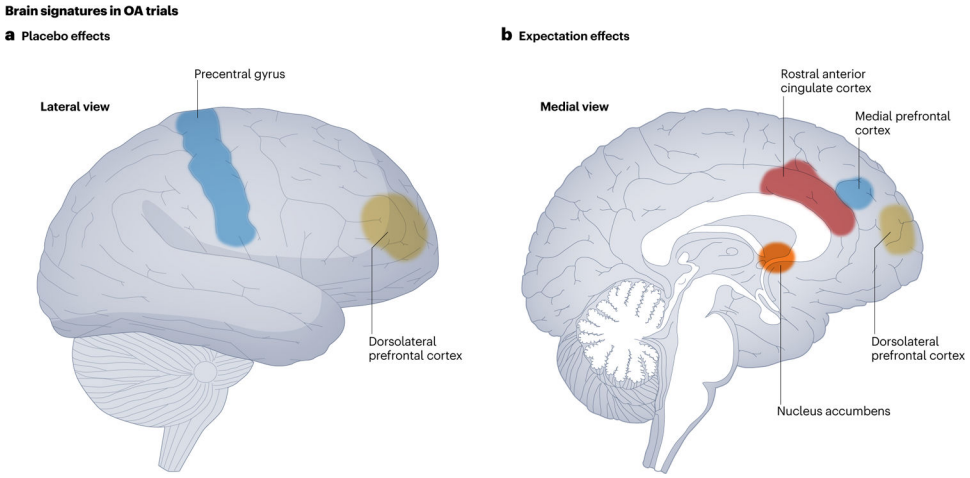

Fig. 1 |. Brain physiology that predicts placebo effects in OA trials.

a, Functional connectivity of the dorsolateral prefrontal cortex with the precentral gyrus is associated with placebo responses in patients with chronic low back pain and osteoarthritis (OA). **b**, Functional connectivity of the nucleus accumbens with the medial prefrontal cortex/rostral anterior cingulate cortex and the dorsolateral prefrontal cortex is associated with expectation effects in these patients. Higher expectations are associated with lower post-treatment OA pain and higher activation in the nucleus accumbens.

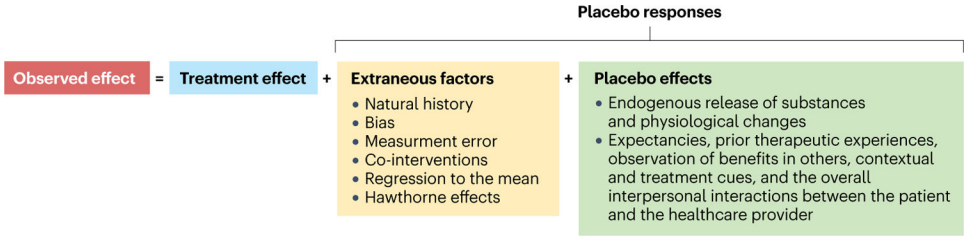

Fig. 2 |. Observed effects involve treatment effects, extraneous factors and placebo effects. Placebo responses are the combination of placebo effects and extraneous factors, such as the nature of the illness, bias, co-interventions and the characteristics of the treatment itself. Placebo effects are linked to physiological and biological changes that can occur in concomitance with expectancies. Understanding what comprises the observed effects in the active intervention group requires understanding of treatment effects, extraneous effects and placebo effects.

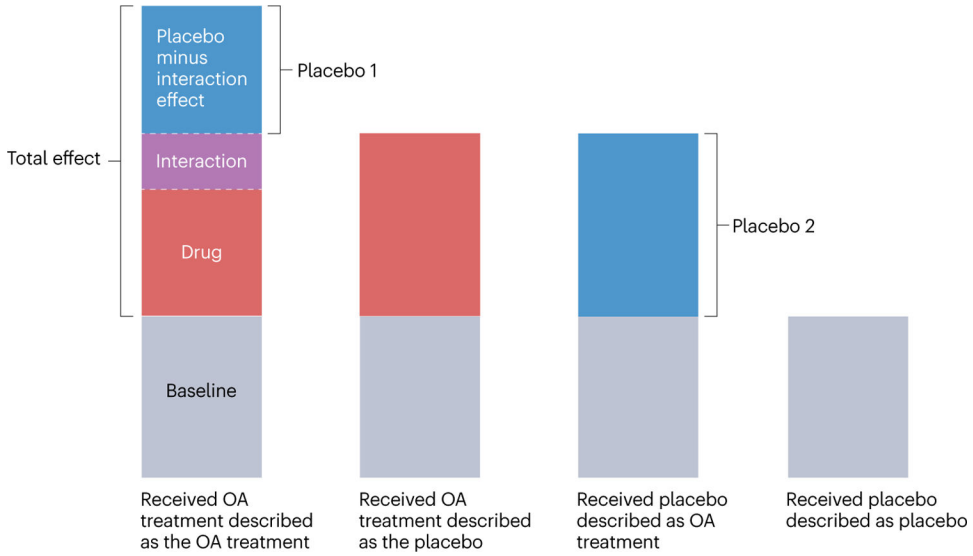

Fig. 3 |. Interaction between drug and placebo effects in a hypothetical balanced (crossover) placebo OA trial.

The model examines the effects of a treatment and a placebo, as well as their interaction in a hypothetical osteoarthritis (OA)trial. The total effect is determined by comparing the treatment under investigation with a placebo. The balanced-placebo design predicts two types of placebo effects. Placebo 1, which includes both the placebo effect and the interaction effect, is determined by comparing the treatment described as the treatment with the treatment described as a placebo. Placebo 2, which includes only the placebo effect, is determined by comparing a placebo described as the treatment with a placebo described as a placebo.

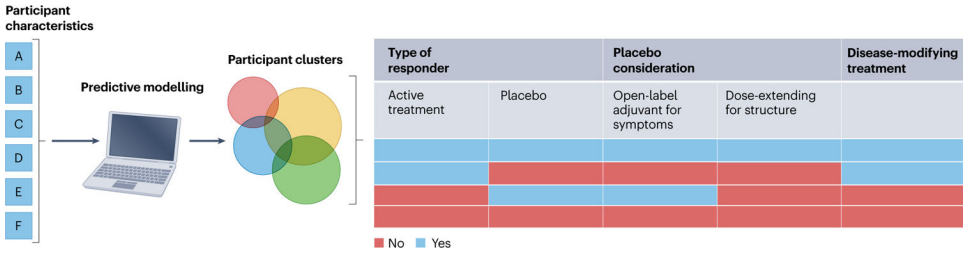

Fig. 4 |. Translational research from bench to bedside.

This conceptual model illustrates how predictive approaches can guide clinical-care decisions. By incorporating various participant characteristics via predictive modelling (using traditional statistical analysis, machine learning or artificial intelligence) it is possible to identify key features that can phenotype individuals (and investigators) as likely to be treatment responders, placebo responders, or both. This knowledge can be incorporated into decision-making about adjunct placebo-related treatment options such as open-label placebo or dose-extending placebo (or both), or simply harnessing placebo effects without any placebo treatments.