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Mechanisms of the placebo response in pain in osteoarthritis

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SUMMARY

Introduction: Administration of a placebo associates with symptomatic improvement in many conditions – the so-called placebo response. In this review we explain the concept of placebo response, examine the data that supports existence in osteoarthritis (OA), and discuss its possible mechanisms and determinants.
Methods: A Pubmed literature search was carried out. Key articles were identified, and their findings discussed in a narrative review.
Results: Pain, stiffness, self-reported function and physician-global assessment in OA clearly improve in response to placebo. However, more objective measures such as quadriceps strength and radiographic progression appear less responsive. Although not directly studied in OA, contextual effects, patient expectation and conditioning are believed to be the main mechanisms. Neurotransmitter changes that mediate placebo-induced analgesia include increased endogenous opioid levels, increased dopamine levels, and reduced levels of cholecystokinin. Almost all parts of the brain involved in pain processing are influenced during placebo-induced analgesia. Determinants of the magnitude of placebo response include the patient–practitioner interaction, treatment response expectancy, knowledge of being treated, patient personality traits and placebo specific factors such as the route and frequency of administration, branding, and treatment costs.
Conclusion: Clearer understanding of the neurobiology of placebo response validates its existence as a real phenomenon. Although routine administration of placebo for symptomatic improvement is difficult to justify, contextual factors that enhance treatment response should be employed in the management of chronic painful conditions such as OA where available treatments have only modest efficacy.

Introduction

The word 'placebo' (Latin: I shall please) came into common use with St. Jerome's incorrect translation of the first word of the ninth line of the 116th psalm where he translated the Hebrew 'I will walk before the Lord', to 'I will please the Lord'[1]. The hired funeral mourners in fourteenth century Europe who frequently chanted this incorrect translation repetitively were called the 'placebos'[1]. Therefore, it is not surprising that 'placebo' which implied deception and substitution in the middle ages was the name chosen by Chaucer for a flattering courtier in his book the Canterbury Tales[2].

The first published medical use of the word placebo was in the New Medical Dictionary (c 1785), in which it was described as a commonplace method or medicine[2]. Similarly, in the biomedical context placebo is any inert substance, such as a lactose pill or a fake procedure (e.g., sham acupuncture), which is not expected to improve either the symptom or the disease process. Paradoxically, the administration of a placebo associates with symptomatic improvement in a number of conditions, the so called placebo response (*Syn.*: placebo effect)[3]. The placebo response does not result from the inert substance itself but is due to the therapeutic ritual, context effects, and expectation of improvement that accompany its administration. Placebo response was recognized as far back as the eighteenth century. For example, in 1811, the revised Quincy's Lexicon-Medicum defined placebo as 'an epithet given to any medicine adapted more to please than to benefit the patient'[2]. However, it is important to dissociate placebo and contextual responses, which can be optimized to advantage in the management of chronic diseases, from the deceitful and currently unethical administration of placebo to achieve improvement in symptoms. In this review, we will explain the concept of placebo response, examine the data that supports its existence in osteoarthritis (OA),

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and discuss its mechanisms and determinants. This is an expert summary of the definition, mechanisms, determinants, neuropharmacology, and neuro-anatomy of placebo response based on supporting evidence. This is not a systematic or exhaustive review of the literature on placebo responsiveness.

What is placebo response?

Placebo response is the symptomatic improvement experienced by a patient on receiving an intervention, or a set of interventions that are regarded as inert and non-therapeutic for the condition ('placebo') compared to those who receive no such intervention(s). Placebo response is believed to be predominantly due to the context in which it is administered i.e., the special interaction between the patient and the healthcare practitioner which is intimately associated with the delivery of treatment[4]. This was highlighted by Shapiro, Gotzsche, and Brody in their definitions of placebo effect (Box 1)[5–7].

Placebo response is not necessarily equivalent to the improvement in symptoms observed in the control (or 'placebo') arm of randomized control trials (RCTs). The symptomatic improvement observed in the control arm of RCTs can be influenced by many factors other than the placebo response including regression to the mean, natural variation in disease severity, spontaneous improvement, additional undeclared treatments, Hawthorne effect (behaviour change through being observed) and response bias[8]. Therefore, placebo response can only be reliably measured in RCTs when there is both a placebo and a 'no-treatment' (simple observation) comparator group, the difference between these indicating the improvement that results from the placebo response alone. However, since most RCTs do not have a 'no-treatment arm' this distinction is often obfuscated by many researchers.

What is the evidence for existence of a placebo response?

In a landmark paper reviewing 15 RCTs in 1955, Henry Beecher reported that 35% patients improved in the placebo arm of these studies[3]. This paper which kindled much interest in placebo response was criticized since only two trials included a no-treatment arm, and none of these demonstrated a placebo response[2,9].

However, since then studies have found evidence for a placebo response in several conditions[4,10,11]. In a systematic review and meta-analysis comparing placebo and no-treatment, placebo response was most evident in the treatment of pain (pooled standardized mean difference (SMD) (95% confidence interval (CI)) −0.27 (−0.40 to −0.15))[10]. A subsequent systematic review[11], and a recent Cochrane review[4] carried out by the same group confirmed that placebo response in RCTs occurs in the treatment of pain (pooled SMD (95% CI) −0.28 (−0.36 to −0.19)), nausea (pooled SMD was −0.25 (−0.46 to −0.04)), and possibly phobia and asthma. However, the authors suggest that the latter two associations may be biased[4]. The existence of a placebo response in pain is also supported by systematic reviews of neuropathic pain and OA RCTs[8,12]. Placebo response is independent of age and social and physical demographics, but may be influenced by gender (men showing greater placebo-induced reduction in heat-induced pain and anticipatory stress than women)[13].

Although some placebo responses mediated by conditioning (see later) may mimic biological functions such as drug induced immunosuppression[14,15], recent systematic reviews suggest that placebo response is mainly observed when continuous subjective measures of disease activity are used, and not when binary subjective or objective (physical or laboratory) measures of disease activity are used[4,10,11]. This suggests that placebo does not affect disease pathophysiology *per se* but does have a mild-moderate effect on symptoms sufficient to influence the continuous subjective measures of disease activity. However, such significant improvement in symptoms may be beneficial in the management of chronic conditions like OA where most physical and pharmacological treatments have only a mild or modest effect size (ES)[16].

What is the evidence for the existence of a placebo response in OA?

A systematic review and meta-analysis involving 193 placebo (16,364 patients) and 14 untreated control groups (1,167 patients) from OA RCTs confirmed that placebo response occurs in OA[8]. In this review, the presence of placebo response was examined in RCTs that investigated a wide range of non-pharmacological, pharmacological, and invasive treatments. The key results are:

- Pain in OA is responsive to placebo (Box 2).
  - Overall ES (95% CI) for pain relief is 0.51 (0.46–0.55) for placebo, and 0.03 (−0.13 to 0.18) for untreated controls.
  - In three head to head trials where placebo and no-treatment arms were present the ES of placebo was greater, with overall ES (95% CI) of 0.77 (0.65–0.89) for placebo, and −0.08 (−0.65–0.48) for untreated controls.
  - Greater pain relief from placebo was observed in trials that did not allow rescue medications, perhaps due to a greater expectancy of pain relief in these trials.

Box 1
Definitions of placebo response (syn. placebo effect)

Brody	A change in a patient's illness attributable to the symbolic import of a treatment rather than a specific pharmacologic or physiologic property[5].
Gotzsche	The difference in outcome between a placebo treated group and an untreated control group in an unbiased experiment[6].
Shapiro	The psychological or psycho-physiological effect produced by placebos[7].
Doherty	Symptomatic improvement on receiving any inert/non-therapeutic ('placebo') intervention(s) compared to those who do not receive it.

Box 2
Predictors of magnitude of placebo response in OA pain

Treatment effect size (ES)*	The higher the ES the greater the placebo response, possibly due to high expectation of benefit.
Baseline pain*	Higher baseline pain results in greater placebo response.
Invasive route of delivery*	Repeated needling e.g., acupuncture, intra-articular hyaluronan, and repeated intra-articular corticosteroid injections have very high placebo effects.
Joint with OA†	Placebo response magnitude reduces from hands, to knee to hip.
Topical application‡	Topical NSAID application has a high placebo effect.

* Statistically significant.
† Not statistically significant.
‡ Not examined in multivariate model.

- Studies with large sample size were more likely to demonstrate a larger placebo response, most likely due to the need for a greater power to separate a clinically meaningful effect of the intervention above that of placebo.
- Placebo response was also present in other subjective outcomes such as stiffness (ES (95% CI) 0.43 (0.38–0.49)), self-reported function (ES (95% CI) 0.49 (0.44–0.54)), and physician's global assessment (ES (95% CI) 0.66 (0.53–0.78)).
- Placebo response was not present for most objective outcomes such as quadriceps strength, knee swelling circumference, range of movement, and radiographic joint space narrowing.
- For objective measures which require patient co-operation and effective analgesia e.g., timed specified walking distance, placebo had an intermediate ES (95% CI) (0.22 (0.08–0.35)) compared to the ES for placebo analgesia in the same studies.

What is the mechanism of placebo response?

Although not studied specifically in OA, there is a significant literature on the mechanism of placebo response in pain, behavioural sciences, and Parkinson's disease. Expectation and conditioning are believed to be the principal mechanisms of placebo response[17]. Verbal, conditioned, and observational clues can create strong expectations which mediate the placebo response[17]. Other mediators of placebo response include verbal suggestion mediated relief in anxiety, previous experience of effectiveness, and observing drug effectiveness in others in a social context without any deliberate reinforcement[18–20]. Reward mechanisms have also been implicated to be activated during placebo response[21]. It is likely that all mechanisms interact to drive the placebo response. Studies over the last 30 years have defined the neuro-pharmacology, and the neuro-anatomy of placebo response. In this review we focus on the neurobiology of placebo analgesia.

Neuro-pharmacology of placebo response

Placebo analgesia appears to be mediated predominantly by enhancement of descending inhibitory systems. High levels of endogenous opioids, dopamine release, and low levels of cholecystokinin (CCK) are implicated as the principal pharmacologic mediators of placebo analgesia. Of these, the strongest evidence exists for the role of endogenous opioids acting predominantly via their μ-receptors[22–25]. For example, in a PET study measuring in-vivo receptor binding in which a μ-opioid receptor selective radiotracer [^{11}C] carfentanil bound to the available μ-opioid receptors, the administration of a placebo reduced the uptake of this radiotracer by the μ-opioid receptors and the reduction in binding correlated with analgesia[22]. In previous classic studies involving tooth extraction[26] and ischaemic arm[27] models of pain, naloxone (an opiate antagonist) blocked the placebo response induced by verbal suggestion, and by verbal suggestion with a preconditioning procedure designed to further induce the expectation of analgesia. Similarly, the CSF concentration of endogenous opioids is higher in chronic pain patients who are placebo responders than in those who are placebo non-responders[28]. Placebo-activated endogenous opioid systems also act on the respiratory centre to induce respiratory depression[29], reduce the β-adrenergic activity of the heart[30], and these effects are blocked by naloxone. The key role of opioids in mediating placebo analgesia is further supported by the fact that the coupling between the cerebral cortex and the subcortical antinociceptive networks such as the peri-aqueductal grey (PG) and the amygdala nuclei is mediated by opioids[24,25,31]. Similarly, the increased activity within the descending pain modulatory pathway that accompanies placebo analgesia is principally mediated by opioids[22,25]. However, not all placebo-induced analgesia is mediated by endogenous opioid. A tooth extraction study showed that placebo analgesia could still occur despite the presence of an opioid antagonist (naloxone) suggesting that placebo effects can occur independent of opioid mechanisms[32]. Similarly, while placebo analgesia produced by expectation and prior conditioning with opiate analgesics is mediated by the release of endogenous opioids, placebo analgesia produced by prior conditioning with ketorolac, a non-steroidal anti-inflammatory drug (NSAID), is not mediated by the release of endogenous opioids as it is naloxone insensitive[27]. These studies confirm that there are neurochemical mechanisms of placebo analgesia other than opioids and that conditioning with different classes of analgesic drugs may result in different stimulus-specific mechanisms of analgesia.

Dopamine release which mediates the motor placebo response in Parkinson's disease also mediates placebo analgesia[21]. In an experimental pain model activation of dopamine in the nucleus accumbens (NA) was related to both placebo responsiveness and to monetary reward[21]. There was a strong correlation between NA activation in placebo analgesia and response to monetary reward, suggesting that reward mechanisms mediated by dopaminergic transmission may in part mediate placebo responsiveness[21]. In a study of 20 healthy volunteers aged 20–30 years, dopamine and opioid neurotransmission was shown to be increased in states of placebo analgesia and conversely reduced during nocebo states (nocebo is when symptoms are worsened or induced by an inert treatment)[33]. Interestingly NA activation explained 28% of the variance in placebo analgesia, suggesting that dopamine may have a significant role in placebo analgesia[33]. However, this study was carried out in healthy individuals and the findings need to be confirmed in patients with chronic painful conditions like OA. Further evidence supporting the role of dopamine in placebo response is provided by a study of sham acupuncture in people with irritable bowel syndrome (IBS) where the effect of no-treatment ("waiting-list" observation group), placebo treatment alone ("limited" sham acupuncture) and placebo treatment "augmented" with a supportive patient-health care provider interaction were compared using the IBS symptom severity scale[34]. These patients were genotyped for the val158met polymorphism in the catechol-O-methyltransferase (COMT) gene. Patients with the met/met polymorphism – which associates with reduced dopamine catabolism – had a greater placebo response than those with a val/val polymorphism, whereas those with val/met polymorphism had an intermediate placebo response[34]. Constitutional genetic variation in pain physiology may therefore influence placebo analgesia.

CCK, the other neurochemical mediator of placebo response, inhibits placebo analgesia[35]. This is supported by the fact that proglumide, a CCK antagonist, enhances placebo analgesia[35] and blocks the hyperalgesic nocebo response[36]. Thus CCK and opiates antagonize each other in the generation of placebo analgesia. However, the nocebo response is not blocked by naloxone suggesting that it is not mediated by the opioid pathway[36]. Serotonin (5-HT) which mediates placebo-induced increase of growth hormone secretion, and decreased cortisol secretion after pharmacological preconditioning with sumatriptan has not been implicated in mediation of placebo analgesia[37].

Neuro-anatomy of placebo analgesia

Several neuroimaging studies have identified areas of the brain that are involved in placebo response (Fig. 1). Almost all parts of the pain pathway are influenced during placebo analgesia (Box 3). Parts of the frontal lobe e.g., the pregenual rostral anterior cingulate cortex (RACC), dorsolateral prefrontal cortex (PFC), and orbitofrontal cortex are activated during both the anticipatory and late

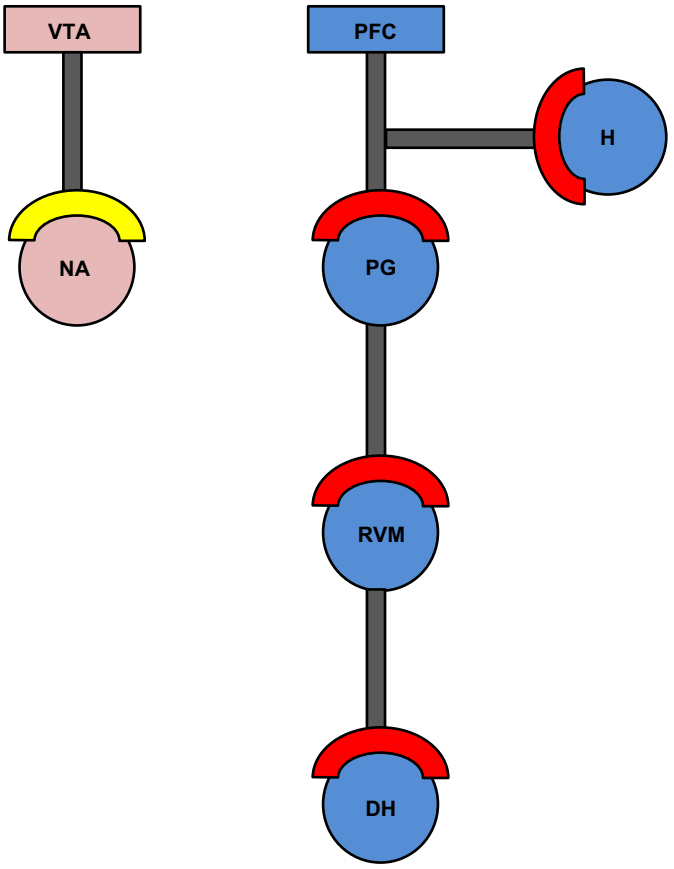

Fig. 1. *Neuro-anatomical basis of placebo analgesia.* Placebo analgesia is mediated by dopaminergic (yellow in diagram) transmission from the ventral tegmental area (VTA) to the NA, and by opioidergic (red in diagram) transmission from the cerebral cortex – predominantly the PFC to the PG in the midbrain, which in turn projects to the rostral ventral medulla (RVM), and to the dorsal horn ganglia (DH) in the spinal cord. The opioidergic pain modulating pathway also projects to the hypothalamus (H).

phases of placebo response[22,33,38,39]. Studies suggest that this frontal lobe activation drives changes in other parts of the brain in response to at least some types of placebos. For example, frontal lobe disconnection either induced experimentally by trans-cranial magnetic stimulation, or due to Alzheimer's disease associates with a loss of verbally induced placebo responses[40,41]. Cortical, for example RACC activation stimulates subcortical anti-nociceptive networks such as the PG and amygdala nuclei[24,25,31]. During placebo analgesia there is increased activity within the descending pain modulatory pathway[22,25], and reduced activity in the nociceptive pain processing pathways in the dorsal horn of the spinal cord[42]. Deeper parts of the cortex, such as the NA which is involved in the reward mechanism, and parts of the insula are also activated during placebo analgesia[33]. The activity of regions involved in pain transmission, such as the thalamus, anterior insula, and caudal RACC, are decreased by placebo indicating a reduction in nociceptive transmission in the pain pathways[39].

Box 3
Parts of brain involved in placebo analgesia

Frontal cortex and limbic system
Subcortical reward mechanism
Sub-cortical pain transmission centres
Descending pain modulatory pathway
Nociceptive pain processing pathways in the dorsal horn of the spinal cord

What are the determinants of placebo response?

In order to harness the phenomenon of placebo response in routine clinical practise it is important to understand the predictors of the magnitude of placebo response. The key physician, patient, and intervention specific determinants of placebo response summarized in Box 4 are discussed below.

Context of the consultation

A warm consultation provided by a confident physician who is perceived as competent by the patient and who provides a good outlook results in a larger placebo response[43–47]. In the study mentioned above of sham acupuncture in IBS patients randomized to waiting list (assessment and observation), sham acupuncture with only limited patient–practitioner interaction (therapeutic "ritual"), or sham acupuncture with the usual patient–practitioner interaction augmented by warmth, attention and confidence (augmented interaction) the augmented treatment associated with 62% of patients reporting pain relief at 3 weeks, while 28% of the observation only and 44% of the limited "ritual" group reported pain relief[43]. Similarly, in a primary care based study of 200 patients with various symptoms but no abnormal signs, those given a "positive" consultation comprising of a confident diagnosis and reassurance that things would improve soon were approximately twice as likely to feel better than a "negative" consultation, where the doctor admitted "I cannot be certain of what is the matter with you". The option of being prescribed a placebo (thiamine tablets) did not affect the feeling of improvement[44]. The overriding factor that improved symptoms appeared to be the patient response to the certainty of diagnosis and reassurance concerning prognosis[44]. Other contextual aspects that may promote a positive placebo response include: the patient's perception that the practitioner is experienced and competent[45,46]; an optimistic clinician who suggests that the treatment will help[45,46], and when the practitioner wishes to see the patient again to monitor progress[47].

Clinician's confidence in treatment

Patients are influenced by the clinician's optimism or pessimism concerning the treatment even if this feeling is subconscious and not explicitly expressed. For example, in a double blind dental pain

Box 4
Determinants of placebo response

Physician factors	Warm, attentive, confident, and optimistic 'positive consultation'.
	Physician's optimism about treatment, reassurance about prognosis, and desire to follow-up.
Patient factors	Perception that the physician is competent.
	Patient's expectation of what an intervention will do to them.
	Knowledge of being treated.
	Personality factors e.g., optimism, state anxiety.
Placebo (intervention) factors	Invasive, frequent interventions.
	Reputable brand, higher cost, and greater number of tablets.
	Colour of tablets.

study, patients could either receive fentanyl (to reduce pain), naloxone (to potentially increase pain), or a placebo[48]. In this study, the investigators were told that the first group of patients could only receive naloxone or placebo (i.e., no active analgesic), and that the second group of patients could receive fentanyl, naloxone, or placebo. In fact all three drugs were administered to both groups in a double blind fashion. Interestingly, there was less improvement in pain after the administration of placebo in the first group of patients than in the second group of patients[48]. This suggests that the clinician's pessimism or optimism about the proportion of patients receiving the active drug, was unintentionally transmitted to the patient and influenced treatment efficacy[48].

Response expectancy, concealment and knowledge of being treated

The patient's expectation of what an intervention will achieve is an important determinant of placebo response. In a study of effects of aerobic exercise on physical capacity, patients who were told that they would also feel better as a result of the intervention reported an improvement in their wellbeing despite having a similar improvement in their aerobic capacity when compared to the group of patients who were not given this information and who did not report such improved wellbeing[49]. Similarly, study participants given decaffeinated coffee but who were told that they would all receive regular coffee (i.e., 100% expectancy of caffeine) had a greater increase in alertness, heart-rate, and blood pressure than a group of participants who were told that they would receive either regular or decaffeinated coffee (i.e., only a 50% chance of receiving caffeine)[50].

Knowing that a treatment is being administered is important. In a post-operative analgesia study covert administration of parenteral morphine resulted in slower onset of pain relief than when patients knew when the morphine was administered, implying that the initial rapid relief from our strongest analgesic is largely effected through a placebo response[51]. Similarly, open discontinuation of morphine led to rapid return of pain whereas covert discontinuation did not[51].

Personality effects

In a recent review Watson *et al.* suggested that personality traits such as optimism, pessimism, trait anxiety, and neuroticism influence the placebo response[52]. Optimism may influence the extent to which a patient given a placebo treatment persists in the treated state and interprets it positively. In a recent study involving experimental placebo analgesia (inert cream) tested on two separate occasions, optimists experienced greater and more reproducible placebo analgesia[53]. On the contrary, pessimists are more likely to be influenced by negative expectations. For example, in one experiment pessimistic healthy volunteers reported feeling worse after receiving negative expectation about the placebo administered[54]. People with state anxiety ('situational anxiety') show placebo response, but not those with trait anxiety ('habitually anxious')[52]. This may be because state anxiety reflects responsiveness to the context whereas trait anxiety, an intrinsic personality trait, is independent of the environment[52]. In an experimental study involving IBS patients, reduction in state anxiety after the first placebo session correlated with placebo analgesia after the second session[55].

Method and frequency of administration

In general, the more invasive and the more frequently administered an intervention the higher the placebo effect[8]. Sham arthroscopy in the context of OA, and sham bilateral ligation of the internal mammary artery (BIMAL) in the context of angina, both associate with the same high rate of symptom improvement as the actual treatments, and despite the absence of a no-treatment control group in these studies, they suggest that surgery associates with a very large placebo response[56–58].

Colour and number

Medical students given either a blue or a pink tablet containing an inert substance and told that one was a stimulant and the other a sedative, reported that pink tablets caused stimulant effects and blue tablets sedation, and those receiving two tablets reported greater effects than those receiving one[59]. These effects are explained by the meaning associated with the colour (pink for hot, blue for cool) and the expectancy that a double is more potent than a single dose. One systematic review concluded that green and blue may have more sedative, and red and orange more stimulant effects[60]. In an Italian study, however, blue tablets had a sedative effect in women but an opposite effect in men, perhaps because blue is the national soccer team colour and associates with excitement in men[61]. Thus, it is the meaning attributed to a colour by an individual, not the colour itself that influences the outcome ("meaning response")[62].

Branding and cost

Brand, expense, and novelty of treatment clearly influence the placebo response[62–65]. In a placebo-controlled trial of aspirin for headache, patients were randomized to either: aspirin labelled with a well-known brand; unbranded aspirin; placebo marked with the same brand; or plain placebo. Aspirin was more effective than placebo, and branded tablets (both active and placebo) were more effective than their unbranded counterparts[63]. In another study, patients who were told that their tablets were obtained at full cost had better pain relief than those who were informed that their tablets were heavily discounted[64]. Similarly 'new' interventions have a greater placebo response than well-established older treatments[62,65]. This has been shown for a number of drugs that have been examined in similar study designs over many years, including paracetamol for OA[66], in which the ES of both active and placebo treatments diminishes with time.

Placebo response – not all is in the mind

While the studies presented so far suggest that placebo response originates in the brain, several other studies have demonstrated that placebo can influence physiology in other body systems including leucocyte count[15] and physical function[14]. For example, in one study, multiple sclerosis patients were treated at regular intervals initially with cyclophosphamide paired with anise flavoured syrup but then with placebo plus the same syrup. After the switch, eight out of 10 patients showed a similar decrease in leucocyte count on placebo plus syrup as was achieved with cyclophosphamide plus syrup[15]. In a similar classic conditioning study involving healthy individuals treated initially with cyclosporine paired with a flavoured drink but subsequently placebo with the same drink, measurable reductions in leucocyte interleukin 2 (IL-2) and interferon (IFN)-ɣ mRNA expression, intracellular production and release of IL-2 and IFN-ɣ, and lymphocyte proliferation *in vitro* were obtained by administration of the placebo capsules and flavoured drink alone[14]. These studies suggest that behavioural conditioned immunosuppression is possible in humans. However, although these studies provide an insight into the extent of placebo responsiveness, this approach is not applicable to clinical practice.

Placebo response in clinical practice

Placebo and contextual effects should be recognized and optimized in routine clinical care, especially in the management of chronic distressing conditions for which there are no definitive treatments. While it is unreasonable to consider changing a treatment to make it more invasive, frequent, or expensive to elicit a placebo response; it is important to have a positive consultation, to assess the patient thoroughly, to fully inform the patient and show confidence in treatment offered, and to follow-up the patient to see how they are doing. This is especially true in conditions like OA where the ES of placebo (0.5–0.7) is larger than that achieved with most conventional pharmacological therapies such as oral analgesics and NSAIDs (0.2–0.3)[16]. However, it is debatable when it becomes unethical to increase expectations in this manner[67]. Is it correct for the healthcare professional to induce more expectation for effective interventions, and less expectation for the less-effective interventions *per-se*? While it may seem reasonable to optimize placebo response in the context of medically proven interventions, the use of ineffective interventions to elicit placebo response alone is controversial, and may be difficult to justify, both ethically and financially. However, the fact that active treatment associates with concomitant contextual effects should be recognized and utilized in routine clinical practise[48].

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Both authors have *contributed to* conceptualizing the review, drafting the article, revising it critically for important intellectual content, and approving the final version of the article.

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