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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.
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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.

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