



Placebo effect in osteoarthritis: Why not use it to our advantage?

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effective. The present article discusses the history of placebo effect and its scientific evidence, comments on ethical issues and provides insights about how it may be used to our advantage when treating osteoarthritic patients.

Key words: Osteoarthritis; Placebo; Treatment

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Core tip: Osteoarthritis is a major cause of pain and reduced quality of life in the elderly population, as well as an economic burden. Unfortunately, there is no currently effective treatment, and most of them show small to moderate effect sizes, according to main meta-analyses. On the other hand, literature has demonstrated that placebo has a considerable effect size in osteoarthritis clinical trials. So why not use it to our advantage?

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Abstract

Osteoarthritis is a major cause of pain and reduced quality of life in the elderly, as well as a major economic burden. Unfortunately, there is no currently effective therapeutic strategy to prevent the progression of Osteoarthritis, and its treatment poses a great challenge to the medical community. Most of the treatment modalities currently available for osteoarthritis have small to moderate effect sizes, according to main meta-analyses and treatment guidelines. On the other hand, literature has demonstrated that placebo is considerably

INTRODUCTION

Osteoarthritis (OA) is a major cause of pain and reduced quality of life in the elderly^[1]. It is also an economic burden, associated with high direct and indirect health-related costs, as well loss of adjusted life years^[2]. Unfortunately, there is no currently effective therapeutic strategy to prevent the progression of the disorder, and its treatment poses a great challenge to the medical community^[3].

Most of the treatment modalities currently available for OA have small to moderate effect sizes (ESs),

according to main meta-analyses and treatment guidelines^[4-8]. An ES of 1 indicates that the mean at endpoint is 1 standard deviation below the mean at baseline^[9]. In terms of symptomatic improvement, an ES around 0.2 implies a minor benefit, 0.5 indicates mild effect and 0.8 and higher indicates a major effect^[9].

A 2011 meta-analysis found only moderate benefits of self-management programs on measures of arthritis-related pain and disability^[4], with estimated ES for pain relief of 0.06 (0.02-0.10)^[4]. Acupuncture (ES = 0.28)^[5], exercise (ES = 0.34)^[6], weight management (ES = 0.20)^[10], paracetamol (ES = 0.13)^[11], NSAIDs (ES = 0.37)^[12] and viscosupplementation (ES = 0.37)^[13] are another examples of recommended non-surgical treatments for OA, with small to moderate ESs. In light of the current complete lack of structure modifying treatments, there is a need to reassess the current paradigm.

In 2008, a systematic review to examine the placebo effect and its potential determinants in the treatment of OA has demonstrated that placebo is effective with considerable ES^[14]. For pain relief the overall ES was 0.51 [95% confidence interval (CI): 0.46 to 0.55] for placebo, but nearly zero for patients who were in "no treatment" groups. Such large effect is certainly a surprising and impressive finding. So why not use it to our advantage?

HISTORY OF PLACEBO

Placebo is the Latin word of "I will please". In the thirteenth century, hired mourners often repetitively chanted the 116 psalm "I will please the Lord". The term "placebos" became popular and referred to their fake behavior^[15]. Until 1945, placebos were used by physicians as a "morally" useful but innocuous tool without ethical issues^[16]. When paternalistic ethics prevailed, placebo was considered "The Humble Humbug", a means of reinforcing a patient's confidence in his recovery, to comfort patients with terminal conditions, "especially those low in intellect"^[17,18].

After World War II, the use of the double-blind randomized controlled trial (RCT) began to establish itself as the standard method for "rational therapeutics", and the placebo went through a dramatic transformation, imbued with powerful therapeutic effects that could mimic potent drugs^[16]. This, along with effective drug discovery, brought concern about the ethics of its use. The modern concept of placebo was consolidated a few years later with Beecher's paper entitled "The Powerful Placebo"^[19]. In this analysis, the author found evidence that placebos have an average high therapeutic effectiveness of 35%^[19]. He also stated that "the total drug effect is equal to its active effect plus its placebo effect"^[19]. From this moment, anything aside the predictable cause and

effect outcome was considered "placebo effect", or "placebo response", a new and much larger concept of placebo.

PLACEBO RESPONSE

The placebo response can be defined as the symptomatic improvement provenient from a treatment or intervention that does not result from the substance or intervention itself, but is due to the therapeutic ritual, context, expectations or any other patient, caregiver or environmental factor involved in the treatment. It's a very complex and omnibus concept, previously defined by other authors as "symptomatic improvement on receiving any inert/non-therapeutic (placebo) intervention(s) compared to those who do not receive it"^[20] or "a change in a patient's illness attributable to the symbolic import of a treatment rather than a specific pharmacologic or physiologic property"^[21]. The former definition meets the classical placebo role in RCTs, but the latter acknowledges that it's rather impossible to separate the "placebo effect" from the real effect of a given drug or intervention. Furthermore, the placebo effect is built-in to any given treatment, even when no physical placebo is given.

EVIDENCE OF PLACEBO RESPONSE

A 2004 update on a systematic review found only limited evidence of clinical effects as a consequence of placebos, pointing out that they had possible benefits only in studies with continuous subjective pain outcomes^[22]. Nevertheless, literature on significant placebo response is abundant.

In a classic experiment, medical students were told they would receive tablets with sedative or stimulant effects. All of them received either one or two blue or pink pills. However, every pill was placebo. It was found that "two capsules produced more effects than one, and blue capsules were more sedative than the pink ones"^[23]. Commercial variables also affect expectations and influences therapeutic efficacy. When patients were given a famous pain killer in a branded or unbranded form with either an inert or an active formulation, Aspirin was more effective than placebo, and branded tablets (both active and placebo) were more effective than their unbranded counterparts^[24]. Another study found that patients who were told their pills were more expensive (USD\$2.50) had more symptomatic relief than those who were told their pills cost just 10 cents^[25].

The placebo response may also be observed by increasing expectations about an intervention. In a study of the University of Connecticut^[26], subjects were given decaffeinated coffee, with deceptive or double-blind instructions. One group was told they would receive regular coffee, and the other group was

told they would receive either regular or decaffeinated coffee. The first group had a greater increase in alertness, heart rate and blood pressure than the second group (and no one actually received caffeine!). Verbal suggestions can alter patient's expectations and lead to placebo effects. A patient can make use of a topical placebo cream with two different suggestions: that the cream is inert or that it is a powerful analgesic. The outcomes will surely be different^[27].

Knowing that a treatment is being administered, also known as open-hidden paradigm, is one of the most evident findings supporting placebo effect in clinical care. Patients who could see the medication being administered experienced greater symptom relief than when treatment was given in a hidden manner, *i.e.*, without the patient's knowledge. Interestingly, in this case, no actual placebo has been given^[28]. Practitioner's expectations are also shown to influence patient outcomes as well. In a RCT on dental pain, patients could either receive fentanyl, naloxone or placebo. This time the investigators were the ones deceived. In the initial phase of the study they were told patients would only receive naloxone (to increase pain) or placebo. In a second phase investigators were told that a fentanyl group (for analgesia) was included. Placebo in the first group led to less improvement than in the second group, meaning that investigator pessimism about proportion of patients receiving correct therapy could have negatively influenced the outcome^[18].

PLACEBO RESPONSE IN OA

The placebo response is best documented for pain and distress, two main targets in patients with OA^[20]. In a systematic review involving 16364 patients that received placebo in OA, RCTs confirmed that placebo response occurs in OA. Moreover, the overall ES for pain relief was 0.51, a very substantial number and greater than most specific effect obtained from any other individual treatment for OA^[14]. In a randomized controlled trial of acupuncture for OA, traditional Chinese acupuncture was found not to be superior to sham acupuncture. However, "acupuncturists' styles had significant effects on pain reduction and satisfaction, suggesting that the analgesic benefits of acupuncture can be partially mediated through placebo effects related to the acupuncturist's behavior"^[29]. Telephone contact is shown to be a useful intervention that can enhance the functional status of OA patients by reducing pain and improving psychological health^[30]. Although patients may actually receive useful treatment information by phone, the call itself surely exerts a powerful placebo effect.

The method of delivery is also very important. In general, the more invasive and the more frequently administered an intervention the higher the placebo

effect^[14]. Bannuru *et al*^[31] showed that some types of placebo interventions are associated with greater responses in patients with OA (intra-articular and topical placebo effects higher than oral). Thus, it is not surprising that sham arthroscopy of the knee has a very large placebo effect^[32]. Even the way that practitioners interact with patient can be of influence. Contextual aspects, such as a warm, attentive, confident and optimistic consultation, as well as the patient's perception that the practitioner is competent and wishes to monitor his/her progress, may also positively influence the outcome. In a study by Thomas^[33], all patients received thiamine tablets as placebo medication. A "positive" consultation, with confident diagnosis and reassuring attitude produced better outcomes than a "negative" consultation.

FINAL CONSIDERATIONS

Since the second half of the 20th century, the use of placebo has been loathed and, apart from the common use as a control in RCTs, it is sometimes used with negative purposes, like to determine if a patient is faking its symptoms. In light of recent publications, we need to have a better understanding about how the interactions between patients, physicians and context work. It is well proven that the placebo effect is real, especially in painful disorders like OA. However, with such a large and varied amount of available treatment modalities, it's obvious that we are not considering giving sugar pills or saline solutions when talking about the use of placebos in OA treatment. Moreover, it is neither acceptable nor ethical to prescribe more frequent and/or invasive treatments, or more expensive ones to achieve a placebo response.

The greatest impact that placebo effect can have on our practice is to give us new insights about patient care. Controversial treatment modalities such as insoles^[34], viscosupplementation, mind-body therapies, physical therapies and chondroprotective drugs perhaps would not be controversial at all if the only evidence accepted didn't come from methods of evidence-based medicine that are currently very rigorous, with strict inclusion criteria, minimum follow-up requirement and the use of minimum clinically important improvement concept. It seems unrighteous, for example, to obtain statistically significant results favoring chondroprotective agents used as monotherapy and compared to a powerful placebo and consider it "not clinically relevant"^[35].

We are far from treating effectively our OA patients. And the burden of the disease only grows, since population is aging. Maybe we should make more use of non-pharmacological tools and chondroprotective agents. Even in light of the current lack of "high level of evidence" data, we should give such tools more credit, and genuinely believe that they may help. In

a positive expectation environment, with a warm and reassuring consultation and a desire for follow-up, we can surely improve practitioner-patient relationship and be more effective. We certainly can use the placebo effect to our favor.

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