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Review

The power and value of placebo and nocebo in painful osteoarthritis

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SUMMARY

This paper reviews some recent advances in our understanding of the effects of sham or dummy interventions on pain and other symptoms in osteoarthritis (OA), and outlines two new approaches to the investigation of placebo and nocebo effects.

We argue that the placebo effect provides us with a valuable way of investigating the nature of conditions like OA. For example, by examining which symptoms, biochemical markers or imaging features do or do not respond to placebo, we might learn more about the relationships between pathology and symptoms in OA.

Placebo and nocebo effects are positive or negative outcomes resulting from the human interactions and contexts in which healthcare consultations take place. Subtle changes in behaviours and the environments in which consultations take place can have major effects on pain and other symptoms being experienced by people with OA. Nocebo effects are particularly powerful, leading to many health-care professionals (HCPs) causing unintended harm to their clients.

Based on our own research, we conclude that beneficial outcomes are most likely to occur when both the (HCP) and the client feel safe and relaxed, and when the experiences of the client are validated by the (HCP). These findings have important implications for clinical practice.

We believe that research in this field needs to be 'trans-disciplinary', escaping from the constraints of the purely biomedical, deterministic, positivist paradigm of most medical research. We provide the example of our own work which combines performance studies and scholarship, with psychology and medicine.

Introduction

The placebo response is generally described as the improvement in health status that occurs with the administration of a sham intervention[1,2]. Following the uptake of the randomised controlled trial (RCT) as the central method for assessing the efficacy of interventions, it became commonplace to contrast the effect of a therapy that was targeting a particular problem (such as pain) with a sham therapy, as identical as possible to the 'real' one. This resulted in the trials-based definition of the placebo response. But, as pointed out recently, the idea that placebo is about a sham treatment is misleading and unhelpful[2].

Some authors have questioned whether the placebo effect exists, as improvement with no active intervention could occur for other reasons, such as regression to the mean[3,4]. Yet we believe that phenomena termed 'placebo' offer a rich source of data, and suggest that better understanding, and clearer delineation of terms, could enable their beneficial use. As suggested by Kirsch[5], we separate placebo *responses* from placebo *effects*. As shown in Fig. 1, the placebo response is the change seen in response to a sham intervention, whereas the placebo effect is the difference in response between *doing* nothing (a no-treatment control group), and *giving* 'nothing' (giving a sham treatment that should do nothing).

In this article, we concentrate on the placebo effect rather than response. We focus on changes in health status occurring after a health-care consultation involving no administration of a specific drug or other medical intervention. We are not concerned with

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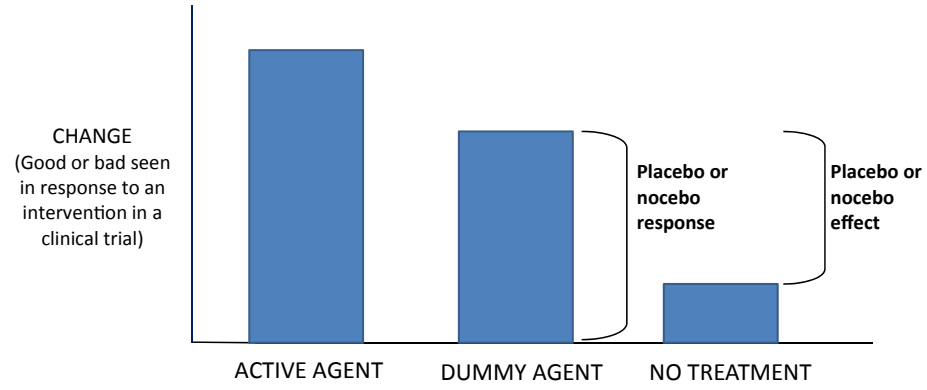

Fig. 1. Diagrammatic representation of what is meant by the placebo response and the placebo effect when dummy or sham 'control' treatments are compared to an active intervention, or a no-treatment control group, in a randomised controlled clinical trial (RCT) (after Kirsch[5]).

trials, rather our interest is in the contextual factors[6,7] that can allow people to improve as a result of an encounter with a health-care professional (HCP) even if no specific therapy is used.

This article is based on extensive primary and secondary research by a multi-disciplinary team that includes a doctor with an interest in OA (PD) a humanities scholar (SG) and a psychologist (M G-H), who have been working together on this topic for the last 5 years. It is split into two parts; first we review some of what is known about the importance of placebo and nocebo effects and their mode of action, with an emphasis on pain in OA, secondly we describe the different research approaches that we are using to investigate the topic further, which emphasize client–practitioner interactions.

Part 1. Placebo and nocebo effects

The placebo effect appears to be particularly important in the relief of symptoms such as pain and depression[1,2,8,9]. But sham interventions and encounters with HCPs can do harm as well as good, a phenomenon called the nocebo effect[10]. Nocebo reactions have been noted to worsen both pain and anxiety[11,12]. Pain, anxiety and depression are amongst the most important symptoms occurring in people with osteoarthritis (OA)[13]; this article will concentrate on pain, the dominant symptom for most people, but almost everything we say about pain and placebo/nocebo could also apply to anxiety and/or depression, and to other common symptoms and chronic disorders.

The efficacy and effectiveness of placebo on pain in OA

The efficacy of an intervention describes the changes that occur when the treatment is used in the artificial test conditions of a RCT. Effectiveness refers to the changes that occur when that treatment is used in routine clinical care[14]. Efficacy demonstrated in a trial may not translate into effectiveness because of the influence of numerous context-related effects. Efficacy is often calculated and presented as the effect size of an intervention, which is the difference between the standardised mean effects of the intervention compared to that of no intervention.

It has been possible to calculate the effect size of placebos in OA trials, because an examination of the literature uncovered enough RCTs that included a no-treatment control group to allow a valid statistical comparison of the effects of dummy treatments to no treatments. Zhang *et al.*[15] found that the effect size of placebo for pain in OA was 0.51 (95% confidence intervals 0.46–0.55) in comparison with 0.03 (± −0.13–0.18) for untreated control groups. An effect size of 0.5, or thereabouts, is of considerable clinical value, and comparable to that of many of our commonly used interventions[16]. The same group published a further analysis, in which they used random-effects modelling to calculate the amount of pain relief that could be attributed to placebo (contextual) effects, and how much to the treatment being tested for its effects on pain in OA[17]. They report that on average 75% of the overall treatment effect is due to the contextual factors rather than the specific intervention. Another recent review used a network meta-analysis technique to synthesize data from 149 RCTs of adults with knee OA in which placebos were used[18]. The findings confirmed the power of placebo in OA, and also showed clearly, as reported in the aforementioned papers, that 'all placebos are not equal': intra-articular and topical sham therapies were superior to oral treatments in pain control. Sham surgical interventions can also result in a great deal of pain relief[19]. This work suggests that we need to take more account of contextual factors when trying to interpret clinical trials in OA.

The effectiveness of placebo in OA is unknown, as no large-scale pragmatic trials of sham treatment, or of a purely context-based intervention, compared with no treatment control groups have been undertaken. However, it seems likely that the effectiveness of placebo for pain relief in OA can be considerably larger than its efficacy. The artificial conditions of a trial constrain the extent to which context effects and the behaviours of clinicians, thought to be crucial to the placebo effect[2,6,7], can be used to enhance the value of an intervention. Conversely, an appropriate consultation, within a safe environment, as explained below, could greatly enhance the effects of an intervention.

Recent trials indicate that consultation style can enhance the size of a placebo response in OA and other chronic disorders. In one study comparing Traditional Chinese Acupuncture (TCA) to sham acupuncture in patients with OA of the knee, no difference between the TCA and sham acupuncture was found, but the consultation style used by the acupuncturists made a big difference to outcomes[20]. A secondary analysis of the data suggested that the communication of optimism about likely outcomes led to a greater degree of pain relief[21]. A similar study has been undertaken in irritable bowel syndrome[22], and secondary analysis of the data from that study indicates not only that communication styles matter, but suggests that some practitioners obtain good outcomes, whether they are trying to communicate in a positive way or not, whilst others consistently achieve less placebo-related relief of symptoms[23]. This is in keeping with a large body of research in psychotherapy that indicates that different practitioners have widely varying abilities to help people improve their mental health[24,25].