Placebo Analgesia – Understanding the mechanisms and implications for clinical practice

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SUMMARY POINTS:

- There are neurobiological, cognitive and conditioning processes involved in placebo mechanisms
- Mechanisms research has demonstrated that there is not one placebo effect, but many
- Placebo effects are an inherent element in routine clinical practice
- Modulation of placebo mechanisms in routine practice could provide an opportunity for improving clinical care.

Introduction

The placebo effect is a term that has been widely used in health literature and its nature has been the focus of increasing research in recent years. A key conclusion of recent research, is that there is not one placebo effect, but many, and that these effects are mediated by different psychological and neurobiological mechanisms. In the case of placebo analgesia, several placebo effects have been identified and some have argued that by better understanding how they work, it might be possible for clinicians to ethically augment treatment effects in routine clinical practice.

Conceptualisations of Placebo Effects

The definitions of placebos, placebo effects and placebo responses have been a continuing source of controversy, and confusion. Numerous papers have attempted to define and redefine these terms^{1,2} or advocate for the abolition of the terms altogether³. Recently, we have been attempting to advance this discussion by exploring placebos and placebo effects at a conceptual level⁴.

A placebo is a substance or procedure designed to simulate the psychosocial context surrounding a particular therapy⁴. Therefore, when a placebo is employed, the explanation for any effect should

not be considered in terms of the inert content of the placebo (e.g. the sugar in the pill or saline in the injection), but rather how the placebo mimics a particular psychosocial (therapeutic) context and, in turn, how it might affect a patient's brain, body and behaviour. From this perspective, a placebo effect or response is the response seen in an individual after administration of a placebo, and is mediated by the particular psychosocial context surrounding the administration.

Traditionally, the term 'placebo effect' has referred to the overall group effect following administration of placebos in clinical trials, whereas the term 'placebo responses' has referred to individual patient's responses to placebos. However, consistent with the perspective outlined above, both terms can refer to the psychobiological responses seen after administration of placebos in an individual or groups of individuals⁵.

Historically, the analysis of placebo effects has been complicated by the possible effects of other commonly-occurring factors. The most notable example is that of natural history. When no account is taken of the natural history of a symptom or disease (eg. with an untreated control group), one cannot be sure that the effect seen is due to the administration of a placebo or something that would have happened regardless of any intervention. Accordingly, it is imperative to include a natural history or untreated baseline condition when studying

potential placebo effects. The difference between the two conditions represents the ‘true’ placebo effect. Another potential complication in interpreting placebo studies is the phenomenon of regression to the mean. This is a well-recognised statistical phenomenon whereby amongst a group of individuals, those with more extreme values tend to shift closer to the group average over time. In the case of pain, this means that individuals with very high levels of pain on initial assessment are likely to have lower levels at subsequent follow-up assessments. Accordingly, experimental designs need to take these factors into account when investigating placebo responses to make as sure as possible that these phenomena are not mistaken for true placebo effects.

Mechanisms of Placebo Effects

Traditionally, placebo mechanisms have been divided into psychological and neurobiological categories⁶. In light of current conceptualisations of placebo effects, as well as more innovative experimental designs and technology, it is evident that this differentiation is somewhat artificial. Nonetheless, it has been a useful way of separating and studying some of the mechanisms that underpin different placebo effects, keeping in mind that these effects are real psychobiological responses driven by different psychosocial contexts and therefore represent some of the interactions between the mind, brain and body.

Psychological Mechanisms

Expectations for change in symptoms have been shown to mediate placebo effects⁷. In the case of placebo analgesia, simple verbal cues and suggestions aimed at manipulating patients expectations have been shown to mediate placebo analgesia⁸. Furthermore, manipulations in verbal instructions and the employment of specific conditioning protocols intended to increase expectations have been shown to alter the magnitude of placebo analgesia. In this case, patients subjected to a conditioning protocol (repeated symptom reduction prior to testing) and verbal instructions suggesting pain relief (such as “the drug I am giving you is a powerful pain killer”), had larger responses than those whose had just verbal instructions^{9,10}. In another set of studies, subjects who had been given uncertain instructions (e.g. you may or may not receive a powerful drug) which reduce the expectations for symptom change, had reduced placebo analgesia^{11,12,13}. Expectations have also been shown to interact with other cognitive and emotional factors, such as expressed desire for pain relief and reduction in anxiety, to codetermine placebo effects⁴.

Although expectations have the strongest evidence for contributing to placebo effects, particularly placebo analgesia, there is also support for the role of classical conditioning in some placebo effects. In classical conditioning, repeated associations between one stimulus (e.g. the therapeutic environment) and the active drug (the “unconditioned stimulus”) results in conditioning or “learning” whereby the therapeutic environment becomes able to elicit a response (“conditioned response”) in the absence of the active drug. In this manner, learning mechanisms (i.e. conditioning) have been demonstrated to mediate placebo effects. To date, a

variety of placebos (such as creams, needles or tablets) have been able to simulate particular therapeutic contexts, resulting in placebo responses^{14,15,16}. However, there is considerable difficulty in separating the cognitive (expectations) and conditioning processes in humans. For example, conditioning protocols are used to modulate expectations in many studies^{9,10}. To this extent, it is believed that both conditioning and expectations are not mutually exclusive and may be seen as inextricably connected^{5,2}.

Neurobiological Mechanisms

The neurobiological mechanisms of placebo analgesic effects can be considered from both pharmacological and neuroanatomical viewpoints. The pharmacological mechanisms of placebo analgesia were first identified in 1978 by Levine and colleagues who were able to reverse placebo analgesia by injection of the opioid antagonist naloxone, demonstrating the involvement of endogenous opioids in placebo analgesia¹⁷. Ensuing studies have been able to fully or partially replicate these results, further demonstrating the involvement of the endogenous opioid system in these responses but also suggesting that multiple responses may be present (by virtue of the fact that some placebo analgesic responses are blocked by naloxone and others not)^{9,18}. One example of the presence of different placebo analgesic mechanisms in the same experiment involved conditioning protocols with both opioid and non-opioid analgesics. When a placebo was administered following a conditioning protocol, the subsequent placebo analgesic response was only reversible by naloxone in the group who were conditioned with an opioid drug and not in the group conditioned with the non-opioid analgesic⁹. Interestingly, due to the standardisation of the protocols, these pharmacological mechanisms seem to be independent of the verbal suggestions and psychosocial context surrounding the patients in the experiment and may represent a different relationship between learning and specific pharmacological systems.

Further support for the role of endogenous opiates in placebo analgesia comes from studies looking at the interactions between the opioid and cholecystokinin (CCK) systems. Specifically, administration of a CCK antagonist can potentiate placebo analgesia, whereas naloxone abolishes it, demonstrating that alterations in the activity of these competing systems may be involved in placebo analgesia^{19,20}. Pharmacological mechanisms of placebo analgesic effects are not limited to “pain pathways” but can involve other systems that are related to the experience or treatment of pain, such as opioid-mediated placebo mechanisms affecting respiratory centres^{21,22}, and the heart²³. Equally, non-opioid mechanisms can affect hormone secretion¹⁴. Together, this research suggests that placebo analgesic effects are mediated by endogenous opiates on some, but not all, occasions, and multiple body systems may be involved. Finally, there have been several studies which have been able to demonstrate that placebo analgesic responses are not only opioid mediated, but that they can be localised to different parts of the body, implying that opioid mediated placebo responses have a somatotopic organisation²⁴. Recently, based on these data and improved experimental design and technology, investigators have

begun to look closer at the neuroanatomical mechanisms of placebo effects.

Developments in imaging technology have assisted in the investigation of the neuroanatomical mechanisms of placebo effects, particularly placebo analgesia. Firstly, these studies provide support for opioid mediated placebo effects, whereby using functional magnetic resonance imaging (fMRI), similar brain activation patterns have been demonstrated between patients taking a strong opioid medication and those taking a placebo in the same context²⁵. Furthermore, using sensitive molecular imaging techniques, a direct relationship has been established between placebo effects and mu-opioid receptor activity at several key sites in the brain²⁶.

Specifically, these imaging studies have demonstrated that placebo administration results in decreases in activity in those areas associated with pain processing and increased activity in those areas involved in emotional regulation²⁷. Importantly, the decreases in pain processing associated with placebo administration have been shown to occur not only in anticipation to and following pain (in the reporting phase)²⁸, but also during the administration of the painful stimulus demonstrated that these mechanisms are active throughout the context of the experiment and the changes in symptoms are not simply a reporting bias²⁹. Furthermore, the findings of increased activity in brain areas associated with emotional regulation to provide some of the neurobiological correlates to expectations, desire and reward systems. The latter is particularly interesting given the relationship between opioid and dopaminergic circuitry and an emerging literature demonstrating functional neuroanatomical, pharmacological and behavioural changes following placebo administration in Parkinsons Disease⁴. In sum, it is becoming clear that studies of pharmacological and functional neuroanatomical mechanisms of placebo analgesia have identified the presence of more than one placebo analgesic effect. These findings point to complex interactions between psychological constructs and physiological processes.

Implications for clinical practice

The recent developments in our understanding of placebo effects have called for a shift in thinking about the clinical implications of research on placebo mechanisms. At the forefront of this shift is the fact that placebo effects are an inherent (and inevitable) element in routine clinical practice, even when a placebo is not intentionally given. When one considers the newer conceptualisation of placebo effects, it becomes apparent that the outcome of any medical intervention may be the result of the specific intervention and the psychosocial context in which it is delivered. The latter may be seen as the placebo component of the therapy, or what happens when one substitutes a particular intervention with a placebo. From this perspective, studies of placebo effects are essentially studies of one of the two main components of routine clinical practice.

Perhaps the most potent demonstration of the presence of placebo effects in routine clinical practice is the open-hidden paradigm for

drug administration. In this case, a drug can be administered in two different ways; the open administration, whereby the drug is administered by a clinician in full view of the patient, and hidden administration, whereby the same drug is administered by an automated machine and in the absence of the clinician. The open administration represents routine clinical practice and the hidden administration the true pharmacological effects of the drug with the psychosocial context and its influence removed. The difference between the two administrations represents the placebo component of a therapy, and has been shown to be significant with a variety of different analgesic medications and treatments for other conditions, such as anxiety and Parkinson's Disease³⁰.

The evidence for the presence of placebo effects in routine clinical practice is further supported by recent studies aimed at manipulating the placebo component of therapy to alter the outcomes. In one example, patients with postoperative pain were treated with buprenorphine, on request, for three consecutive days. Simultaneously, each patient had a basal saline infusion. However, the explanation provided for this basal infusion was varied across three groups. The first group was told that the infusion was simply a rehydrating solution (natural history), the second group was given classical double blind instructions "the solution may or may not be a potent pain killer" and the third group was given deliberately deceptive instructions "this is a strong pain killer". The only differences between the three groups was the manipulation in verbal instructions surrounding the placebo administration. A modest decrease (by 20%) in buprenorphine intake, compared with the natural history group, was found with the double-blind administration, and a greater decrease (up to 33%) was found in the group with the deceptive administration of the saline basal infusion. Importantly, the time-course of pain was the same in the three groups over the 3-day period of treatment, thus the same analgesic effect was obtained with different doses of buprenorphine¹¹.

More recently, Kaptchuk et al³¹ described a trial of acupuncture for irritable bowel syndrome. Patients were divided into three groups; an observation group and two groups who received placebo acupuncture. The first placebo acupuncture group was a "limited placebo" group, where there was minimal interaction and engagement with the practitioner. The second placebo acupuncture group was an "augmented placebo" group, where every effort was made to enhance the placebo component of the therapy through a variety of strategies, such as improved verbal communication and a variety of behavioural methods to improve the patient-clinician relationship. At follow-up, researchers found significant differences between groups in a manner resembling a graded dose escalation of placebo components; that is, the augmented group had significantly better outcomes in multiple dimensions when compared with the limited group and then wait list control, demonstrating the presence, magnitude and manipulability of placebo effects in this treatment.

The modulation of placebo effects in both the above-mentioned trials underscores the potential relevance of this research to routine clinical care. It also shifts the focus from the ethical issues surrounding deceptive administration of a placebo in clinical practice to deliberate

and conscious augmentation of the placebo components of routine clinical practice using standard therapies.

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