

REVIEW

Placebo analgesia: cognitive influences on therapeutic outcome

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Abstract

The therapeutic response to a drug treatment is a mixture of direct pharmacological action and placebo effect. Therefore, harnessing the positive aspects of the placebo effect and reducing the negative ones could potentially benefit the patient. This article is aimed at providing an overview for clinicians of the importance of contextual psychosocial variables in determining treatment response, and the specific focus is on determinants of the placebo response. A better understanding of the physiological, psychological, and social mechanisms of placebo may aid in predicting which contexts have the greatest potential for inducing positive treatment responses. We examine the evidence for the role of psychological traits, including optimism, pessimism, and the effect of patient expectations on therapeutic outcome. We discuss the importance of the patient-practitioner relationship and how this can be used to enhance the placebo effect, and we consider the ethical challenges of using placebos in clinical practice.

The clinical relevance of placebo

Evidence from clinical studies emphasizes the relevance of contextual psychosocial variables, including physician-patient interactions, for treatment outcome [1]. Positive psychosocial influences on treatment outcomes are termed placebo effects, whereas negative influences are termed nocebo effects. Experimental research reveals that the psychosocial context of therapy induces biochemical changes in the brain and body and that these changes may affect the natural history of a disease and the response to a treatment [2,3]. Along these lines, negative responses to drugs have been shown to be much

better predicted by the patient's individual beliefs and negative expectations regarding a drug's effect (nocebo effects) than by the specific pharmacological properties of the drug [4] itself.

Placebo and nocebo effects are therefore centrally important in medical practice, whether these are intentionally used by health-care practitioners or not. A more widespread recognition of this fact may enable and encourage patient-physician interactions that are conducive to positive treatment outcomes. Such interactions are important in determining a number of factors that may affect outcome, including patients' mood, their concepts of disease, treatment expectations, and their willingness to endure therapeutic side effects. However, this knowledge should be taken in the context of the observation that, in the US, 50% of patients leave after a visit with their doctor without an adequate understanding of what the doctor has told them [5]. Therefore, there is clearly an opportunity for improving therapeutic responses to current treatments and a need for more research into and greater understanding of what factors affect those responses.

Until recently, placebo analgesia has been regarded as a nuisance phenomenon in clinical trials. This has shifted to the idea that studying placebo effects allows us to gain insight into the mechanisms of the endogenous control of pain. Research over the last few decades has improved our understanding of the neuropsychology and neurobiology that underlie placebo and nocebo effects. These insights have potentially far-reaching implications for future research and clinical practice. Further understanding of these mechanisms may aid in predicting which contexts (physiological, psychological, and social) have the greatest potential for inducing positive treatment responses. This may help to improve the design of clinical trials. It may also help to understand treatment mechanisms by allowing the separation of drug-specific responses from non-specific (contextually mediated) responses.

This article is aimed at providing an overview for clinicians of the importance of contextual variables in determining treatment response, and the specific focus is on placebo response. We will examine psychological

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traits that can lead to variability in the placebo response of the patient, the practitioner's role in amplifying the placebo response, the physiological mechanisms of placebo in relation to patient and practitioner variables, and finally how the placebo effect can potentially be used for patient benefit.

Psychological variables that influence placebo responses

Placebo responses are highly variable between individuals, having a range of responses from 0% to 100% depending on the context [6]. Responses to a placebo treatment are independent of age and social and physical demographics, but recent evidence suggests that gender may play a part in placebo response rates [7]. However, psychological variables appear to be much better predictors of placebo responses [8].

Research into the psychological context of the placebo response has focused largely on the role of treatment expectations [9]. Treatment expectations, which may be based partly on past experiences with individual physicians and treatments, have a major effect on the therapeutic response. If treatment experiences have been negative and frustrating, these may compound over time and shape the expectation for future treatments. Furthermore, accompanying negative mood states, especially in patients with chronic conditions [10], lend themselves to generating negative treatment expectations. In these situations, drug efficacy competes with the negative treatment expectations of the patient. Negative expectations can modulate or, in the worst case, completely abolish positive therapeutic effects of drugs. For example, Bingel and colleagues [11] demonstrated the effect of positive and negative information about a drug. They found that positive treatment expectations substantially enhanced the analgesic benefit of remifentanyl, a potent μ -agonist. Negative treatment expectation interfered with the analgesic potential of remifentanyl to the extent that the effect of the potent analgesic was completely abolished.

There is also growing evidence that personality may affect the placebo response. The main personality traits for which there is evidence of an effect are optimism, pessimism, trait anxiety, and neuroticism [12-17]. Dispositional optimism and pessimism are habitual styles of expecting good or bad outcomes in life and therefore can be regarded as a dispositional bias in expectation. Optimists demonstrate an attentional bias for positive information [18] and, even when faced with negative information, will tend to reframe the information in positive ways [19]. Optimism correlates negatively with trait anxiety and neuroticism and positively with reported use of positive coping strategies in general. Scheier and Carver [20] suggest that the general positive expectations

associated with optimists lead to persistence and striving toward goals in the face of adversity. Optimism may therefore influence the extent to which a patient, given a placebo treatment, persists in the treatment and interprets it positively.

A recent study [17] showed that dispositional optimism predicted the reproducibility of experimental placebo analgesia in an experiment in which experimental placebo analgesia (in response to an inert cream) was tested on two separate occasions. (Importantly, dispositional optimism correlated highly with the change in pain over the two experimental sessions.) It is possible that optimists, having received the 'treatment' once, were more likely to expect a subsequent positive treatment response.

In contrast, pessimists are more likely than optimists to be influenced by negative or unpleasant expectations. This is because the pessimist dispositional tendency is to believe that negative events are likely to occur, and pessimists are even more negatively reactive when given such information [21]. There is evidence for a relationship between dispositional pessimism and nocebo response in a study by Geers and colleagues [14]. A pill was given to healthy volunteers who had been divided into optimists and pessimists to see whether providing negative expectations about the treatment would make them feel worse. The authors found that pessimists were more likely to produce a nocebo response.

In addition to expectations and the positive or negative biases in expectation, a psychological (but not necessarily orthogonal) factor that is known to influence the response to pain is anxiety. The bi-directional relationship between anxiety reduction and analgesia is crucial to the pain response, and anxiety reduction commonly leads to reduced pain experience [22,23]. Some theories of placebo analgesia have included anxiety reduction as a central mediator [24]. However, it is necessary to differentiate between state and trait anxiety as both have a distinct impact on the placebo effect. State anxiety is an immediate and often transient response to an external stressor. This form of anxiety reflects an acute psychological state of expectation in response to specific contextual cues. A study on placebo reproducibility showed that low state anxiety was a moderator of placebo response and a predictor of how an individual would respond on repeat exposure to the same placebo [17]. In this study, the reduction in anxiety that preceded the reduced anticipation of pain in the second placebo session suggests that the reduction in anxiety may be mediating the positive effects on expectations. A similar result was obtained by Vase and colleagues [25] in patients with irritable bowel syndrome. They showed a positive correlation between state anxiety reduction and pain tolerance following placebo administration.

In contrast, trait anxiety relies on the susceptibility of an individual's personality to experience anxiety in a way that is less dependent on environmental context and more driven by internal factors [26]. Unlike state anxiety, trait anxiety usually has no correlation with pain tolerance following placebo treatment, possibly because trait anxiety is not as externally manipulable as state anxiety [27,28].

The patient-practitioner relationship

At least a part of the benefit of some therapies may depend on the non-specific verbal and physical interaction – termed a 'healing ritual' – that takes place between a physician and patient. This benefit, which is part of a placebo effect, has been considered important in explaining the use of alternative medicines and treatments used in chronic pain for which the physical or physiological mechanisms are not fully understood.

It has been thought that the quality of the physician-patient relationship is integral to positive outcomes, but until now, data to confirm such beliefs have been hard to find. Through a landmark study, a research team from Thomas Jefferson University (Philadelphia, PA, USA) has been able to quantify a relationship between physicians' empathy and their patients' positive clinical outcomes, suggesting that a physician's empathy is an important factor associated with clinical success [29].

A further issue is whether the information a patient is given makes a difference to the outcome. Pollo and colleagues [30] conducted a study in a clinical setting to investigate the differences between the double-blind and a deceptive paradigm. Post-operative patients were treated for pain on request for three consecutive days with a basal infusion of saline solution. The symbolic meaning of the saline solution varied in three different groups of patients. The first group was given no specific information, the second was told that the infusion could be either a potent analgesic or a placebo (double-blind), and the third group was told that it contained a potent pain killer (deception). The placebo effect of the saline infusion was measured by recording the doses of buprenorphine requested over the three days of treatment. The authors found a decrease in buprenorphine intake with double-blind administration and an even greater decrease with the deceptive administration of saline. The time course of the post-operative pain was the same in the three groups over the three-day period of treatment. This demonstrates that the same analgesic effect was obtained with different doses of buprenorphine [30], and dose requirement depended on the information provided to patients. This study is an exemplar, in a real-world clinical setting, of the effect of positive information on the therapeutic effect of a drug.

Physiological mechanisms of endogenous pain control which are relevant to placebo

To many clinicians and researchers, the evidence for psychological factors influencing the treatment response may seem unconvincing without knowledge of the physiological mechanisms by which these effects can manifest. Here, we review the neural circuitry in the brain for which there is currently the strongest evidence for a mediating role in placebo analgesia.

Evidence has been mounting over the past 30 years for a central role of descending pain modulatory circuits, notably the endogenous opioid system, in mediating placebo analgesic responses. The endogenous descending pain modulatory circuit consists of the midbrain periaqueductal grey (PAG), the rostral ventral medulla (RVM), and the spinal cord [31]. The PAG integrates input from the limbic forebrain (including the amygdala and pregenual cingulate cortex) and the diencephalon with ascending input from the dorsal horn [30]. Early studies described the PAG-RVM system as a descending inhibitory control that plays a role in endogenous analgesia or in creating sufficient spinal gain for pain sensory signal detection. It is now clear that the descending control is bi-directional and includes facilitatory mechanisms [32]. The final output of this system is determined by the dynamic balance between inhibition and facilitation which can be altered in different behavioral, emotional, and pathological states. Two of the candidate neuromodulatory systems are the endogenous opioid and serotonin (5-hydroxytryptamine, or 5-HT) systems.

Until now, much of the evidence for the role of endogenous opioids and 5-HT in the modulation of pain processing has arisen mainly from animal experiments. These studies suggest that the serotonergic system works together with the opioid system to mediate a nociceptive gateway within the central nervous system via a descending network of serotonergic spinal-raphé projections [33,34]. The actions of pain transmission are further mediated via serotonergic projections to the spinal dorsal horn from brain regions such as the pregenual cingulate cortex, thalamus, hypothalamus, PAG, RVM, and raphe magnus [33,35,36].

In humans, neuroimaging has provided evidence that the endogenous opioid system is central to mediating placebo effects on pain [37-39]. These studies provide evidence that placebo analgesia is associated with activation of the endogenous opioid system and with μ -opioid receptors within a number of brain regions, including prefrontal, limbic, and brainstem regions. Furthermore, the changes in activity in these brain regions are related to reductions in the physical and emotional aspects of the pain experience, indicating that variation in endogenous opioid transmission relates to variances in placebo effects across individuals. A recent functional magnetic

resonance imaging (fMRI) study has shown activity within all key regions of the descending pain modulatory system – rostral anterior cingulate cortex (rACC), hypothalamus, PAG, and RVM – during placebo analgesia, and this activity was significantly decreased when the μ -opioid receptor antagonist naloxone was present during the placebo intervention [40]. Coupling between rACC and PAG was significantly increased during placebo analgesia but in the presence of naloxone was not different versus control. Positron emission tomography imaging has also been used to determine the regional activation of endogenous opioid neurotransmission during placebo analgesia [41]. Expectation-induced placebo analgesia was associated with marked activation of μ -opioid receptor-mediated neurotransmission in an extensive set of brain regions [41], including anterior cingulate cortex. Furthermore, opioid-related activities in several brain regions within this network correlated with changes in specific self-report measures of placebo analgesia, such as pain intensity and unpleasantness, as well as subjects' emotional states.

Despite the above advances in our understanding of the physiological mechanisms of placebo analgesia, there are significant gaps in our knowledge. While there is evidence that a network of brain regions is involved in placebo analgesia (including prefrontal, cingulate, orbitofrontal, limbic, and brainstem regions) and that responses in these brain regions are substantially driven by changes in expectation [42], it is not known precisely where in the brain expectations are generated and maintained or by what mechanism these expectations come to act on the descending pain modulatory circuit, including the endogenous opioid system. Although the prefrontal cortices play an important role in mediating placebo analgesia, there is little evidence outside of the placebo literature for their role in expectation effects on pain. One possible explanation is that the prefrontal cortices are not involved in the expression of expectation but rather in their generation through processes of conditioning and learning. fMRI studies have identified a common prefrontal cortical network that is involved in conditioned placebo analgesia [43,44] and that consists of areas that are also important in memory and recall.

Further gaps in our knowledge of the mechanisms of placebo are in relation to the role of neurotransmitter systems other than opioids. Because of its central role in the central modulation of pain processing, the 5-HT neurotransmitter system is one candidate, and there is emerging evidence for a role of this system in placebo response. Carriers of the S allele of the 5-HT transporter (5-HTT) gene have been linked with a range of anxiety-related personality traits, such as self-reported neuroticism and agreeableness [45-47]. Furmark and colleagues [48] found an association between the human genes

responsible for driving serotonergic activation of the amygdala during social anxiety and placebo-induced reductions in stress. It is currently not known whether this anxiety-related amygdala sensitivity would have an impact on placebo analgesic responses.

There is also interest in further understanding the possible role of the principal stress response pathway, the hypothalamic-pituitary-adrenal (HPA) axis, in placebo response. The HPA axis has a close relationship to negative psychological states such as anticipatory anxiety [49]. Although little evidence links the HPA axis with the placebo response, its activation has been linked to the placebo response. Benedetti and colleagues [50] showed that administration of an inert substance coupled with a negative verbal suggestion upregulates the HPA axis. It is unclear whether placebo and nocebo treatments would have opposing effects on the HPA axis. In rodents, endogenous opioids have been shown to exert both inhibitory and facilitatory effects on HPA activity. One pathway for this inhibition is an effect on cortisol, which is both a product and an inhibitor of the HPA axis. Morphine, for example, was shown to activate adrenocortical release indirectly via the hypothalamus and anterior pituitary and directly via the adrenal gland. In humans, however, endogenous opioids predominantly inhibit HPA axis activity, whereas high doses of the opioid receptor antagonist, naloxone, activate the HPA axis. These findings suggest a possible interaction between the opioid system and HPA axis as part of the placebo response, and opioid release inhibits stress response pathways. Although currently there is lack of direct evidence to support this hypothesis, the association of placebo response and reductions in anxiety makes this an important area for future study.

Enhancing the placebo effect in clinical practice

There is scope for enhancing the effect of positive information regarding the content of a treatment in everyday clinical practice for the treatment of pain. The psychological and physiological benefits of this were outlined in the previous sections. Physicians may deliberately give patients treatments they believe to be placebos more often than one might expect, as suggested by several studies worldwide. Forty-five percent of 231 Chicago metropolitan area physicians who were on medical school faculties and who were given a web-based questionnaire affirmed that they gave placebos to their patients. Reasons provided by these physicians for giving placebos included complying with a patient's wishes and avoiding conflict (70%), applying a perceived 'placebo effect' (48%), avoiding changing another doctor's prescription (40%), avoiding telling the patient that all treatment options were exhausted (40%), testing whether a condition was 'functional' or 'organic' (25%), and 'other' (9%) [51].

There is, however, controversy about whether giving a placebo as a treatment is ethical. Any ethical assessment to promote placebo effects in clinical practice requires knowledge of the clinical advantages of inducing placebo effects [2] and how placebo effects can be promoted without deception.

One of the main advantages that placebo treatment could offer is a reduction in the need for chemically active medications. This would not only benefit the patient by reducing side effects but also be a cost benefit to health-care systems. A placebo might offer the theoretical advantage of an inexpensive treatment that would not cause adverse drug reactions or interactions with other medications, potentially avoiding complications of polypharmacy. The problems with polypharmacy in older patients were recently highlighted by Fox and colleagues [52]. They showed that patients taking a cocktail of drugs with anticholinergic properties had increases in cognitive impairment and mortality. A significant number of the patients were taking selective serotonin reuptake inhibitors for depression, a condition proven to be responsive to placebo treatment [53,54]. This is one example of a condition in which placebos might be used to reduce the need for drugs. Although we cannot currently advocate the use of placebos as treatments, there needs to be an exploration of the therapeutic options of using placebos more systematically. For placebos to be used in place of antidepressants, there would need to be firm evidence from clinical trials that they are at least as effective, carry no risk to the patient, and conform to ethical standards and guidelines in clinical care.

Despite these potential advantages in the use of placebos clinically, it is unclear whether a recommendation of a treatment intended to promote the placebo effect can be made without deception in a way that does not undermine its therapeutic potential. Finniss and colleagues [2] give the example of acupuncture treatment for a patient who has chronic back pain and who has not been helped by standard medicine. The authors suggest that the prescribing physician could give the following disclosure: 'Recently, acupuncture has been shown to be no more effective than sham acupuncture, but both produce substantially greater symptom improvement in patients with chronic low back pain compared with those patients who receive no treatment or conventional therapy. It is possible that acupuncture works by a psychological mechanism that promotes self-healing, known as the placebo effect' [2]. A patient who received this disclosure and subsequently got better after undergoing acupuncture might nonetheless develop a false belief about why it worked. This does not mean that the patient has been deceived, nor is there any intention to mislead the patient. There is simply the intention to

encourage the patient to initiate their own internal mechanisms of self-healing. Another example of the non-deceptive use of placebo was provided by Kaptchuk and colleagues [3]. They reported an open-labeled placebo study in patients with irritable bowel syndrome. Patients were informed that they would be given a placebo treatment and were told that 'placebo pills have been shown in rigorous clinical testing to produce significant mind-body self-healing' [3]. Patients reported significantly higher global improvement in their irritable bowel syndrome symptoms in comparison with the no-treatment control group.

Patient-dependent influences may be as important as direct practitioner influences on the placebo effect in terms of how patients receive information provided to them by a health-care practitioner. As discussed already, psychosocial factors are important determinants of placebo response. A logical step would therefore be to enhance the response to placebos by influencing these factors. This may be possible by using psychosocial interventions, such as cognitive behavioral therapy, which could help alleviate psychological barriers such as neuroticism and negative expectations. Patients who fit a particular psychological profile that predicts poor treatment response would particularly benefit from this approach. Although psychological treatments have been shown to be effective in reducing pain and disability in themselves, it is not known whether the benefits of psychological programs are partly a result of enhancing placebo mechanisms. For example, if a psychological treatment can reduce the tendency to generate negative cognitions, it may also improve the ability of the patient to generate positive expectations regarding a physical or pharmacological treatment. It is not known to what extent this determines the success of a psychological treatment and this is an area that requires further study.

Conclusions

Placebo analgesia is a robust psychological and neurophysiological phenomenon that appears to be dependent largely on expectation. However, further research is needed to better understand how the contextual factors that cause placebo response might actually have an impact on specific symptoms such as pain. What is clear is that placebo mechanisms can and should be enhanced to maximize the effect of currently available therapeutic agents. We assert that it is unethical not to recognize and promote the self-healing opportunities that placebo mechanisms provide and that it is also unethical to deceive or intentionally mislead patients. We need to resolve this paradox. By providing positive and comprehensible information to the patient, fostering empathic patient-practitioner relationships, or using cognitive-behavioral intervention where necessary, placebo

mechanisms could be potentially enhanced without the need for deception. In the future, it may also be possible to act directly on the physiological mechanisms mediating placebo responses by using pharmacological therapies.

This article is part of the series *Evolving understanding of the biology of pain and its application to patient care*, edited by Daniel Clauw and Anthony Jones. Other articles in this series can be found at <http://arthritis-research.com/series/pain>

Abbreviations

5-HT, 5-hydroxytryptamine; fMRI, functional magnetic resonance imaging; HPA, hypothalamic-pituitary-adrenal; PAG, periaqueductal grey; rACC, rostral anterior cingulate cortex; RVM, rostral ventral medulla.

Competing interests

The authors declare that they have no competing interests.

Published: 30 March 2012

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doi:10.1186/ar3783

Cite this article as: Watson A, *et al.*: Placebo analgesia: cognitive influences on therapeutic outcome. *Arthritis Research & Therapy* 2012, **14**:206.