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The Placebo Effect and Its Clinical Implications in Urgent Care

Urgent Message: The placebo effect can produce clinical manifestations of various disease states, particularly for pain. It has practical clinical implications for urgent care clinicians who routinely recommend oral medications for pain.

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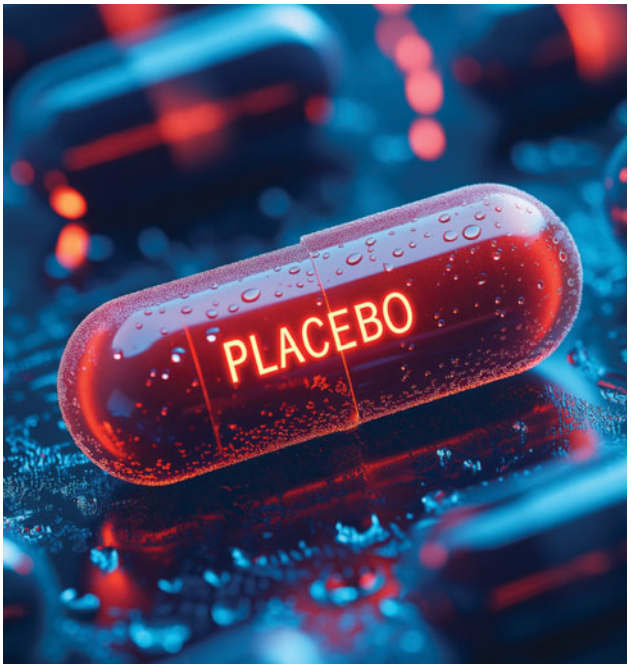
Abstract

The placebo effect—the nonspecific beneficial effect of a medical treatment—involves complex psychological, biological, and physiological interactions. It was first described in the medical literature hundreds of years ago, with a definition that has evolved over recent decades. Much progress has been made in the disciplines of pharmacology, neuroimaging, and physiology in studying the placebo effect, which has contributed to an increased understanding of the neurological pathways, brain receptors, and neurotransmitters responsible for placebo responses. As biomedical ethics has progressed since the early 20th century, researchers and clinicians have wrestled with ethical considerations surrounding the use of placebos in both research and clinical practice. Despite these ethical considerations, placebo-related research continues to grow as medical science strives to elucidate the factors that both contribute to and hinder the placebo response across disease states. This review article will summarize our current understanding of the placebo effect including historical perspectives and the evolution in our knowledge of the underlying mechanisms, modulating factors, and ethical considerations.



While the placebo effect can affect clinical manifestations of various disease states, this review will focus on the placebo effect as it pertains to pain—one of the most common urgent care complaints.

Introduction

The word "placebo" is Latin for "I wish to please." While the term "placebo effect" appeared relatively recently, placebo effects have been described in medicine

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for hundreds of years. One of the earliest mentions of the concept appeared in 1572 in a work by the French philosopher Michel de Montaigne who wrote "there are men on whom the mere sight of medicine is operative."[1] In 1799, John Haygarth first demonstrated the placebo effect experimentally by testing "Perkins Tractors"—metal rods thought to draw illness out of the body. Haygarth found that Perkins Tractors were no more effective in treating illness than sham wooden rods, effectively demonstrating the power of placebo lay within the patient's belief.[2]

One of the earliest reports of the use of a placebo as an experimental control occurred in 1784 when Louis XVI, king of France, commissioned Benjamin Franklin and Antoine Lavoisier to test Franz Mesmer's "discovery" of what he termed "animal magnetism." Animal magnetism, Mesmer claimed, was an invisible force that caused illness when the force was interrupted by "crises." To examine Mesmer's claims, Franklin and Lavoisier exposed patients to "mesmerized" objects or untreated objects (ie, control placebos). They found that patient responses to the objects were equivalent regardless of whether the objects were "mesmerized" or not.[3]

The Placebo Effect

In modern times, the placebo effect has been conceptualized in 2 different ways: clinically in practice; and experimentally in research.[4] The clinical placebo effect consists of prescribing medication or treatment that has no known effect for a patient's condition, such as the idea of the "sugar pill."[4] With the advent of the randomized controlled trial, the placebo effect has also become synonymous with the average aggregate response of patients receiving placebo controls.[5] With this expansion in the definition of placebo, there has been a deflation in the value and utility of placebo in clinical medicine.[4]

Novel therapies are usually validated by comparing their effect to a placebo—which is equated to "no treatment." It is important to note, however, that there is typically an effect from placebo itself. In other words, treatments that are dismissively said to be "no better than placebo" may in fact be more effective than no treatment. In some cases, improvement in a patient's condition may be attributed to an intervention, rather than to a placebo effect. Research investigating the placebo effect in recent decades has uncovered the power of placebo and revealed ways in which this phenomenon can be leveraged in safely treating patients, especially those afflicted with pain.

Mechanisms

The neurophysiological pathways involving pain and the placebo effect have been extensively studied using pharmacological, neuroimaging, behavioral, and physiological approaches. These studies have demonstrated that the placebo effect is multifactorial and rooted in the endogenous opioid, cannabinoid, and reward pathways.[6]

In 1978, Levine and colleagues ushered in an era of renewed interest in the placebo effect when they demonstrated that placebo-induced analgesia could be reversed with naloxone, implying that the placebo effect is mediated, at least in part, by the μ-opioid system.[7] It was hypothesized that placebo analgesia arose from descending pain-modulating systems originating in the cerebrum. Since then, many groups have attempted to directly implicate the role of the endogenous opioid system in the placebo effect. Placebo administered with expected analgesic properties provides a morphine-like increase in pain endurance, which is reversed with naloxone.[8,9]

Zubieta et al. linked this placebo-induced activation of μ-opioid receptor-mediated neurotransmission to specific associative, higher-order brain regions, such as the pregenual and subgenual areas of the rostral anterior cingulate cortex, dorsolateral prefrontal and insular cortex, and nucleus accumbens.[10] Moreover, placebo analgesia was shown to be related to decreased brain activity in some of these regions and increased brain activity in the prefrontal cortex with pain anticipation.[11,12] These regions are important for pain modulation because they integrate sensory, affective, cognitive, and motivational aspects of pain, enabling top-down control over both the perception and emotional response to pain through interconnected cortico-limbic circuits. These regions modulate pain by influencing descending inhibitory pathways, processing pain-related emotions, and linking

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pain relief to reward mechanisms.[13]

The cannabinoid system's role in the placebo effect has also been explored using pharmacological antagonists to reverse placebo effects. One 2011 study by Benedetti et al. conditioned participants with ketorolac, a nonopioid pain medication. Participants in this group had reductions in pain even when given a placebo. This effect was reversed when the participants were given the cannabinoid type 1 receptor antagonist rimonabant, which suggests that the placebo effect is mediated at least in part by the endocannabinoid system.[14]

Recent placebo research has highlighted that having positive expectations about pain relief is a key factor in eliciting the placebo analgesic response. This effect is driven by the patient's belief or anticipation that a treatment will be effective, which activates endogenous pain modulatory systems and leads to reduced pain perception. Positive expectation of placebo analgesia is related to an increase in dopamine signaling in the nucleus accumbens, an area of the brain that is heavily involved in the reward pathway.[15] Moreover, subjects' individual variations in nucleus accumbens response to reward affected the formation of placebo analgesia.[15] The opposite is also true. Decreased dopamine signaling in the nucleus accumbens and decreased opioid release are associated with worse pain scores.[16] Clinically, this could indicate that if a patient expects little or no pain relief from a treatment, they are less likely to experience meaningful pain reduction.

Demographics and Contributing Factors

Variation in individual responses to placebo is influenced by patient factors and characteristics of the caregiver. Contextual factors, such as verbal suggestion, dictate the effectiveness of the placebo effect. Levine and colleagues demonstrated that postsurgical patients experience greater levels of analgesia when a caregiver informs the patient of morphine administration as opposed to covert continuous infusion through a pump.[7,17] A simple verbal cue was so powerful in this study, that administering saline was as potent as a 6-8 mg dose of morphine.[17]

This phenomenon is also present with nonopioid medications. Verbal suggestion reduced the medication required to observe a 50% reduction in pain as well as time course to significant pain reduction with medications such as buprenorphine, tramadol, ketorolac, and metamizole.[18] These findings alone have clinical implications for urgent care clinicians who routinely give patients oral medications, such as acetaminophen, for pain. Simply verbalizing to the patient that they are receiving medication "to help relieve pain" may result in meaningfully greater analgesic effects.

Patient responses to placebo are significantly influenced by a given patient's prior exposure to and benefits from analgesic interventions. Numerous studies have shown that previous experiences with pain relief can induce a placebo effect. Moreover, the combination of prior conditioning to a treatment and positive expectations can produce even more robust placebo effects.[8,19]

In a study involving patients with ischemic arm pain, subjects were initially conditioned with morphine over several days. Subsequently, when given saline, those informed they were receiving morphine reported a more substantial reduction in pain compared to those who were told they were given antibiotics.[8]

Colloca and Benedetti demonstrated that these learned responses also have a temporal effect.[20] Participants were exposed to a conditioning procedure in which the intensity of painful stimulation was reduced covertly without the knowledge of the participants to create the illusion that an analgesic treatment was effective. This procedure produced placebo responses that lasted up to 7 days.[20]

Interestingly, conditioning with negative results produces poorer placebo effects. This reduced placebo analgesia is correlated with higher activation of the posterior insulae (involved in the regulation of afferent nociceptive pain processes) and decreased activation of the right dorsolateral prefrontal cortex (involved in the formation of placebo effects).[11,21] These learned placebo effects are strengthened and last longer with more conditioning trials.[22] Taken together, these studies emphasize the complex interplay between prior experiences, conditioning, and expectations in shaping placebo responses to pain management. The placebo effect is not merely a passive phenomenon, but rather a dynamic process influenced by learning, temporal factors, and neurological mechanisms. Additionally, these findings suggest that in patients without beliefs about the efficacy of oral pain medications such as acetaminophen,

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a placebo effect conferring greater analgesic response would be expected. Patients who believe acetaminophen "doesn't work" will not likely experience improved analgesia.

Furthermore, extrinsic factors, such as healthcare provider characteristics, have also been shown to contribute to the likelihood of placebo responses. Patients treated by more empathetic clinicians, for example, experienced a higher degree of placebo analgesia compared to those treated with less empathy.[23] Empathy from nonclinicians also can enhance placebo analgesia. Participants exposed to a noxious cold stimulus reported lower pain scores when a friend or stranger made encouraging or reassuring remarks, validated their feelings, and expressed concern.[24] This suggests that social support also has an analgesic effect and may mediate a portion of the placebo response.

Clinicians can leverage this phenomenon to ease pain by focusing on building rapport and trust with a patient and approaching encounters with a supportive demeanor. This has been demonstrated in a study of patients with irritable bowel syndrome (IBS) where subjects in the study experienced significantly greater improvement in IBS symptoms when clinicians focused on rapport by maintaining a positive and engaging demeanor through active listening, empathy, and confidence when treating patients.[25]

Nonverbal behaviors, such as facial expressions, affect placebo analgesia as well. Specifically, a happy facial expression was shown to increase placebo analgesia when compared with neutral or negative facial expressions in 1 study.[26] Clinician appearance can also affect the magnitude of patients' placebo responses. Clinicians wearing more professional clothing, for instance, was shown to positively correlate with lower pain scores.[27]

Ethical Considerations

As detailed in this literature review, placebos can create powerful, objective, and subjective responses. Despite this, the ethics of placebo use continues to be a topic of debate in clinical practice. For a placebo to be most effective, it is imperative that patients believe that the inert pill or sham procedure being administered has true therapeutic value. This belief, in turn, must be imparted by a clinician.

Ethical concerns begin to arise when clinicians face the dilemma of conveying the therapeutic potential while simultaneously knowing that the treatment is inert. While the clinician may be well-intentioned, misleading patients infringes upon patient autonomy. The American Medical Association thus has formalized the following position on placebo use in clinical practice: "…the use of a placebo without the patient's knowledge may undermine trust, compromise the patient-physician relationship, and result in medical harm to the patient."[28]

Autonomy is one of the core pillars of biomedical ethics, defined as the ability to make decisions for oneself without coercion or limitations such as an inadequate understanding that prevents meaningful choice.[29] Thus, clinicians have a duty to refrain from interfering with patients' ability to choose freely and thus provide accurate information to allow the patient to make that choice. These obligations together are required to properly obtain informed consent.

The patient-clinician relationship must also be examined when considering the ethics of placebo use in clinical medicine. Trust is one of the most critical yet fragile parts of a therapeutic relationship.[30] The use of placebos without explicit patient consent can severely undermine this trust. Once broken, the bond between patient and clinician may be irreparably damaged. Patients may become skeptical of future treatments, hesitant to disclose crucial information, or even avoid seeking necessary medical care altogether.

In contrast, advocates of placebo treatments argue that deceptive placebos are justifiable in certain clinical situations. Those who espouse this view cite the ethical principle of beneficence and that the safety and efficacy of placebos may outweigh infringements on patient autonomy. Extensive research has demonstrated that placebo treatments can match or even surpass the effectiveness of conventional treatments, especially for pain.[31] Placebo may be an even more attractive option when other conventional therapies have been exhausted[32]. In a comparative study, from a patient perspective, placebo treatments were believed to be ac-

ceptable in general by 25% of survey participants. In the same survey, 63% of participants agreed that placebo treatments were acceptable if treating a patient who is terminally ill.[33]

Unfortunately, it is practically difficult to ascertain whether an individual patient is amenable to a deceptive placebo treatment, leaving clinicians in a perpetual dilemma when faced with clinical scenarios where they feel a patient may improve with a placebo treatment.

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Novel Approach to Placebo Use

In recent years, a novel approach to placebo use has been proposed. The nondeceptive use of placebos would theoretically side-step the ethical hurdles associated with intentionally misleading patients. One method of doing so is to use a neutral disclosure.[34] These disclosures communicate that the medication may help with the patient's disease, but are vague enough to maintain the illusion required for the placebo to work effectively.[32] Many argue that this method of disclosure avoids ethical dilemmas because the placebo may positively modulate the patient's symptoms.[32] However, opponents to this approach cite that patients reasonably assume that prescribed treatments have been tested and approved for their specific condition. While a vague "nondeceptive" disclosure may not contain any lies, it conveys the impression that the prescribed medication will have active ingredients designed to treat pain.[34] Therefore, this method of disclosure still violates the principles of informed consent.

Open-Label Placebos

A final strategy, arguably the most ethically defensible, involves prescribing open-label placebos (OLP). Recent research has demonstrated that even placebos without deception may be effective in treating certain symptoms.[35,36] Researchers are actively exploring how open-label placebos can be prescribed ethically while limiting the influence of patient expectations and avoiding infringements on patient autonomy in order to promote placebo responses.[34,35]

Significant efforts are being directed into researching the effect of OLP on caring for common presenting complaints in the urgent care setting. One group found that OLP made of echinacea extract reduced cold symptom duration and severity compared to no placebo. This effect was greater in patients who believed echinacea was beneficial, regardless of whether the pills actually contained echinacea.[37] Another group demonstrated that OLPs improved quality of life and pain-related disability in patients with chronic migraines.[38] While effective medications exist for symptomatic management of migraine, OLPs may be used as an adjunct to improve care. Moreover, when prescribing OLPs, clinicians should leverage verbal suggestion, patient expectation, and empathetic patient interactions to maximize the placebo effect.

Conclusion

The placebo effect is a complex set of physiologic responses, which can produce profound analgesic effects. Sophisticated studies have elucidated the involvement of endogenous opioid, cannabinoid, and reward pathways to substantiate the mechanism by which inert substances or treatments can reduce pain. Studies have also shed light on the various patient, clinician, disease, and situational factors which affect the likelihood of placebo response.

While certain variables are outside of clinician control, data support the importance of rapport between clinician and patient in favoring positive expectations and thus more robust placebo responses. However, ethical considerations surrounding the use of placebos in clinical practice remain a significant challenge. Future research should focus on developing standardized protocols for ethically leveraging placebo responses in clinical practice, as well as investigating the long-term outcomes for patients receiving placebo.

By embracing a nuanced understanding of placebo responses, clinicians can potentially enhance pain management strategies without exposing patients to many of the harms associated with active ingredient therapies and nonsham procedures. Given the ubiquity of pain in many clinical settings, including urgent care, clinicians who understand how patient expectations influence placebo responses and those who can invoke the placebo effect are likely to provide their patients better pain control without exposure to excess risk.

Takeaway Points

- The placebo effect is mediated by the brain's endogenous opioid, cannabinoid, and reward pathways,

leading to measurable changes in brain activity and pain perception.

- The strength of the placebo response is influenced by a complex interplay of patient factors (eg, prior experiences), clinician characteristics (eg, empathy and demeanor), and contextual cues (like verbal suggestion and conditioning), all of which can be leveraged in clinical practice.
- While placebos can be highly effective, especially for pain, their traditional use requires deception, which undermines patient autonomy and trust. Emerging research on open-label placebos (given without deception) offers a promising and more ethically defensible path to harness this powerful effect in medicine. ■

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