International Journal of Pain Research
2026, Vol. 2, No. 2, pp. 70–74
https://doi.org/10.11648/j.ijpr.20260202.15

Review Article

The Placebo Effect in Pain: Mechanisms, Applications, and Ethical Considerations

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Abstract

The placebo effect — long misunderstood as mere "imagination" or self-deception— is an important and increasingly studied phenomenon in medicine. It is no longer considered a simple psychological effect, but a real mind-body connection of mobilizing the body's internal "pharmacy" for self-healing through expectations and beliefs. By integrating expectations, conditioned reflexes, and social learning, the placebo effect can reduce pain, anxiety, and fatigue by activating endogenous opioid, endocannabinoid, and dopaminergic systems. Pain is one of the great scenarios for the placebo effect, and its potential healing power is emerging. Traditional deceptive placebos (administering inert substances without the patient's knowledge) have gradually been replaced by open-label placebos, which are more ethically acceptable because they emphasize transparency, informed consent, and avoidance of harm, while still producing meaningful clinical benefits. As deceptive placebos are replaced by open-label placebos, the placebo effect in the modern sense may subvert our understanding of "medicine" or "therapy", or it may mean a reshaping of medical processes and doctor-patient relationships. This review summarizes the neurobiological mechanisms, types, clinical applications, ethical challenges, and limitations of placebo analgesia. It emphasizes that placebos should be used only as a complementary or adjunctive therapy and must never replace specific treatments for clearly identifiable organic pathologies.

Keywords

Placebo, Pain, Therapeutic Effect, Clinical Trials

1. Introduction

The placebo effect is one of the most fascinating and complex phenomena in medicine. The word "placebo" is derived from Latin, meaning "I shall please". Placebos (substances containing no active pharmaceutical ingredients) have intrigued doctors for centuries, and officially entered medical

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Received: 27 April 2026; **Accepted:** 22 May 2026; **Published:** 23 June 2026

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terminology in the 18th century. In the 1950s, the famous paper "The Powerful Placebo" by American anesthesiologist Henry Beecher was regarded as a milestone in the development of placebos, laying the foundation for the cornerstone of modern clinical medical research - the randomized controlled trials (RCTs) [1]. In clinical trials (single-blind trials or double-blind trials), a new drug or therapy is considered effective only when its efficacy is significantly superior to that of a placebo. This has become the "gold standard" for verifying the true efficacy of drugs. Recently, it has been suggested that placebos themselves may possess genuine therapeutic effects, rather than merely serving as a negative control in clinical trials. Pain, particularly chronic pain, has emerged as the most well-validated model for studying the placebo effect [2, 3]. In 2016, *Nature magazine* suggested that "substances without active ingredients may potentially be used to alleviate chronic pain" [4]. In 2024, Nature published the first study identifying causal neural circuits for placebo analgesia in rodents using reverse translation [5].

This review aims to provide a balanced, scientifically rigorous overview of current knowledge on placebo analgesia, focusing on its mechanisms, types, clinical applications, ethical considerations, and limitations, thereby informing both researchers and clinicians about the potential—and the boundaries—of harnessing placebo effects in pain management.

2. Mechanisms of the Placebo Effect

The placebo effect involves both psychological and neurobiological mechanisms [4, 6, 7]. The traditional hypothesis held that deception or concealment is necessary for placebos to work. Given that this effect seems to be effective only by doctor-patient communication, it suggested that the brain plays a crucial role in the placebo effect, with expectation, conditioned reflex, and social learning being key components [2, 8]. In the 1970s, research on "placebo biology" gradually revealed that placebos can prompt the brain to release natural analgesics such as endorphins (neurotransmitters), activate endogenous dopamine and cannabinoid, and reduce the levels of prostaglandins. Recently, Giulia Livrizzi's research team identified the neural circuit from the cerebral cortex to the brainstem that mediates placebo analgesia by reverse translating the human placebo paradigm into a mouse model, and found that endogenous opioid peptides play a key role in this process [9]. This process is widely understood as the activation of the body's own internal "pharmacy". Furthermore, neuroimaging studies have confirmed that receiving a placebo increases the activity in two brain regions of the subject involved in emotion and evaluation, specifically the prefrontal cortex and ventral striatum [10, 11]. It is clear that the mechanisms of the placebo effect extend beyond psychological factors, and involve biological processes of the brain and body (mind-body connection).

3. Types and Usage of Placebos

3.1. Types

Placebos are generally categorized as pure placebos (substances containing no active pharmaceutical ingredients) and non-pure placebos (substances containing active ingredients that are not targeted to the disease) [3, 12]. They can be administered in forms as sugar pills, starch capsules, or saline injections [6, 12]. "Sham surgery" or "sham treatment" represents an alternative form of placebos [13], for example, when a patient undergoes anesthesia and skin incision without the actual surgical procedure being performed. Nonmaterial methods can also act as placebos, such as "contextual placebos" or "signaling placebos". Visual cues (e.g., clinical environment, drug characteristics like pill color, size, quantity, and branding), auditory cues (e.g., the doctor's communication style, including tone and rhythm), and even the "ritual" itself (medication administration, treatment procedures) all serve as vehicles for the placebo effect.

3.2. Administration

There are two primary methods of placebo administration. The traditional deceptive placebos, where participants are not explicitly informed that they are receiving a placebo, has been questioned from both scientific and ethical perspectives [6, 14]. Therefore, open-label placebos are gradually becoming an alternative, where participants are transparently informed that they are receiving a placebo with no pharmacological active ingredients. Numerous studies have shown that open-label placebos are as effective as deceptive placebos in pain relief [14, 15]. It is unimaginal that the placebo effect still exists even when patients are informed.

4. Application of the Placebo Effect in Pain Management

4.1. Indications and Contraindications

Pain is an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage. Based on the definition of pain, pain management appears to be an "ideal scenario" for the placebo effect to play a role [6, 13]. However, it is critical to clarify that, at present, placebos can only be used as a complementary or adjunctive therapy, primarily indicated for mild to moderate chronic pain, especially non-specific pain and pain accompanied by anxiety and mild depression. It should be emphasized that the placebo effect should never be used as a replacement for specific treatments for patients with clearly identified causes, such as those with acute, life-threatening conditions.

The unique value of placebos in pain management may lie

in their role as an "effect amplifier": by optimizing the therapeutic context, they can enhance the efficacy of active treatments and reduce the required dose of analgesics (particularly opioids).

4.2. Practical Steps for Clinical Implementation

The specific steps for implementing placebo therapy in clinical practice (as opposed to research settings) include the following [16-18]:

(1) Patient education: Inform patients about the placebo effect and its potential to improve symptoms even in the absence of active pharmacotherapy, while clinicians must not falsely claim that what they prescribe is a specific medicine.

(2) Use of "honest placebos": Explicitly state that the treatment involves a placebo, and explain its rationale as part of an evidence-based approach.

(3) Signing of consent form: Obtain written informed consent from patients, emphasize the voluntary nature of participation, and outline expected outcomes.

(4) Optimization of doctor-patient communication and "treatment ritual": Maximize the analgesic effect by enhancing the "therapeutic context" or scenario, which is the most practical and feasible from the perspectives of ethical and accessibility.

5. Ethical Dilemmas in the Clinical Use of Placebos

5.1. Deceptive Placebos

A core ethical question is whether "the ends" justify "the means"? Firstly, there is a paradox between deception and informed consent. It seems that doctors "must" deceive or conceal information for the placebo to "succeed", informed consent is the cornerstone of medical practice. The use of deceptive placebos deprives patients of their right to know [17]. Secondly, a "kind lie" is still a lie, and its exposure can irrevocably damage the trust in doctors and patients.

5.2. Ethical Guidance for Placebo Use

In clinical trials: "The Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects" outlines the ethical premise for the use of placebos: placebos may be used when no proven intervention is available. However, patients receiving the placebo must not be exposed to any additional risk of serious or irreversible harm due to not receiving the best proven intervention [19].

In clinical practice: Stricter standards apply. The American Medical Association's ethics code prohibits the use of placebos in clinical care unless the patient is informed of and agrees to the use of placebo [20].

5.3. Open-label Placebos (or "Honest Placebos") May Offer an Ethical Pathway

Open-label placebos are more ethically acceptable because they emphasize transparency, informed consent, and avoidance of harm. A 2025 systematic qualitative review identified 37 distinct ethical issues related to open-label placebos, grouped into five themes: sociocultural factors, implementation logistics, informed consent, patient health behavior and dynamics, and the therapeutic relationship. The review concluded that while open-label placebos raise fewer ethical concerns than deceptive placebos, their integration into healthcare still requires thoughtful communication and further research [14].

6. Barriers and Risks of Placebo Use

For placebo analgesia, ethical issues represent the foremost barrier. Second is acceptability, which is heavily shaped by cultural background: can patients accept that a "fake medicine" can treat their illness? Third is accessibility: who is willing to manufacture placebo products and who would dare to openly produce "fake medicine"? Finally, payment issues: is charging patients for placebos an act of fraud?

Medical and legal risks must be addressed upfront. If placebo use fails to achieve a therapeutic effect and delays the diagnosis and treatment of a patient's organic disease, who will bear the responsibility?

There is also an additional potential risk: will the placebo effect become a shield for fake doctors and fake medicines, given that "fake medicine" can also cure diseases? For example, various kinds of folk ancestral recipes, magic medicine, and "miracle doctors" widely can be seen in both traditional and new media. Within the medical field, various great immortals emerge one after another, and various "unique" therapies (such as needling, knife techniques, finger techniques) are popular, and even proudly ascended to the academic realm.

7. Limitations

First, the evidence base for open-label placebo effects, while growing, remains limited in quantity and quality. A 2025 meta-analysis found that all included RCTs had a high risk of bias for patient-reported outcomes because participants were aware of the intervention, and the overall certainty of evidence according to GRADE (Grading of recommendations, development and evaluation, GRADE) was very low [21].

Second, most studies on placebo analgesia have been conducted in controlled laboratory settings with healthy volunteers or specific clinical populations. The generalizability of these findings to real-world clinical practice—particularly to diverse patient populations with multiple comorbidities—remains uncertain.

Third, this review is narrative rather than systematic, and

the selection of studies may not be exhaustive.

8. Summary

In the field of pain management, the unique value of the placebo effect lies in harnessing the power of the mind-body connection to mobilize the body's internal resources for pain relief. Today, "honest placebos" and "therapeutic rituals" are effective ways to realize the placebo effect. This perspective allows us to glimpse the potential value of the placebo effect: to reshape medical processes and doctor-patient relationships, and to urge physicians to reflect on their medical decision-making practices, for example, the prudent use of invasive procedures, given that even "sham surgery" can sometimes be effective.

"To cure sometimes, to relieve often, to comfort always (Edward Livingston Trudeau)". This famous quote emerged in an era when placebos were prevalent, a time when medical and scientific knowledge was extremely limited. It has been regarded as a motto by generations of doctors. Today, it also concretely embodies the essence and highest pursuit of pain management. Make good use of the placebo effect can endow pain management with the human wisdom and brilliance of humanity.

Abbreviations

RCTs	The Randomized Controlled Trials (RCTs)
GRADE	Grading of Recommendations, Development and Evaluation (GRADE)

Author Contributions

Jiaoli Sun: Conceptualization, Data curation, Resources, Writing – original draft

Xianwei Zhang: Conceptualization, Methodology, Supervision, Writing – review &editing

Conflicts of Interest

The author declares no conflict of interest.

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