Since Beecher’s seminal quantitative analysis of “the powerful placebo” 50 years ago,1 the effects of placebo have gained increasing scientific and clinical attention. In the past 10 years, advances in research design and technology have elucidated the psychobiological responses to administration of a placebo (an inert treatment of some kind) and demonstrated that there is not just one placebo response, but many. Studies of the placebo effect center on the surrounding psychosocial context and the different effects of this context on the subject’s brain.2 It is now clear that a true placebo effect accompanied by objective psychobiological responses is seen in carefully designed experiments and in clinical populations whose responses to administration of a placebo are compared with a natural history control group, thereby excluding phenomena such as regression to the mean and spontaneous remission that might be incorrectly interpreted as a placebo response.2 Consistent with the complexity of the mind-body interaction, a variety of psychological, biochemical, and neuroanatomical mechanisms associated with placebo responses have been identified for different populations, experimental manipulations, and contexts.2,3 Advances in understanding of these mechanisms have informed clinical trial design, particularly in pain studies, but more research is needed to translate these mechanisms into optimal clinical practice.4

Placebo Analgesia, Nocebo Hyperalgesia

There is not just one placebo response, but many

The negative counterpart of the placebo effect, the nocebo effect, has been investigated to a lesser extent, because ethical constraints limit the study of a process that is, by itself, stressful and anxiogenic. However, insights into the nocebo effect continue to emerge, with a particular emphasis on pain.

Overview of Placebo Mechanisms

The psychological processes mediating placebo analgesia that have been studied in most detail are those of conditioning and expectancy. The conditioning hypothesis is based on the theory of classical conditioning, whereby a previously neutral stimulus is paired or associated with an unconditioned stimulus, so that the latter becomes a conditioned stimulus that is then able to elicit a response—the conditioned response.5,6 In the case of a placebo injection during pain, the environment or context surrounding the injection is the conditioned stimulus that can elicit analgesia without the administration of an active drug. The conditioning mechanism has been demonstrated using a variety of manipulations and drugs, but it is the expectancy mechanism that has gained the most support.4
Over 70 years ago, early pioneers such as Houston or Wolff and Goodell noted “the relation of attitude and suggestion to the perception of and reaction to pain,” and soon after, articulated the beneficial effect of “placebos thought by the subject to be analgesic drugs.” It is now well established that expectations are powerful mechanisms of placebo responses, particularly placebo analgesia. Studies of expectancy mechanisms have used simple verbal cues and conditioning protocols to manipulate expectations and measure placebo responses.

**Conditioning and expectancy mechanisms play coexisting and often complementary roles in placebo responses**

Although at times they are seen as opposing psychological mechanisms, recent research indicates that both conditioning and expectancy mechanisms play coexisting and often complementary roles in placebo responses. In the case of placebo analgesia, recent research suggests that this response is mediated primarily by expectations—even though a conditioning process may be present—and may represent an integration of prior experience and conscious anticipatory processes mobilized at the time of placebo administration.

Neurobiological studies of the placebo effect and particularly placebo analgesia have focused heavily on the endogenous opioid system. Placebo analgesic responses induced by manipulations of psychological mechanisms (conditioning and expectancies) are fully or partially reversible by the opioid antagonist naloxone, indicating the involvement of the opioid system.

Other, non-opioid mechanisms and systems (such as serotonin, hormone secretion and immune responses) are also involved. Advances in methods and techniques of brain imaging extend support for expectancy mechanisms and the involvement of the opioid system in placebo analgesia.

**Some placebo analgesic responses are fully or partially reversible by the opioid antagonist naloxone**

Several imaging studies have shown neuronal activation in pain-related regions of the brain following placebo administration and during expectation of analgesia. These studies support the involvement of endogenous opioids in placebo analgesia in at least three ways: (1) by showing alterations in neuronal activity in opioid-rich areas of the brain following placebo administration, (2) by showing similar brain responses to a placebo and an active opioid drug, and (3) by direct demonstration of endogenous opioid release using sensitive molecular imaging techniques.

**The Nocebo Counterpart**

The nocebo effect is a phenomenon that is opposite to a placebo effect in that the outcome is negative rather than positive. Whereas placebo effects are mediated at least in part by endogenous opioids, nocebo effects have been found to be mediated predominantly by cholecystokinin (CCK). By definition, a nocebo is anxiogetic, and there is now good experimental evidence that CCK induces nocebo hyperalgesia by “turning anxiety into pain.” In fact, it has recently been found that nocebo suggestions of increased pain evoke concurrent hyperalgesia and mobilization of hypothalamic-pituitary-adrenal (HPA) responses as reflected in increased plasma concentrations of adrenocorticotropic hormone (ACTH) and cortisol. Nocebo hyperalgesia and HPA hyperactivity are both antagonized by diazepam, suggesting that anxiety has a major contribution to both responses. Administration of the mixed CCK type-A/B receptor antagonist, proglumide, blocks nocebo hyperalgesia completely but has no effect on HPA hyperactivity, suggesting selective involvement of CCK in the hyperalgesic, but not the anxiogetic, component of the nocebo effect. Importantly, neither diazepam nor proglumide has analgesic effects upon baseline pain, i.e., in the absence of nocebo-induced hyperalgesia. These findings indicate a close relationship between anxiety and nocebo hyperalgesia and highlight the key role of CCKergic systems as a substrate of this relationship. Taken together, the placebo and nocebo studies indicate that placebo analgesia and nocebo hyperalgesia rely upon, respectively, the activation of functionally opposing endogenous opioidergic and CCKergic systems (Fig. 1).

**Clinical Implications**

Studies of the placebo effect until very recently have focused upon analgesia, and their emphasis has been on mechanisms rather than on clinical application. Nonetheless, the power of the latter has been well shown in the “open-hidden” paradigm. In this paradigm, the patient may receive a treatment in the normal clinical “open” manner, in which the treatment is given by the clinician in full view of the patient, or in a “hidden” manner, with the patient unaware that the treatment is being administered. Open administration of a treatment is significantly more effective than hidden administration for pain and unrelated conditions such as Parkinson’s disease (Fig. 2). Thus, the overall effect of drug administration is a combination of the pharmacological action of the drug and the psychosocial context in which it is given. The open-hidden paradigm underscores the importance of expectation of receiving a treatment.

![Fig. 1. Diagrammatic representation of the activation of functionally opposing endogenous opioidergic (placebo analgesia) and CCKergic systems (nocebo hyperalgesia) following placebo or nocebo suggestions.](image-url)
and the context in which it is given, which represents placebo mechanisms.

The power of expectation and the potential to exploit it clinically were demonstrated in two different studies involving drug administration. In the first study, the authors examined the effects of expectation on regional brain metabolic activity. This controlled study manipulated subjects’ expectations so that one group underwent open administration of a drug that they knew to be a stimulant and the other group received the same drug when they were expecting a placebo. Interestingly, even though both groups received the same dose of the same stimulant drug and had identical plasma concentrations of that drug, there were significant differences in regional brain metabolic activity between those who expected a stimulant and those who expected a placebo. Shaping the subjects’ expectations not only altered regional brain metabolic activity, but also modified subjects’ reported perceived “high” in response to the drug, again demonstrating the power of expectation in altering neurobiological responses that may enhance the response to drug treatment.

**Fig. 2.** Differences in analgesia between open and hidden injections of certain opioid and NSAID drugs, demonstrating the different contributions of true pharmacological effects of the drugs and placebo mechanisms to overall therapeutic efficacy.

The overall effect of drug administration is a combination of the pharmacological action of the drug and the psychological context in which it is given. In a second experimental study, investigators looked at the effects of placebo administration on opioid intake in patients with postoperative pain. In this study, patients were treated with buprenorphine on request for three consecutive days, and with a basal infusion of saline solution (placebo). However, the symbolic meaning or the context of this saline basal infusion differed in three different groups of patients. The first group was told that the infusion was simply a rehydrating solution (natural history or no-treatment group), the second that it could be either a potent analgesic or a placebo (classic double-blind administration with uncertainty), and the third group that the infusion was a potent painkiller (deceptive administration with enhanced expectation). The clinical effect of the placebo infusion was measured by recording the doses of buprenorphine requested over the 3-day treatment. A significant decrease in buprenorphine intake was found during double-blind administration (a 20.8% reduction) when compared with the natural history group. This reduction was even more pronounced (33.8% lower than the natural history group) during deceptive administration of the saline basal infusion. It is important to point out that the time course of mean pain intensity was the same in the three groups over the 3-day period of treatment, indicating that patient self-titration of buprenorphine achieved the same analgesic endpoint despite requiring different doses to do so. These findings show that persons with strong expectations of analgesia request lower doses of analgesic drugs than those without such expectations.

Both studies highlight the efficacy of placebo mechanisms in the clinical setting, in which expectancies and context can modulate the analgesic effects of a drug. Harnessing these mechanisms through innovative therapeutic protocols has the potential to decrease drug intake while maintaining or even improving analgesia.

**Persons with strong expectations of analgesia request lower doses of analgesic drugs than those without such expectations**

The implications of the investigation of the biochemical pathways involved in the hyperalgesic nocebo effect are worthy of mention, although research is still at a very early stage. Identification of a CCK-mediated link between hyperalgesia and anxiety in anticipation of impending pain may rekindle interest in CCK antagonists as new pharmacotherapies. Preclinical and early clinical trials with CCK antagonists such as proglumide have already been conducted based upon earlier indications that CCKergic systems mediate hyperalgesia, including opioid-induced hyperalgesia. This modern, mechanism-based research also echoes clinical studies that first began to appear over 40 years ago, showing that detailed preoperative instruction about upcoming surgical procedures and postoperative care decreased patients’ self-reported pain and analgesic use. The nocebo effect clearly demonstrates the potentially harmful impact of an adverse patient-clinician interaction, whereby negative words and attitudes of the clinician, by altering the context, may induce negative expectations in the patient and subsequent increases in pain.

The clinical implications of research into placebo mechanisms have been discussed in the literature, mostly in terms of context effects and the patient-clinician relationship. Attempts to review the impact of context effects on health outcomes have been thwarted by the heterogeneity of methods employed in studies of the emotional and cognitive aspects of different treatments. Attempts to identify “placebo responders” prospectively or to quantify patient factors that predict placebo responses have likewise been generally unsuccessful. For example, an individual may have differing placebo responses depending on the context in which the placebo is given (such as for pain relief or for alleviation of the symptoms of Parkinson’s disease). One of the difficulties in identifying placebo responders is the wide variety of elements (such as the particular clinical
setting, psychological factors, and cultural beliefs) that comprise the context of treatment at a given time and place.

There is far more work to be done in this area, even to the level of identifying those clinician features and actions that can enhance placebo effects upon the outcome of a given treatment. Some insight into the role of the clinician in the outcome of drug administration emerged from a study in which clinicians were manipulated. Patients were divided into two groups. Patients in both groups were told that they could receive a placebo, an opioid analgesic, or an opioid antagonist. In contrast, the clinicians were alerted to the fact that no one in the first group would receive an active drug. The placebo response was dramatically less in group one (for which the clinician believed that the patient could only receive an opioid antagonist or placebo) than in group two (when the clinician believed that a real analgesic could be delivered). Despite the lack of a natural history group, the study confirms the ability of the clinician to modulate the patient’s placebo response. Similar findings have emerged from a variety of other studies, although as previously mentioned, they are inconsistent in their conclusions as to which clinician factors influence treatment outcomes.

A variety of factors operating in different clinical interactions are likely to activate or modulate different placebo mechanisms and responses. Therefore, it appears important to study the patient-clinician interaction or relationship, which may encompass a variety of factors such as the environment around the patient and the context or meaning of the treatment. The challenge will be to identify which factors are important in particular settings, thus better clarifying multiple placebo mechanisms and their relative impact in a variety of clinical settings. One recent example of such research is a study demonstrating that cognitive impairment in Alzheimer’s disease, and the consequent loss of expectation-related mechanisms, result in decreased analgesic effectiveness, highlighting the need to consider these mechanisms when prescribing an analgesic regimen to patients with cognitive impairment.

Mechanistic studies and clinical observations together show that differences in the context of a therapy can, through multiple effects, alter the responses to both a placebo and an active treatment. Although much more research is required on the understanding and clinical application of placebo mechanisms, the power of the clinician’s words and of the patient’s own narrative in modulating the context of a therapy is evident. Future research may provide more information on the identification and exploitation of particular factors in different contexts, opening up new directions in the treatment and management of pain.

References


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