

Placebo and nocebo

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KEY LEARNING POINTS

- A placebo is a treatment with no specific therapeutic action and the placebo effect is the outcome following its administration.
- The placebo effect is a psychobiological phenomenon and must not be confounded with other phenomena, such as spontaneous remission.
- The effects following the administration of a placebo are due to the psychosocial context around the therapy.
- A positive psychosocial context may induce a placebo effect whereas a negative context may lead to a nocebo effect.
- There is not a single placebo effect but many, in different systems and diseases and with different mechanisms.
- The placebo analgesic effect is mediated by the endogenous opioid systems in some circumstances.
- The nocebo hyperalgesic effect is mediated by anxiety-induced activation of cholecystokinergic systems.
- If an analgesic treatment is administered covertly, its effects are smaller than when given overtly.

INTRODUCTION

Over the past two decades the placebo effect has shifted from being a nuisance in clinical research to a promising model of an emerging neuroscience of mind–brain–body interactions. In fact, the interest in and the success of placebo research resides in its multifaceted meaning, which involves key issues in modern science – from neurobiology to philosophy, from ethics to social psychology, and from clinical trials design to medical practice.¹ Thus, the placebo effect, which has long been neglected by the neuroscience community, is today considered a real and detectable biological phenomenon, and the question of whether placebos work has been reframed

as to how they work. The purpose of this chapter is to introduce the reader to the nature and extent of the placebo phenomenon and to present the interesting implications of the new evidence that arises from recent research in this field. The relatively extensive overview and reference base will permit a more detailed exploration of specific topics, issues, and questions. Overall, this chapter presents what we know today about the neural mechanisms underlying the placebo effect, as well as the clinical and ethical implications in routine medical practice and in clinical trials.

Placebo is the Latin word for “I shall please” and although it would seem that there are some anomalies in both the origin and the translations of the word placebo,

the term “placebo” entered the medical lexicon to indicate sham treatments and inert substances (such as sugar pills and saline solutions) that physicians give deliberately to please or placate anxious patients.^{2, 3, 4}

Physicians have perhaps always been conscious of the fact that patients get better after taking inert drugs.^{5, 6, 7} However, it is clear that the history of placebos is not the history of the placebo effects. In fact, the history of placebos concerns their use in clinical trials for the validation of new treatments, whereas the history of placebo effects pertains to the studies on the psychosocial therapeutic effect following the administration of inert medical treatments.

Brody⁸ emphasized the role of symbolic meaning, defining the placebo effect as a change in the body, or the body-mind unit, that occurs as a result of the symbolic significance which one attributes to an event or object in the healing environment. This definition is embedded in the notion that symbols induce expectations of an outcome, thus emphasizing the crucial role of meaning^{9, 10} and expectation.¹¹ In other words, the therapeutic context has a meaning that induces expectations which, in turn, shape experience and behavior, as emphasized by Kirsch.^{11, 12, 13} According to Moerman,^{9, 10} the term placebo effect deflects our attention from what is really important (the meaning and the meaning-induced expectations), and aims it at what is not (the inert pills and, in general, the inert medical treatments).

The concept of the placebo effect as a context effect has been stressed by several authors.^{14, 15} The context is made up of words, attitudes, provider’s behavior, and medical devices, or in other words what Balint¹⁶ called the whole atmosphere around the treatment. It has often been pointed out that the term “context effect” and “placebo effect” could be used, at least in part, interchangeably^{14, 15} in order to overcome the negative connotations associated with the term placebo and to highlight the therapeutic nature of the healthcare context. The weight of context in facilitating cognitive and emotional modulation of a therapeutic outcome definitively emerges from different therapeutic outcomes after an open or hidden administration of the same drug. The main finding is that when the patient is completely unaware that a treatment is being given, the treatment is less effective than when it is given overtly according to routine medical practice.¹⁷ Therefore, under such conditions, the placebo effect can be defined as the difference between open and hidden administration of the treatment, even though no placebo is given. The result of this subtraction represents the placebo component of a treatment. According to the context and to context-induced expectations, placebos may produce either positive or negative outcomes. To distinguish the pleasing from the noxious effects of placebo, several authors introduced and elaborated the term *nocebo*.^{18, 19, 20, 21} The term *nocebo* (“I shall harm”) was specifically chosen to denote the counterpart of the term *placebo*. If the meaning of the context is reversed in the

opposite direction, a *nocebo* effect can be obtained. However, Kennedy¹⁸ and Kissel and Barrucand¹⁹ differentiate *nocebo* from placebo only in terms of negative or positive outcomes, not in terms of expectations.^{20, 21, 22}

In spite of all these definitions, the term placebo/*nocebo* effect often remains a source of confusion and of dangerous misconception. “Placebos are inert and don’t cause anything” asserts Moerman.⁹ As an anthropologist, he suggests the use of the formulation “meaning response” rather than “placebo response.” The meaning response is defined as the physiological or psychological effects of meaning on the treatment or illness. Conceptualizing the issue in terms of meaning may be important from an evolutionary perspective.²³

ATTEMPTS TO QUANTIFY THE PLACEBO EFFECT

Over the years, many researchers have turned to clinical trials literature to learn more about the placebo effect. We will be presenting the most representative. The first attempt to quantify the therapeutic effect of placebos was by Henry K Beecher in 1955,²⁴ who published “The powerful placebo,” a paper reviewing 15 controlled trials involving 1802 patients. Defining positive outcomes as “percent satisfactorily relieved by placebo,” Beecher reported effect sizes ranging from 26 to 58 percent with an average of 35 percent. The notion that approximately one-third of patients respond to placebo has since permeated medical text and teachings, even though Henry K Beecher did not report that number. This early work has been criticized on methodological grounds.^{7, 25, 26}

However, despite some methodological limitations, Beecher’s view represents a seminal demonstration of the placebo effect in medical practice.²⁴ In the 1950s, he suspected that some surgical treatments may also lead to a placebo effect. At the time, mammary artery ligation was provided for patients suffering from angina pectoris. In 1959, Cobb and co-workers²⁷ tested this procedure using a double-blind design. Surgeons were shown a randomization card after skin incision, telling them whether to proceed with surgery or to close the wound (sham procedure). Patients and outcomes observers were blinded as to the allocation of the real or the sham procedure. Patients in both groups improved dramatically, with trends favoring skin incision. After further similar results,²⁸ Beecher²⁹ concluded that a placebo effect is also demonstrable for surgery.

Opposite claims about the placebo effect are made by Hróbjartsson and Gøtzsche.³⁰ These authors conducted a systematic review of clinical trials in which patients were randomly assigned to either placebo or no treatment. Today, this review remains a source of intense debate. The goal was to study the clinical effect of placebos discerning whether patients randomized to placebo under blind conditions have better outcomes than those randomized to no treatment. One hundred and thirty trials were

identified and 40 different clinical outcomes investigated by selecting binary (e.g. the proportion of alcohol abusers and nonalcohol abusers) and continuous (e.g. the amount of alcohol consumed) outcomes. They considered the effect of three types of placebos: pharmacological (e.g. a pill), physical (e.g. a manipulation), and psychological (e.g. conversation). They calculated the pooled relative risk for binary outcomes and the pooled standardized mean differences for continuous outcomes, where pooled relative risk was defined as the ratio of the number of patients with an unwanted outcome to the total number of patients in the placebo group, divided by the same ratio in the untreated group. The standardized mean difference was defined as the difference between the mean values for unwanted outcomes in the placebo and untreated groups divided by the pooled standard deviation. A negative value indicated a beneficial effect of placebo both for binary and continuous outcomes. The findings of Hróbjartsson and Gøtzsche's review did not detect a significant effect of placebo, as compared with no treatment, in pooled data from trials with subjective or objective binary or continuous objective outcomes. However, they found a significant difference between placebo and no treatment in trials with subjective outcomes and in trials involving the treatment of pain. There was also some evidence that placebos had greater effect in small trials with continuous outcomes than in large trials, with an inverse relation between trial size and placebo size. Furthermore, in an update of their first review, Hróbjartsson and Gøtzsche argued further that when a large effect of a placebo intervention is not present, small effects on continuous outcomes, for example in pain, could not be clearly distinguished from biases.³¹ Thus, the observed significant effect of placebo on subjective outcomes may have been due to biased reports of subjects rather than to true placebo effects.

However, it is important to note that they used very broad inclusion criteria and failed to recognize that placebos are not expected to work uniformly across diseases or disorders.^{32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46} Aggregating without regard to the heterogeneity of disorders does not allow us to discern whether a placebo effect really exists. In fact, different sizes of placebo effects might occur among different disorders that do not have the same mechanism of action. Another problematic aspect of the Hróbjartsson and Gøtzsche's meta-analysis is the fact that in this analysis, it is impossible to consider many critical factors involved in placebo responses, such as the consideration of the patient's and physician's expectations, the healing context, and the many cues and factors that can influence the efficacy of an intervention.^{1, 9, 14, 15, 22, 47}

In another study aimed at investigating the placebo effect in analgesic studies only, Vase *et al.*⁴⁸ conducted one meta-analysis that included 23 of the 29 clinical trials from the meta-analysis by Hróbjartsson and Gøtzsche³⁰ and another meta-analysis of 14 studies that investigated

placebo analgesic mechanisms. Although this study has been criticized by Hróbjartsson and Gøtzsche,⁴⁹ Vase *et al.*⁴⁸ found that the magnitudes of the placebo analgesic effects were higher in studies that investigated placebo analgesic mechanisms compared with clinical trials where the placebo was used only as a control condition. Vase *et al.*⁴⁸ suggest that this difference might be due to the different placebo instructions and suggestions given in the clinical trial setting compared to the experimental setting. In fact, clinical trial investigators typically avoid giving oral suggestions of analgesia in favor of neutral instructions, whereas investigators of the placebo effect typically emphasize the analgesic suggestions.

The literature is full of other studies indicating that beliefs and expectations can play a relevant role in human health. For example, it has long been known that placebo injections are more powerful than placebo pills,^{50, 51} placebos taken four times a day are more powerful than placebos taken twice a day,³ red and yellow tablets make better stimulants, while blue or green tablets better tranquilizers,⁵² and sham devices (validated sham acupuncture needle) have greater effects than placebo pill on self-reported pain and severity of symptoms.⁵³

In general, these meta-analyses are worthy of consideration because they present the scenario for two different ways of investigating the placebo effect: on the one hand the randomized clinical trial (RCT), and on the other, the clinical/experimental setting specifically designed to investigate the placebo effect.

HOW TO DETECT REAL PLACEBO RESPONSES

The term "placebo effect" is often used interchangeably with the term "placebo response." However, the term "placebo effect" refers to any average improvement in the condition of a group of subjects that has received a placebo manipulation. Conversely, the term "placebo response" refers to the change in an individual caused by a placebo manipulation. In order to detect a real placebo response, it is important to consider some confounding factors in addition to the appropriateness of the experimental design. In fact, the investigation of the placebo effect is full of drawbacks and pitfalls because for a placebo response to be demonstrated several other phenomena must be ruled out.^{1, 54, 55, 56} These phenomena are natural history, regression to the mean, false-positive errors, and co-interventions (**Figure 41.1**).

For example, many pathological conditions show spontaneous variation and fluctuation of symptoms over time that is known as natural history.^{57, 58} Relapses and remissions can occur in the absence of any treatment manipulation. If a subject takes a placebo just before his/her discomfort starts decreasing, he/she may believe that the placebo is effective, although that decrease would have occurred anyway. Clearly, this is not a placebo effect but a spontaneous remission that leads to a misinterpretation

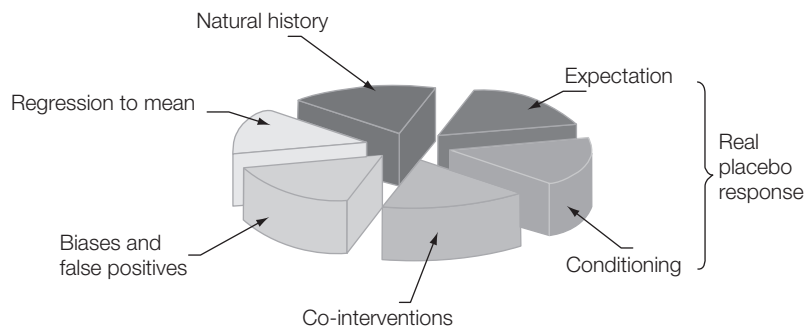


Figure 41.1 Confounding factors which must be ruled out in order to demonstrate real placebo responses (expectation and/or conditioning). The percentages of each factor does not necessarily reflect reality, as there are no studies providing this information.

of the cause–effect relationship. To demonstrate a placebo effect one must show a difference between the natural history and the placebo intervention. Another example is related to regression to the mean. This refers to the phenomenon where a variable will tend to move closer to the center of the distribution from initial to later measurements. This is a mathematical property of all measurements subject to random error. Subsequent measurements tend to be lower, because of the regression to the mean, even if no biologically or psychologically mediated placebo effects are present.⁵⁹ If individuals tend to receive their initial clinical assessment when their pain is near its greatest intensity, then their pain level is likely to be lower when they return for a second pain assessment. In this case also, the improvement cannot be attributed to any intervention they might have undergone. Regression to the mean often appears together with placebo effects in clinical trials, and the only reliable way to see what proportion of an observed improvement might actually be attributable to the placebo manipulation is again to compare a group receiving a placebo to a group receiving no treatment. A further source of confusion is represented by a particular type of error made by the patient and/or physician, a false-positive error. This is known as signal detection theory (SDT) and was described by Allan and Siegel⁶⁰ as a possible mechanism of placebo effects. The ambiguity of a symptom may lead to biases following verbal suggestion of benefit. In other words, a patient can report that a substance makes him or her feel better, detecting by mistake a symptomatic relief – this is termed false-positive errors. False-positive errors are common in medical decision-making, both by physicians who diagnose a patient’s symptom and by patients who report symptom severity.

Thus, in clinical practice and uncontrolled trials, the reported success rate may be due to one or more of the described phenomena – natural history, regression to the mean, and subject biases. The success rate may also be due to unidentified co-interventions, producing parallel effects on the observed benefit, and to the effect of being under study (Hawthorne effect).

The literature is full of examples where investigators have failed to account for these artifacts. This point is definitely clarified by Ernst and Resch⁶¹ who suggested a distinction between the perceived and the true placebo

effect. The former is the response observed in the placebo group of a randomized controlled trial. The true placebo effect equals this response minus the confounding effects described above. Thus, the perceived placebo effect is equal to the true placebo effect only if no effects are observed in the untreated control group when compared with the placebo group.

WHAT PARADIGM TO STUDY THE PLACEBO EFFECT

Together with the exclusion of the above-mentioned confounding factors, it is crucial to select an appropriate paradigm when we want to investigate the placebo phenomenon.

The use of placebo and untreated groups in clinical trials is not aimed at identifying the true placebo effect.^{61, 62, 63} Trialists, clinicians, and drug companies are mainly interested in seeing whether the active drug is more effective than the placebo, and they are not interested in the placebo effect itself. Fortunately, clinical trials are not the only methodology available and are not the best model for investigating the placebo effect. Most of our knowledge of the placebo effect comes from the laboratory setting where the experiments are designed to shed light on its neurobiological aspects. Studying the placebo effect in the laboratory setting gives us the opportunity to control psychological and physiological variables, and to rule out possible confounding factors for the placebo effect. For example, in the laboratory setting it is possible to conduct trials using three randomly selected, equally matched groups: (1) the natural history (NH) group or untreated group, which receives no treatment of any kind; (2) the placebo group, which receives an inert treatment that simulates the active one; (3) the active treatment, which receives the real treatment. The comparison between the placebo and the natural history group allows us to detect and measure the placebo effect. Regression to the mean can be ruled out by using, for example, experimental pain. False-positive errors and scaling biases can be eliminated through the evaluation of objective physiological parameters (e.g. hormones, autonomic responses).

Although most clinical trials use the placebo-controlled design, other experimental paradigms have been devised, including the balanced placebo design, the double-blind versus deceptive design, and the open-hidden paradigm (Figure 41.2). A brief overview of the characteristics of these paradigms follows.

The balanced placebo design, formulated by Ross and co-workers,⁶⁴ refers to a methodology for studying many aspects of human behavior and drug effects, orthogonally manipulating instructions (told drug versus told placebo) and drug administered (received drug versus received

		GET	
		Placebo	Active treatment
TOLD	Placebo	Baseline	Treatment effect
	Active treatment	Placebo effect	Treatment effect + Placebo effect

(a)

		GET
		Placebo
TOLD	Placebo or active treatment (double-blind)	Placebo effect following uncertain expectation
	Active treatment (deceptive information)	Placebo effect following certain expectation

(b)

		GET
		Active treatment
TOLD	Active treatment (open administration)	Treatment effect + Placebo effect
	No information (hidden administration)	Treatment effect

(c)

Figure 41.2 Paradigms to study a placebo response. (a) Balanced placebo design. The table shows the different combinations of what the patients receive and what they are told, allowing investigators to identify the modulation of drug action by verbal suggestions. (b) Double-blind versus deceptive design. Placebos are administered to patients by changing the information about the treatment. In fact, double-blind design provides uncertain expectations whereas the deceptive design provides certain expectations. (c) Open-hidden administration of an active treatment. It consists in the administration of the active treatment while the patient is either aware or unaware that a medical therapy is being given.

placebo) (Figure 41.2a). It has been used in many conditions, such as alcohol research,^{65,66} smoking,⁶⁷ amphetamine effects,⁶⁸ and psychiatric disorders.^{69,70} This design is particularly interesting for the investigation of placebo effects because it indicates that verbally induced expectations can modulate the therapeutic outcome, both in the placebo group and in the active treatment group. For example, Flaten *et al.*⁷¹ showed that carisoprodol, a centrally acting muscle relaxant resulted in different outcomes, either relaxant or stimulant, depending on the combination of verbal suggestion and drug administration (including the placebo) and Keltner *et al.*⁷² confirmed that different activation patterns are produced in the brain following different combinations of suggestions. The balanced placebo design produces information that cannot be derived from conventional clinical trials. For example, it provides a baseline against which drug and placebo effects can be measured, and provides a direct assessment of the drug effect with the placebo component removed. The problem with the balanced placebo design is that it entails deception (Table 41.1).

The second example is the double-blind versus deceptive design (Figure 41.2b). This design compares the therapeutic outcomes of a double-blind administration of an active drug with a deceptive one. Although outside the clinical setting, Kirsch and Weixel⁷³ showed that different verbal suggestions produce different outcomes. In one group, they administered regular coffee or decaffeinated coffee according to the usual double-blind design, and the subjects received the information that either the active or decaffeinated substance was being administered. In the second group, decaffeinated coffee was deceptively presented as real coffee. The authors found that the placebo responses were higher following the deceptive administration than the double-blind paradigm, concluding that uncertainty induces less expectation and, in turn, smaller placebo effect.

Similar findings arise from a study by Pollo and co-workers.⁷⁴ Thoracotomized patients were treated with buprenorphine on request for three consecutive days, together with a basal intravenous infusion of saline solution. However, the verbal instructions that were given to the patients were changed in three different groups of patients. The first group was told nothing

Table 41.1 Manipulation of expectations through different experimental designs. Use of a placebo (+) or not (–) is reported along with the use of deception.

	Placebo administration	Deception
Balanced placebo design	+	+
Double blind/deceptive design	+/+	-/+
Open-hidden design	–	–

about any analgesic effect (natural history). The second group was told that the basal infusion was either a powerful painkiller or a placebo (classic double-blind administration). The third group was told that the basal infusion was a potent painkiller (deceptive administration). The analgesic effect of the saline basal infusion was measured by recording the doses of buprenorphine requested over the three-day treatment. It was found that buprenorphine requests decreased in the double-blind group by 20.8 percent compared with natural history, and the reduction in the deceptive administration group was even greater, reaching 33.8 percent. These results indicate that little differences in verbal instructions (“It can be either a placebo or a painkiller and therefore we are not certain that the pain will subside” versus “It is a potent painkiller, and therefore we expect the pain will subside soon”) produce different placebo analgesic effects, which in turn trigger a dramatic change of behavior leading to a significant reduction in opioid intake.

Recently, the open-hidden paradigm has become an interesting way to isolate the placebo effect as a context effect. Also termed “overt-covert design,” the name refers to the modality of administration of a treatment: doctor-initiated versus machine-initiated therapy. The former is the classical situation of routine medical practice whereby an active treatment is administered to the patient, who is conscious that a medical therapy is being carried out. In this case, the therapeutic outcome is represented by the sum of the specific effects of the treatment itself and the placebo effect. The latter (machine-initiated) consists of the administration of the active treatment while the patient is completely unaware that it is being given (**Figure 41.2c**). It is possible to perform this hidden administration of a drug by means of a computer-controlled infusion pump that is pre-programmed to deliver the drug at the established time. The crucial point here is that the patient does not know when the infusion starts and ends, but he/she knows that a drug will be given.¹⁷ Therefore, in this case there is full informed consent without any deception (**Table 41.1**).

Despite its obvious appeal, the open-hidden paradigm has been studied in only a few situations. In studies of analgesia, Levine *et al.*⁷⁵ and Levine and Gordon⁷⁶ found that in postoperative pain following the extraction of the third molar, a hidden injection of morphine (6–8 mg) provided the same effect as the injection of saline solution administered in full view of the patient. To obtain an effectiveness greater than the placebo, the hidden morphine dose needed to be increased to 12 mg. Recently, a careful analysis of the differences between open and hidden injections has been performed where the effects of four widely used painkillers (buprenorphine, tramadol, ketorolac, and metamizol), administered in either open or hidden manner, were investigated.⁷⁷ In all cases, a hidden injection was less effective than an open one. These results have been further extended to conditions other than pain, such as anxiety and Parkinson’s disease.^{17, 78, 79} What

these studies tell us is that the knowledge about a treatment and the expectation of clinical benefit affects the therapeutic outcome. The importance of this point has been recently demonstrated in a clinical condition, Alzheimer’s disease (AD). The cognitive impairment that occurs in this pathological condition is a natural model to assess the difference between the open (expected) and hidden (unexpected) treatments, as the disruption of expectation/placebo-related analgesic mechanisms may eliminate the weight of the psychosocial component. Benedetti *et al.*⁸⁰ applied a local anesthetic, either overtly or covertly, to the skin of AD patients to reduce burning pain after venipuncture. They correlated the placebo component with both cognitive status and functional connectivity among different brain regions. They found that AD patients with reduced Frontal Assessment Battery scores showed a reduced placebo component of the analgesic treatment. The disruption of the placebo component occurred when reduced connectivity of the prefrontal lobes with the rest of the brain was present. Remarkably, the loss of these placebo-related mechanisms reduced treatment efficacy, such that a dose increase was necessary to produce adequate analgesia.

The findings from studies using the open-hidden paradigm underscores the active role of cognition in the overall therapeutic outcome and highlights the interesting possibilities for both clinicians and scientists. The open-hidden paradigm, where applicable, gives us the chance to study the placebo effect without the administration of any placebo, overcoming certain ethical constraints. This design has some similarities with the balanced placebo design without recourse to deception.^{81, 82} Therefore, by isolating the psychosocial component of the context from the medical treatment itself, it is possible to shed light on the interaction between biopsychosocial and pharmacological processes.

Finally, conditioning protocols represent a good way to elicit a placebo response. Apart from expectation theories which are based on the assumption that a placebo produces an effect because the recipient expects it,^{12, 13} classical conditioning may be another mechanism that generates placebo responses. However, expectation and conditioning theories do not necessarily contrast each other, and may represent two sides of the same coin.⁸³ In fact, placebo responses seem to be mediated by expectation and cognitive factors when conscious functions, such as pain and motor performance are involved, whilst they appear to be mediated by conditioning when unconscious functions, such as hormone secretion, come into play.⁷⁹

NEUROCHEMISTRY OF PLACEBO/NOCEBO EFFECTS

Studies conducted in the laboratory setting have been able to minimize many of the problems encountered in the clinical trial setting and have provided important and

reliable evidence about the nature of the placebo effect. Pain has been the main area of study of the placebo effect and comprises the largest body of research examining the placebo response. If we want to critically look at current knowledge about placebo effects, we must begin with a review of the literature on placebo analgesia.

Starting in the 1970s, placebo analgesia received considerable support in its legitimacy by way of two distinct but converging lines of research that demonstrated a physiological pathway for the placebo effect. Levine *et al.*⁸⁴ and Grevert *et al.*⁸⁵ showed that placebo analgesia is antagonized by the opioid antagonist, naloxone, thus suggesting that it is mediated by endogenous opioids. These findings have been confirmed and extended by other studies.^{76, 86, 87, 88} First, Fields and Levine⁵⁷ hypothesized that placebo analgesia may be mediated by nonopioid mechanisms as well.^{57, 89} The involvement of opioids depends on the procedure used to induce the placebo analgesic response.⁹⁰ In fact, by using the experimental ischemic arm pain model, it was found that if the placebo response is induced by means of strong expectation cues, it can be blocked by naloxone, whereas if the expectation cues are reduced, it proves to be naloxone-insensitive. In addition, if the placebo response is obtained after previous exposure to opioid drugs, it is naloxone-reversible. Conversely, if the placebo response is obtained after prior exposure to nonopioid drugs, it is naloxone-insensitive. All these data clearly suggest that

opioid and nonopioid mechanisms come into play in different circumstances. There is also evidence of somatotopic organization of placebo analgesia. Specific placebo analgesic responses can be obtained in different parts of the body^{91, 92} and these responses are naloxone-reversible.⁸⁷

Placebo-activated endogenous opioids have also been found to affect the respiratory centers and to induce respiratory depression.^{88, 93} The cardiovascular system has also been found to be influenced by endogenous opioids during placebo analgesia,⁹⁴ thus indicating that placebo-induced release of opioids affects different systems and apparatuses (**Figure 41.3**).

In a second line of research, the cholecystikinin (CCK) antagonist, proglumide, has been found to enhance the placebo analgesic effect,^{86, 95} thus suggesting that CCK has an inhibitory role in placebo-induced analgesia.

In addition, an extension of the action of CCK as an anti-analgesia system comes from work on nocebo hyperalgesia.^{96, 97, 98} By using experimental ischemic arm pain in healthy volunteers, it was found that verbally induced nocebo suggestions produced hyperalgesia and hyperactivity of the hypothalamic–pituitary–adrenal (HPA) axis, as assessed by means of adrenocorticotropic hormone and cortisol plasma concentrations. The administration of the CCK antagonist proglumide blocked nocebo hyperalgesia completely, but had no effect on HPA hyperactivity, suggesting a specific involvement

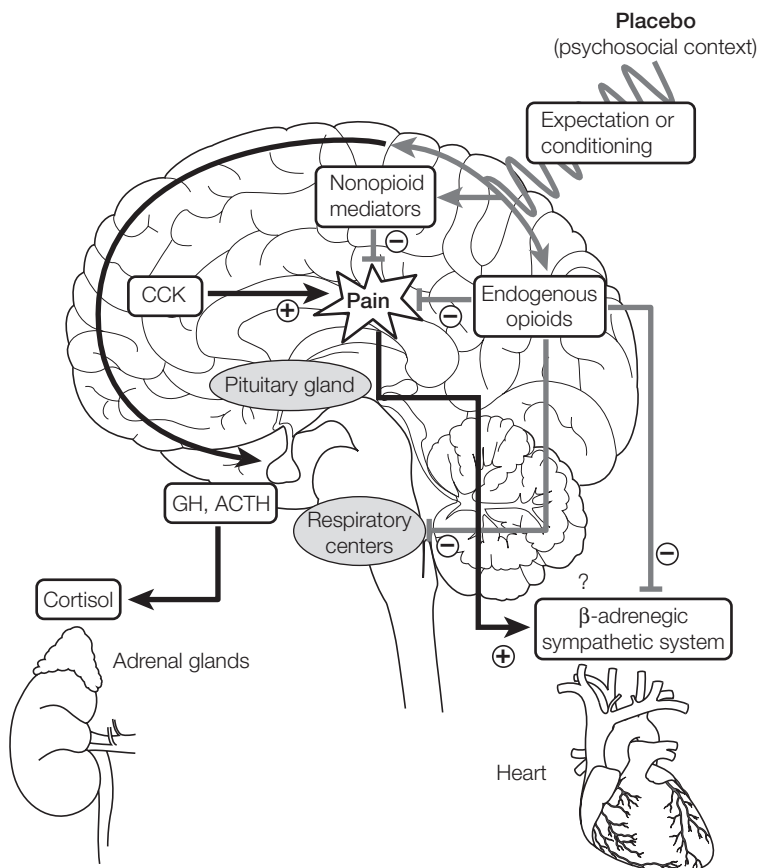


Figure 41.3 Cascade of biochemical events that may take place in the brain after placebo administration. Placebo administration along with verbal suggestions of analgesia (psychosocial context) may reduce pain through opioid and/or nonopioid mechanisms. Placebos have also been found to affect the respiratory centers, the cardiovascular system, and serotonin (5HT)-dependent hormone secretion. Redrawn by permission from Colloca L, Benedetti F. Placebos and painkillers: is mind as real as matter? *Nature Reviews. Neuroscience*. 2005; **6**: 545–52.

of CCK in the hyperalgesic but not in the anxiety component of the nocebo effect. These findings are in line with the study by Andre *et al.*⁹⁹ who demonstrated that the CCK-B receptor antagonist, CI-988, prevents anxiety-induced hyperalgesia in rodents. Thus, placebo suggestions activate endogenous opioids, whereas nocebo suggestions activate CCK, which confirms the antinociceptive action of opioids versus the pro-nociceptive action of CCK.

NEUROANATOMY OF PLACEBO/NOCEBO EFFECTS

Although the pharmacological approach with agonist and antagonist drugs has produced important information on the biochemical events triggered by context-induced expectations, pharmacological analysis does not allow identification of specific brain regions. Recently, functional imaging techniques, such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and electroencephalography (EEG) have provided the opportunity to also define the neuroanatomical bases of placebo analgesia.¹⁰⁰

The first imaging study of placebo analgesia showed that a subset of brain regions are similarly affected by either a placebo or a μ -opioid agonist. In fact, by using PET, it was found that the very same regions in the brain are affected by both a placebo and the opioid agonist remifentanyl, thus indicating a related mechanism in placebo-induced (psychological effect) and opioid-induced analgesia (pharmacodynamic effect).¹⁰¹ In particular, the administration of a placebo induced the activation of the rostral anterior cingulate cortex (rACC), the orbitofrontal cortex (OrbF), and the anterior insula (aINS), and there was a significant covariation in activity between rACC and the lower pons/medulla, and a subsignificant covariation between rACC and the periaqueductal gray (PAG), therefore suggesting that a descending rACC/PAG/pons/medulla pain-modulating circuit is involved in placebo analgesia, as previously suggested by other authors.^{102, 103}

An opioid neuronal network in the cerebral cortex and the brain stem has been described as a descending pain-modulating pathway that connects, either directly or indirectly, the cerebral cortex to the brain stem.^{92, 102, 104} In particular, ACC and OrbF project to PAG which, in turn, modulates the activity of the rostral ventromedial medulla (RVM). The ACC and PAG, together with some other nuclei in the brain stem (e.g. the parabrachial nuclei), are rich with opioid receptors. Therefore, this pain-modulating circuit appears to be the same, which is activated in placebo analgesia. The activation of μ -opioid receptors is implicated in a number of functions and the current hypothesis is that they work through a descending pattern of activation that is identifiable in the rACC-PAG-pons-medulla circuit.¹⁰³ The μ -opioid receptors are

heavily distributed involving cortical and subcortical regions such as the thalamus, the ACC, the nucleus accumbens, the amygdala, and the PAG.^{105, 106}

Recently, Zubieta *et al.*¹⁰⁷ have confirmed the role of μ -opioid receptors in placebo analgesia. By using PET imaging and carbon-11-carfentanil, which binds selectively to the μ -opioid receptor, it was shown that the placebo analgesic response involved μ -opioid transmission. The pain stimulus was associated with a significant activation of endogenous opioid in the dorsal ACC, medial prefrontal cortex (mPFC), right INS, ventral basal ganglia (nucleus accumbens extending to ventral pallidum), medial thalamus (mTh), right amygdala, temporal cortex, and PAG. Placebo administration increased μ -opioid transmission in the left dorsolateral PFC, rACC, ipsilateral nucleus accumbens, and aINS.

Further studies performed with functional magnetic resonance imaging analyzed the brain regions involved in placebo analgesia. These studies revealed that the activity of pain regions, particularly the thalamus, aINS and caudal rACC, was reduced by a placebo treatment, thus indicating that placebos reduce nociceptive transmission along the pain pathways.^{108, 109, 110, 111} In addition, during the anticipation phase of the placebo analgesic response, an activation of the dorsolateral prefrontal cortex (DLPFC), OrbF, rostral medial and anterior PFC, superior parietal cortex (SPC), and PAG was found, suggesting the activation of a cognitive-evaluative network just before the placebo response.¹⁰⁹ The increased activity of the PAG also suggests the activation of endogenous opioids in the anticipatory phase of the placebo response.^{109, 112}

Cognitive factors, such as anticipation and expectation, have also been found to affect the pain matrix when a pain increase is expected.^{113, 114, 115, 116, 117} For example, fMRI activation is significantly reduced when a high-intensity noxious stimulus is anticipated and accompanied by a low-intensity visual cue,⁷² whereas expectation of painful stimulus enhances brain responses to a nonpainful stimulus.^{118, 119} The hypothesis is that top-down mechanisms could inhibit pain signals at the level of the spinal cord.¹⁰³ This idea is supported by a recent study showing that expectancy induces a reduction of secondary hyperalgesia, which is known to involve spinal mechanisms.¹²⁰ Constantly, ACC is reported to be involved in placebo analgesia, suggesting its activation in response to a homeostatic imbalance requiring motivation for protective behavior.

These experimental approaches are important in better defining the neuroanatomy of placebo effect and further understanding the neuroscience of placebo phenomena.

PLACEBO EFFECTS IN CONDITIONS OTHER THAN PAIN

The release of endogenous substances following a placebo procedure is a phenomenon which is not confined to the

field of pain, but it is also present in motor disorders, such as Parkinson's disease, depression, endocrine and immune systems, and addiction.¹²¹

It has been shown that parkinsonian patients respond to placebos quite well.^{122, 123} A first study used PET in order to assess the release of endogenous dopamine. This study showed that placebo-induced expectation of motor improvement activates endogenous dopamine in the striatum of parkinsonian patients.¹²⁴ Interestingly, it was also shown that a placebo manipulation affects the firing pattern of neurons of the subthalamic nucleus and this is correlated to clinical improvement and subjective report of well-being.¹²⁵

Depression is another condition that has been investigated, although several ethical constraints limit our understanding of the action of placebos in depressed patients. In fact, although both electrical and metabolic changes in the brain have been described, adequate controls are still lacking. Placebos have been found to induce EEG changes in the prefrontal cortex of patients with major depression, particularly in the right hemisphere^{126, 127} and changes in brain glucose metabolism, as assessed by PET, in subcortical areas, including the brain stem and hippocampus, and cortical regions, such as the posterior ACC, the DLPFC, the premotor cortex, the dorsal ACC, and the inferior parietal posterior INS.¹²⁸

The immune system has also been found to be affected by placebos.¹²⁹ In 1896, MacKenzie showed that some people who are allergic to flowers developed an allergic reaction when presented with something that superficially looks like a flower, but contains no pollen (a placebo flower).¹³⁰ Ader and colleagues widely demonstrated that a conditioned (placebo) enhancement of antibody production is possible using an antigen as an unconditioned stimulus of the immune system.^{131, 132, 133, 134, 135} Recently, these findings have been confirmed in humans. In fact, repeated associations between cyclosporin A (unconditioned stimulus) and a flavored drink (conditioned stimulus) induced conditioned immunosuppression, where the flavored drink (the placebo) alone produced a suppression of the immune functions, as assessed by means of interleukin-2 (IL-2) and interferon-gamma (IFN- γ) mRNA expression, *in vitro* release of IL-2 and IFN- γ , as well as lymphocyte proliferation.¹³⁶ In this case, the placebo response can be interpreted as a genuine conditioned response.

Robust evidence also corroborates the presence of conditioning-mediated placebo effects in the endocrine system. By using the analgesic drug sumatriptan, a serotonin agonist of the 5-HT_{1B/1D} receptors that stimulates growth hormone (GH) and inhibits cortisol secretion, it was shown that a conditioning procedure is capable of producing hormonal placebo responses (**Figure 41.3**). In fact, if a placebo is given after repeated administrations of sumatriptan, a placebo GH increase and a placebo cortisol decrease can be found. In contrast, verbally induced expectations of increase/decrease of GH and

cortisol do not have any effect on the secretion of these hormones, suggesting a pivotal role of conditioning.^{78, 79}

Recently, the effect of methylphenidate on brain glucose metabolism has been analyzed in two different conditions in both cocaine abusers and nondrug abusers: (1) when they expected to receive the drug; and (2) when they expected to receive a placebo. In the former case, the effect was approximately 50 percent greater than in the latter, thus indicating that expectation enhanced the pharmacological effect of the drug.^{137, 138}

All these studies need to be considered when placebo analgesia is studied, as they support the integration of the understanding of placebo mechanisms in pain and analgesia with other illnesses. This is fundamental and necessary to identify similarities and differences that may help to better understand of the many facets of the placebo effect.

CLINICAL IMPLICATIONS

Many of the studies discussed in this chapter raise implications for both clinical practice and clinical trial design. Interestingly, there has been far less investigation into the nocebo response, even though the clinical implications may carry the same degree of importance as those of placebo mechanisms. As the study of placebo and nocebo mechanisms advances, it is hoped that more is learned about how to identify and exploit these mechanisms to improve both clinical practice and patient's quality of life, and to develop new clinical trial designs.

The open-hidden paradigm has been discussed as an interesting paradigm for studying placebo effects.¹³⁹ Overall, at least three important clinical and methodological implications derive from this paradigm.¹⁷ First, the lesser effectiveness of hidden treatments indicates the crucial role of the patient-provider interaction. Second, by using the hidden paradigm, the efficacy of some treatments can be assessed without the need for placebo administration, thus overcoming the ethical problem of placebo administration and deception. Third, the hidden paradigm can change the conception of how clinical trials must be viewed and conducted. In fact, it is possible to isolate the specific action of a treatment (such as the pharmacological properties of a drug) from the overall effect of the treatment (the specific action plus the context-driven placebo mechanisms). One important implication of this paradigm is that it can demonstrate that even though a drug may show strong analgesic efficacy in a normal RCT design, it may in fact have little or no specific analgesic properties. This was demonstrated in a study by Benedetti and coworkers,⁹⁵ whereby the CCK antagonist proglumide was tested in both a standard RCT design and a hidden fashion. When administered in full view of the patient, proglumide was shown to be an effective analgesic. However, when the patients did not know they were receiving the drug, it had no effect on

pain, demonstrating that the drug had no specific analgesic properties (**Figure 41.4**). The action of the CCK antagonist proglumide consists in the potentiation of top-down placebo mechanisms and it does not act directly on pain pathways. This valuable information would not be obtained using a standard RCT design and therefore the open-hidden paradigm may represent an excellent alternative for studying certain treatments. It also underscores the power of the expectation component of an active treatment on the overall effectiveness of the treatment. In other words, proglumide induces a reduction of pain if, and only if, associated with a placebo procedure. Today we know that proglumide is not a painkiller, but it acts on placebo-activated opioid mechanisms.

We have no *a priori* knowledge of which substances act on pain pathways and which on expectation mechanisms, and indeed virtually all drugs may interfere with the top-down mechanisms. In the same way as the Heisenberg uncertainty principle of physics states that a dynamical disturbance is necessarily induced on a system by a measurement, in clinical trials a dynamical disturbance may be induced on the brain by virtually any kind of drug. Thus, this uncertainty cannot be solved with the standard clinical trial design.¹ The only way to partially solve this problem is to make the expectation pathways, so to speak, silent.

The power of patient's perception or expectations is also highlighted by some of the previously mentioned studies,

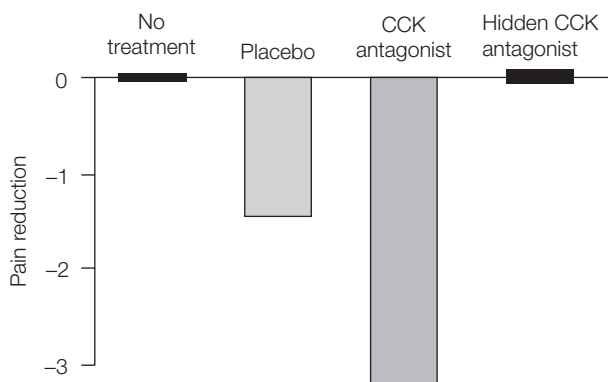


Figure 41.4 How the open-hidden paradigm is changing our conception of clinical trials. A clinical trial with three arms (No treatment, Placebo, CCK antagonist) shows that placebo is better than no treatment and proglumide (CCK-antagonist) is better than placebo in relieving pain. According to classical clinical trial methodology, this leads to the erroneous belief that the CCK-antagonist acts specifically on pain pathways as a painkiller. This interpretation is wrong, as demonstrated by the total ineffectiveness of the same CCK-antagonist when it is given covertly, with the patient completely unaware that a drug is being administered (Hidden CCK antagonist). Since the drug has analgesic effects only in association with a placebo procedure, its action is not specifically directed to the pain pathways, but rather to the expectation pathways, enhancing the placebo analgesic response (data from Benedetti *et al.*⁹⁵).

whereby the manipulation of expectations were able to improve the efficacy of a stimulant drug^{137, 138} and result in reduced drug intake in postoperative pain.⁷⁴ This is also underscored by some recent clinical trials whereby the patient's perceived assignment to either a placebo or active treatment better predicted the outcome to human fetal mesencephalic transplantation (a treatment for Parkinson's disease)¹⁴⁰ and acupuncture^{141, 142, 143} than did the actual allocation. These studies clearly demonstrate that those patients who experienced placebo responses show better therapeutic outcomes and request fewer drugs than those who are not under the effect of expectations.

Whether one wishes to look at placebo responses in the light of meaning or context effects, it is clear that the psychosocial context surrounding a given treatment can play a significant role in the outcome of the treatment by the activation of placebo and nocebo mechanisms. At the center of this is the clinician, the patient, and the overall treatment environment, and at this stage much more research is needed to identify how changes in these factors can potentiate placebo mechanisms and improve therapy.

At the same time, an ethical debate aimed at avoiding the misuse of placebos in clinical trials, surgery, and medical practice is necessary.^{1, 54, 55, 144}

The Declaration of Helsinki maintains that it is unethical to assign patients to receive a placebo when effective treatment exists.¹⁴⁵ However, the note of clarification on paragraph 29 of the WMA Declaration of Helsinki reads:

...a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

- where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or
- where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm;
- all other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.¹⁴⁶

Significant and controversial criticism has been made in relation to the document. In general, the arguments that are advocated for or against the use of the placebo in clinical studies can be summarized as follows. Placebo defenders sometimes use the utilitarian argument whereby exposing subjects to placebo treatment is justified by the knowledge gained for future patients, whereas placebo opponents reply that ethical obligations to the single individual take precedence over science and society. Placebo defenders also affirm that the approval of the Institutional Review Board and the patient's informed

consent are sufficient, whereas placebo opponents contend that most informed consent forms are incomprehensible, thus making the patient unable to judge the experimental situations. Another point raised by many placebo defenders deals with the use of placebos for symptomatic treatments and not for curative therapies. Placebo opponents argue that there is no justification even for minor discomfort.

An emergent view among researchers and ethicists argues that not only is the use of sham surgery ethical, but that it should also be mandatory when conducting trials to evaluate the effectiveness of surgical procedures.¹⁴⁷ There are, however, some opponents to placebo surgery who emphasize the role of evidence-based medicine.¹⁴⁸

As far as medical practice is concerned, a positive therapist–patient interaction does not require an ethical discussion and is, indeed, an essential ingredient of any therapy. Yet, deception remains a critical issue. On the one hand, it is considered to damage the medical profession, contributing to the erosion of confidence and trust in medical staff and caregivers.^{149, 150} On the other hand, it may be justified by the concept of paternalism, in which the physician's purpose is not actually to deceive but to cure.^{151, 152}

What is clear now is that when looking at a given therapy, one needs to not only look at the active properties of the intervention but also at the context in which it is given and the particularly powerful role the clinician's words on the patient's brain.¹⁵³ It is hoped that future research will further identify placebo mechanisms and ways of accessing and harnessing these mechanisms in the clinical setting for the benefit of the patient.

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