SPECIAL SECTION

Placebo Theory and Its Implications for Research and Clinical Practice: A Review of the Recent Literature

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Abstract: Although placebo effect is a common phenomenon in medicine and research, its mechanisms are not well understood. With the advent of modern medicine, placebo became a symbol for an outdated, morally questionable practice implying deceit and paternalism. However, in recent years, there has been an increasing amount of rigorous research into the mechanisms of placebo response and placebo analgesia with most studies coming from the field of pain medicine. New theories on placebo mechanisms have shown that placebo represents the psychosocial aspect of every treatment and the study of placebo is essentially the study of psychosocial context that surrounds the patient. Therefore, its understanding is essential for researchers and all medical practitioners, particularly those dealing with patients suffering from pain, depression, and motor disorders. In this article, we review the theories on placebo mechanisms and discuss their implications for clinical practice and the design of clinical trials.

Key Words: placebo, research, expectation, conditioning, meaning, context

INTRODUCTION

Placebo effect is a widespread and universal phenomenon, which has accompanied the practice of medicine from its very beginning.1–4 With the advent of modern medicine and empiricism, the psychological dimension of medical treatment that placebo represents has long been ignored. Placebo has been seen as something that stands in the way of “proper medicine” whose role is only to serve as a foil against which effective (“real”) treatment is being tested. It remains a poorly understood phenomenon if not mysterious, mystical, and surrounded by confusing terminology.

In clinical trials, placebo is usually considered a nuisance, a tiresome and expensive artifact.5,6 Even though researchers include placebo groups in every major clinical trial, little do they know about the mechanism of placebo itself and consequently about what happens in the arm of the study where placebo is being administered. In clinical practice, placebo is a much debated issue that provokes discomfort and is often confused with quackery.7 So far, medical practitioners have seen no scientific rationale for the use of placebo in clinical practice. The notion of “benevolent deception” that was proposed to overcome some of the ethical issues surrounding placebo is still debatable.8

In recent years, new research has led to considerable progress in our understanding of the mechanisms of
placebo. This research has shown that placebo represents the psychosocial aspect of every treatment and the study of placebo is essentially the study of psychosocial context that surrounds the patient. Therefore, its understanding is essential for all medical practitioners, particularly those dealing with patients suffering from conditions that have shown to be most influenced by placebo effect such as chronic pain, depression, and impaired motor function. Placebo has a multifaceted meaning ranging from neurobiology to philosophy, from ethics to social psychology, and from clinical trial design to medical practice. Understanding this phenomenon could help analyze the interaction between humans and humans and their environment and shed new light in the mind–body and body interaction.

Despite the recent increase of rigorous research in the mechanisms of placebo response, there remains widespread misunderstanding of this phenomenon among both practicing physicians and clinical researchers. The goal of this article is to review this research and discuss its implications for medical practice and the design of clinical trials.

**DEFINITION OF PLACEBO**

“Placebo” is a Latin word that means “I shall please.” According to Robert Hooper’s Quincy’s Lexicon-Medicum (1811), placebo denotes “an epithet given to any medicine adapted more to please than benefit the patient.” Placebo is an “inert substance or treatment.” The term “placebo effect” refers to the changes in an individual caused by a placebo manipulation. Placebo effect is also defined as the “response of a subject to a substance or to any procedure known to be without any therapeutic effect for the specific condition being treated.” The term “placebo analgesia” refers to the analgesic response after the administration of a substance known to be nonanalgesic when the subject is told that it is a painkiller. For example, if a subject is given a sugar pill and told that the pill is a potent painkiller, the pain relief that the subject experiences represents the placebo effect. Although there is a distinction between the term “placebo response” and “placebo effect,” they will be used interchangeably in this review. “Nocebo” is the phenomenon opposite to placebo.

**DO PLACEBOS HAVE ANY IMPACT ON THE OUTCOME OF TREATMENT?**

This question has provoked a lot of debate in both the media and the medical literature. In 2000, Talbot wrote a cover article for The New York Times Magazine, concluding that placebos are very potent, and medicine should regularly make use of “the powerful placebo.” This article triggered a wave of similar articles on the same theme. A year later, an article by Hrobjartsson and Gotzsche published in New England Journal of Medicine concluded that placebos have no significant effect on the objective outcomes of treatment and there is no justification for the use of placebos outside the setting of clinical trials. This article prompted a wave of articles that now question the very existence of placebo effect.

Do placebos really have any impact on healing process and recovery? Buckalew and Coffield demonstrated that perceptual characteristics of drugs played a major role in patients’ expectancies and response to the drugs. For example, capsules with colored beads were perceived as more effective than colored tablets, which were perceived as more effective than white tablets with corners and round white tablets. Wall showed that the route of administration affected the treatment efficacy. For example, the intravenous route was perceived as more effective than intramuscular route, which was perceived as more effective than tablets. Sox found that laboratory tests that had no diagnostic value were independent factors of recovery. He randomly assigned 176 patients with nonspecific chest pain into a group that underwent investigations such as electrocardiography and serum creatinine-kinase and a group that underwent no investigations (the control group). The group that underwent investigations reported less short-term disability than the control group. Thomas studied 200 patients who presented in general practice with symptoms of pain, cough, nasal congestion, and tiredness but no abnormal physical findings and in whom no definite diagnosis could be made. Patients who were given a firm diagnosis and therapeutic assurance recovered faster than patients who got no reassurance. Other studies have shown that doctor–patient relationship plays an important role in the outcome of illness.

The perceptual characteristics of drugs, the route of administration, laboratory tests, diagnosis, and doctor–patient relationship all are part of what we call the “context of treatment” or the “nonspecific effects of treatment.” The “context of treatment” is the “atmosphere around the treatment,” including doctors, nurses, hospitals, syringes, pills, and so forth. Kapchack categorizes the nonspecific effects of treatment into three groups: the patient, the clinician, and the patient–clinician relationship.
indicated that from patient’s perspective, the nonspecific effects of treatment are the most important aspects of therapy. Studies presented so far show that the context can influence the outcome of treatment. Any medical treatment is carried out within a context, therefore, although a placebo may be an inert substance per se, it is administered within a context, and it is this context that plays an important role in the outcome of treatment. As a result, the potential for developing a placebo response exists with any treatment.

It is important to point out that placebo response is bidirectional. The verbal instruction may differ by only one word in order to produce an opposite effect (nocebo effect). For example, when subjects are given a saline solution (placebo) and told that they are receiving a drug that decreases pain, a placebo effect is produced and subjects report less pain. When subjects are told that they are receiving a drug that increases pain, a nocebo effect is produced. Subjects report more pain although they received an inactive substance. The replacement of only one word (“increase”) with another word (“decrease”) produced a response in opposite direction.

Verbal instructions are not the only way to induce a placebo response. It can also be induced by visual, auditory, or olfactory stimuli. Every environmental setting such as the hospital, syringes, doctor’s charming smile, and stylish clothes can produce a placebo response.

HOW STRONG IS THE PLACEBO EFFECT?
After recognizing that placebos can affect the outcome of treatment, the next step is to review the literature regarding the magnitude of this effect. From pharmacology, we know that the efficacy of an unknown analgesic is expressed as the ratio between the amount of pain decrease with that analgesic and pain decrease with morphine. For example, the ratio codeine/morphine is less than 1, indicating that codeine is less powerful than morphine. If we calculate the ratio for placebo, we find a surprising 0.56, meaning that placebo is 56% as effective as morphine. In one study, placebo was as powerful as a hidden injection of 8 mg morphine intravenously. In other words, in this study, just telling the patients that they were taking an effective painkiller was equal to giving them 8 mg morphine intravenously. In another study involving 278 patients after thoracic surgery, placebo was as powerful as intravenous injection of 0.14 mg of buprenorphine, 31 mg of tramadol, 12 mg of ketorolac, and 521 mg of metamizol. One study showed that placebo cream resulted in a mean pain reduction of 46% to 57% compared to a nontreatment group. Jospe indicated that 20% to 30% of clinical improvement can be explained by placebo response, whereas Sartorius stated that as much as 40% of the effects of active drugs is due to placebo effect.

Using the group comparison approach (including responders and nonresponders), several studies have found that the magnitude of placebo analgesic effect across all individuals is 2 out of 10 on a visual analog scale. If one looks, however, only at placebo responders, the average pain reduction from placebo effect alone is even more impressive: 5 out of 10 in a visual analog scale in one study and 3.3 out of 10 in another study. When analyzing these data, one should keep in mind that, according to a very well-designed study, a reduction of 2 points on a visual analog scale represented a clinically important difference.

Literature has shown that not only the magnitude of placebo response, but also the length of response can be quite remarkable, lasting from as long as 1 year in one study to as long as 5 years in another study.

MECHANISMS OF PLACEBO EFFECT
Placebo effect is a complex psycho-physiological response that involves motor cognitive-verbal and physiochemical responses. Numerous theories have been put forth to explain the mechanism of placebo. This review will present two theories that have received most support in the literature, namely the “classical conditioning” and the “expectancy theory.” Two other theories that the reader may frequently encounter in the literature, namely the “reward” theory and the “response-appropriate sensation” theory, will also be briefly mentioned. It is important to stress at this point that these theories may not be mutually exclusive but may merely represent an explanation of placebo response at different levels.

Conditioning Theory
This theory suggests that placebo response represents a form of classical conditioning that is based on learning through association. Pavlov noticed that dogs were salivating to a neutral stimulus such as ringing a bell (conditioned stimulus), which was previously associated with food (unconditioned stimulus). Several studies have shown that conditioning can occur in humans, too. For example, patients with headache taking regular aspirin (unconditioned stimulus) can associate the shape, color, and taste of aspirin (conditioned stimulus)
to pain decreases. After several associations, pain decreases when patients are given a placebo that looks and tastes like aspirin.51 Lang reported tachycardia when a conditioned stimulus was substituted for glyceryl trinitrate.48 Knowles reported an increase in reaction time in subjects who were given decaffeinated coffee (placebo).49 In three other studies, placebo responders were conditioned to a neutral cream following conditioning trials in which the cream was associated with pain relief.50–52 Wickramasekera argued that not only pharmacological agents can be classically conditioned when associated with previously ameliorative effects that occurred in these settings, but also neutral places (e.g., doctor’s offices, hospitals), persons (e.g., doctors, nurses), things (e.g., syringes), and rituals (e.g., physical examinations).46,53,54 Furthermore, Phil and Altman showed that the strength of conditioned response increases with the increasing number of paired associations.55

It is assumed that human conditioning does not involve cognition; therefore, it is inevitable and occurs without the individual knowing it.2,7,11,46,54 The response to any unconditioned stimulus will necessarily come to involve an unconditioned response (a placebo response). This response will depend on the individuals’ learning history, also called the “response generalization.” According to such a model, the unexplained variability in placebo response within subjects is due to individuals’ past medical history and individuals’ differences in learning history with a particular treatment, in a particular environment.54 Nocebo effect can also be conditioned through the association with negative stimuli.44

**Expectancy Theory**
This theory was developed by Goldstein in 1962.56 It postulates that placebo response is related to patients’ expectations of improvement, which are connected to the changes that take place.29,57–59 For example, placebo alcohol produced increased sexual arousal to erotic stimuli,60 increased aggressive behavior,61 and increased craving for alcohol.62 Volkow et al. found that patients who expected to receive treatment showed more significant changes in brain metabolic activity than those patients who expected to receive placebo although both groups were given an active drug.63 Expectancies can even override the pharmacological effects of a drug, the effect of expectation overrides that of the drug.66 In another study, the sympathomimetic effects of epinephrine were reduced when subjects were misinformed on the action of this drug.57

There is an overlap between expectancies and conditioning as expectancies are formed through conditioning. However, expectancies can be produced without direct personal experience, for instance, through observational learning, verbal information, and persuasion.56 As already mentioned, conditioning is an unconscious process, whereas expectation is a conscious one.2 Therefore, expectation could replace conditioning when conscious perception is involved (e.g., association of contextual cues with the outcome).

In 2003, Benedetti et al. designed a study to better understand how conditioning and expectations produce a placebo response.2 They found that in healthy volunteers, verbally induced expectations that subjects are going to receive injections that increase the level of cortisol and growth hormone did not really have any effect on the secretion of these hormones. However, administration of placebo after subjects were conditioned with a substance that increases the level of cortisol and growth hormone resulted in changes in plasma level of these hormones. The authors concluded that the context can either act as a conditioned stimulus to produce the unconscious conditioned hormonal response or have a conscious meaning that induces conscious expectations. In another study, Voudouris et al. compared the placebo response in two experimental conditions: expectation and conditioning. They found that conditioning was more powerful than expectation in producing a placebo effect.52

But how do the expectancies and conditioning work? Some authors have suggested that expectancies might help to reduce stress and pain.29 Others believe that expectancies bring about behavioral changes or increase self-esteem and improve coping.57 Recent studies from pain medicine have shown that the cognitive and motivational factors such as expectation may produce placebo analgesia by activation of the endogenous opiate system (Note that placebo analgesia is a type of placebo response as explained previously). Hughes in 1975 discovered that the brain synthesizes endogenous opioids which act at the same receptor site as exogenous opioids such as morphine.68 These endogenous opioids and their receptors spread in discrete sites of the brain are part of the descending opioid pain-modulating network also called the “top-down pathway.”12,69 It connects the limbic forebrain areas (including anterior cingulate cortex, hypothalamus, and central nucleus of amygdala) with periaqueductal gray in the midbrain and, farther down,
with rostral ventromedial medulla and the dorsal horn of spinal cord. This pathway can exert both inhibitory and facilitatory control through off-cells and on-cells. When off-cells fire, the transmission of potentially tissue-damaging stimuli are inhibited thus leading to reduced or no pain. When on-cells fire, the transmission of potentially tissue-damaging stimuli is facilitated leading to pain perception. It has been demonstrated that injection of morphine in the rostral ventromedial medulla causes the off-cells to fire and renders the on-cells silent, whereas the injection of the opioid antagonist naloxone has the opposite effect. From a placebo response perspective, the most important point here is that the opioid-sensitive pain modulating pathway links the cortex and limbic system with pain signal transmitting pathways in dorsal horn of spinal cord. Therefore, at least theoretically, it is possible that emotional state, thoughts, and expectations could potentially alter pain perception.

A milestone in the neurobiology of placebo effect was the discovery by Levine et al. that the opioid antagonist naloxone inhibits the analgesic placebo response. These results have been replicated by another study. Lipman showed that patients who responded to placebo had higher level of endorphin B in cerebrospinal fluid compared to patients who did not respond to placebo. In 1999, Amanzio and Benedetti designed a study to find out if descending pathways are involved in expectation and conditioning. They included 229 subjects in whom pain was induced experimentally by the tourniquet technique. Expectations were generated by giving subjects intravenous injections of saline in their presence and telling them that it was a powerful painkiller. Conditioning (without expectations) was produced by using daily ketorolac injections, which were administered by a pump connected to a computer hidden from the subjects. As a result, the participants did not know when they were taking the painkiller (ketorolac); therefore, they had no expectations. The authors found that conditioning produced a placebo response that was not always blocked by naloxone. The authors concluded that conditioning produced a placebo response that was not always blocked by naloxone. The authors concluded that conditioning is likely not mediated by opioid-sensitive pain modulating pathway. Expectations, on the other hand, produced placebo responses that were completely blocked by naloxone. The authors concluded that expectations are likely mediated by opioid-sensitive pain modulating pathways. Based on the above, it is plausible that cognitive and motivational factors such as expectation and desire of pain relief are capable of interacting with the neurochemical system and producing an analgesic effect. This assumption has been supported by recent neuroimaging studies.

In 2002, Petrovic et al. designed a landmark study in which they injected study participants with a powerful opioid (remifentanil) and mapped the areas of the brain that were activated in positron emission tomography. Next, they induced a placebo effect by giving their subjects saline infusions and telling them that they were taking a powerful analgesic. Again they mapped the areas of the brain that were activated in positron emission tomography. They found a remarkable overlap of the areas of the brain that were activated during placebo response and opioid pain-modulatory pathways that were activated by remifentanil. These results suggest that placebo analgesia may work by stimulating the secretion of endogenous opioids and activating the descending pain-modulatory pathways. In 2004, Wager et al. performed an fMRI study showing that activation of the anterior cingulate cortex and periaqueductal gray correlated with placebo analgesia, thus providing further direct support for the hypothesis that placebo-induced analgesia is mediated by the same modulatory circuitry that controls pain transmission through endogenous opioid system.

This new knowledge has been important in changing how people think about the placebo effect. It has placed the placebo response within the field of neuroscience and biomedicine. As Hoffman and Fields noted in 2005, “For those who might previously have insisted that this phenomenon could never be more than a nuisance factor in modern medical research, the counterproposition is now firmly on the table that it is in fact fair game for modern biomedical research in its own right.”

In conclusion, the expectancy and conditioning theories suggest that placebo effect is a phenomenon that can be learned either consciously or unconsciously. In the first case, after repeated association of contextual cues with the outcome, an increased expectation is likely to occur. In the second case, a Pavlovian conditioning likely takes place in which contextual cues and outcomes are unconsciously associated because of their contiguity. It is possible that expectations produce a placebo response that is mediated by endogenous opioid system.

Other theories on mechanisms of placebo response. “Reward theory” postulates that it is the expectation of reward that triggers the placebo response, which, at least in part, is mediated by dopamine. Indeed, many of us have witnessed the calming and pain-
relieving properties of a candy given to a crying child.1 From the patient perspective, pain relief, return of lost dexterity, and ability to walk again could serve as reward. Religious beliefs also implicate rewards from God. Hahn realized that: “Belief sickens, belief kills”76 and long before him, Paracelsus (1490–1541) stated: “Whether the object of your faith is real or false, you will nevertheless obtain the same effects.” In fact, several studies have brought evidence for the healing power of religious experience.77–79 All of us are familiar with Bible stories of Jesus healing the lepers or the Indian fakir withstanding the physical pain of the bed of nails on which he is sitting in expectation for recognition (reward) from the God. Thus, placebo response may be related to the healing power of the mind. Literature has suggested that that faith may be at very heart of placebo response.80,81

A body of literature had shed light on the neuroanatomy of reward. Expectation of reward is thought to activate dopamine cells in the midbrain.82 There are three major dopamine cell groups localized in the retrorubral, nigrostriatal, and tegmental areas.83,84 Nucleus accumbens, which is localized in the nigrostriatal area, is thought to be the most important structure of reward. For example, it has been shown that the release of dopamine in this nucleus is associated with drug dependency.85 The dopamine system is connected to the limbic system and the opioid system (periaqueductal gray and thalamus).86–89 It is conceivable that the activation of dopamine cells could control the opioid release and therefore play a role in the transmission and perception of pain.90 This provides a plausible (but, as yet, untested) basis for believing that placebo analgesia may be mediated, at least in part, by dopamine release. On the other hand, there is an anatomical substrate to support the notion that the release of opioids may influence dopamine release in nucleus accumbens.91 Therefore, activation of brain opioid system could lead to reward via stimulation of dopamine release. Based on the above-mentioned literature, the dopamine–opioid connection is likely bidirectional.1

It is possible that each system (dopamine or opioid) is activated in different disorders. For example, the opioid system may predominate in placebo analgesia and the dopamine system may predominate in motor disorders or depression. Placebo-induced dopamine release especially in nucleus accumbens could be a major biochemical substrate for the placebo effect encountered not only in patients suffering from pain, but also in other conditions such as motor disorders and depression.1 For example, one recent study demonstrated that in patients with Parkinson’s disease, placebo was able to induce dopamine release in the dorsal and ventral striatum.80 Interestingly, such dopamine release is more related to the expectation of reward than to reward itself.92 As de la Fuente-Fernandez stated in 2002, “If this hypothesis will prove to be correct, it would represent a major advance in our understanding of the self-healing process and the mind–body interaction.”1

The “response-appropriate sensation” theory was proposed by Wall in 1993. This theory suggests that expectation-conditioning may determine the appropriate behavior pattern with its associated sensation. The best example would be that of a wounded soldier when the fear of being caught by the enemy and dying produces behavior pattern aiming to preserve the life and inhibiting the painful sensation produced by the injury. As a result, the soldier experiences less or no pain. The injury becomes painful when the risk of dying has resolved and the soldier reaches a safe place. Wall explained that the noxious input is used in two ways: the first way is to assign the priority and the second to guide the motor behavior. Wall believed that these mechanisms apply to placebo as well: before taking the placebo the priority is assigned to the painful sensation, whereas after a stimulus associated with pain relief (placebo) is administered, the priority is given to a nonpainful state.

In summary, although the literature mentions various theories on placebo effect, we believe that in fact only two mechanisms exist: conditioning and expectation. The so-called “endogenous opioid theory” is in fact the biological mechanism of which conscious expectation is mediated, the “reward theory” (a dopamine-related phenomenon) is a specific example of “expectation for reward” and the “response-appropriate sensation” theory is based on the behavior patterns determined by expectation-conditioning.

WHO RESPONDS TO PLACEBO?

Henry Beecher, in his influential article “The Powerful Placebo,” reported that 35.2% of the population responds to placebo.93 Levine94 found that 39% of patients responded to placebo analgesia. In a recent review of 75 randomized placebo-controlled trials, Welsh et al. found that the proportion of patients suffering from depression who responded to placebo ranged from 12.5% to 51.8%.95 There was an association between the year of publication and the response rate. The rate of placebo responders was shown to
increase significantly in recent years’ publications. Petrovic found that 56% of subjects responded to the placebo treatment, whereas Liberman found that nearly 100% of population responded to placebo. In fact, most people have experienced placebo at one time or another, suggesting that we all have the potential to develop a placebo response. Wickramasekera reviewed the literature on placebo in 1985 and came to the conclusions that: (1) a subset of subjects show a significant response to placebo in any clinical study, (2) it is not possible to identify in advance this subset of patients, (3) any procedure can, under right condition, generate placebo effects, and (4) these right conditions are not possible to identify in advance this subset of patients, (3) any procedure can, under right condition, generate placebo effects, and (4) these right conditions are unknown.

**IMPLICATIONS FOR THE DEFINITION OF PLACEBO**

As already mentioned here, placebo is defined as an “inert substance or treatment.” But, is placebo really inactive or is this simply a definition that we have temporarily adopted to label a group of effects whose mechanism of action we do not yet understand? The body of research presented here showed that a placebo may have an effect on its own right. For example, the expectancy theory suggests that expectations are likely mediated by opioid-sensitive pain modulating pathways. The “reward theory” suggests that the placebo effect is mediated by reward-related mechanisms and may be, at least in part, mediated by dopamine. There is growing literature, part of which was already discussed here, to support the notion that cognitive and motivational factors are capable of interacting with neurochemical system in the body. We already described how placebo was able to induce dopamine release in dorsal and ventral striatum in patients with Parkinson’s disease. In a recent study, Mayberg showed that paroxetine for the treatment of depression and placebo produced exactly the same changes in brain glucose metabolism as measured by positron emission tomography studies. Based on the above and other examples from the literature, two important questions arise. Does such a thing as placebo (inactive substance or treatment) exist? Is there any substance we could give to a human in the context of medical setting that is inert and causes no changes at all?

There is a paradox with our definitions of placebo and placebo effect. If placebos are inert substances, they can not cause an effect. If an effect occurs, the placebos are not inert. Many attempts have been made in the literature to resolve this paradox. Brody defined the placebo effect as a “change in a patient’s condition that results from the symbolic aspect of encounter with a healer or with a healing setting, and not from the pharmacological or physiological properties of any remedy used.” In this definition, “symbolic” alludes not only the psychological process that occurs within the patient but also the social and cultural beliefs that give meaning to the healing process. Further, Brody distinguished between a “pure placebo” (no pharmacological effect at all, for example, a saline solution) and an “impure placebo” (pharmacological potency under some circumstances, vitamins for example). By emphasizing the role of context of treatment, this definition goes beyond the “sugar pill” notion of placebo. It reminds us that although the placebo itself may be inert, the process of administering and receiving the placebo treatment may not be, embedded as it is with learned expectancies and symbolic meaning.

As mentioned in previous paragraphs, any medical treatment is carried out within a context (nonspecific effects of treatment) that is the “atmosphere around the treatment.” Although placebo is an inert substance or treatment, it is given within this context. Ample research previously presented shows that this context affects the healing process and recovery. As we will see in examples to come, an active substance or real procedure can also have a placebo effect. Moreover, in 1994 Thomas showed that a placebo effect can also be produced by a consultation in which no treatment is given at all. To clarify that it is the context that influences the outcome of treatment, Di Blasi proposes the broader term “context effect” and further suggests that the terms “context effect,” “placebo effect,” and “nonspecific effect” be used, at least in part interchangeably. Based on this definition, a treatment with placebo should not be considered as absence of treatment, but just as absence of a specific (active) treatment.

Moerman has taken an important step in clarifying the above-mentioned paradox by introducing the term “meaning response.” He defines the “meaning response” as the physiologic or psychological effects of meaning in the origins or treatment of illness. “Placebo effect” is defined as a desirable meaning response elicited after the use of an inert or sham treatment. If the meaning response is undesirable, it is defined as “nocebo effect.” Although placebos are inert and cannot have any effect in healing process, their meaning can. While there is still room for refinement, this framework seems to be more consistent with the recent research. It is of note that this definition does not mention the “nonspecific effects” of treatment. Moerman explains that
although many elements of treatment are nonspecific, they become specific once they are understood.

**IMPLICATIONS FOR RESEARCH**

**Ethical Implications**

The use of placebo in research has been the subject of heated debate. On one hand, the literature shows that the use of placebo in research is not as harmless as one might think. For example, a review of 109 phase I trials found that 10% of volunteers in the placebo arm experienced adverse events. On the other hand, many researchers would argue that using a placebo arm in a research study entails deception and therefore raises a number of ethical issues. The researcher faces the dilemma of telling the subjects the truth about the placebo treatment, thus risking the lost of valuable data that may improve the health care of population, or not telling the subjects about the placebo arm of the study, in which case the researcher disrespects their autonomy.

To resolve this ethical dilemma, the American Psychological Association allows investigators to “deceive” subjects in four situations, when: (1) the study is expected to have significant social and scientific values, (2) any equally effective nondeceptive approach is not feasible, (3) participants are not deceived about any aspect of the study that would affect their willingness to participate, and (4) deception is explained to participants at the conclusion of the study. In a position statement issued in April 2005, American Pain Society recommended the use of placebo in clinical trials when there is limited harm to patients from delayed treatment, when the alternative active treatment is unproved, when there is a substantial potential benefit to future patients in establishing the efficacy of a treatment and/or avoiding side effects of a treatment.

Wendler and Miller argued that “authorized deception” may be another way to resolve the dilemma. Subjects are informed of the deception and asked to consent to it without being informed of the nature of deception. Subjects are told they will be fully informed at the end of the study. “Authorized deception” allows subjects to decide for themselves and does not threaten public trust in research. Yet, some argue that a valid consent requires subjects to know exactly the nature of the procedure they will undergo. The supporters of “authorized deception” have responded to the above by arguing that investigators can still obtain valid consent as long as they do not deceive about any aspect of the study that would affect their willingness to participate (e.g., telling participants about a drug being used but not about technical details such as the dose, rate, or timing of infusion).

**Implications for the Research Setting**

Recent advancements in our understanding as to the mechanisms of placebo response are starting to change the way research trials are designed. Traditionally, when undertaking a clinical trial, the assumption is made that the “research setting” is the same as “clinical setting.” Is this assumption true? Let us examine it in the light of the new knowledge from placebo research. Kirsch and Weixel studied 100 undergraduate students who were self-reported coffee drinkers. Participants were randomly assigned to a “double-blind administration” group that was supposed to simulate a research setting: a “deceptive administration” group, which was supposed to simulate the clinical setting, and a “no beverage” control group. The participants in the “double-blind administration” group were led to believe that they may or may not receive coffee. Subjects were shown two cans and were told that only one contained coffee. Participants in the “deceptive administration” group were told that they were assigned to the group that is going to consume coffee. Subjects in this group were shown a single can bearing the label of a well-known coffee brand. In fact, none of the groups received coffee. All cans contained decaffeinated coffee. Outcome measures were mood (which was measured on a 10-point Likert scale from which three subscales derived indicating alertness, relaxation, or tension), behavioral measures (digit span and reaction time), and physiological parameters (blood pressure and heart rate). All variables were measured before and 20 minutes after the experiment. The results were quite surprising. The “double-blind” setting produced curves in opposite directions as compared to the “deceptive administration” setting in each of the outcomes measured. What is more, all curves were similar for all variables, adding more credibility to the results of the study. These data showed that the double-blind randomized experimental designs setting may not be the same as the clinical or real-life setting, thus challenging the validity of double-blind experimental designs. The authors conclude that this method of drug assessment may lead to spurious conclusions.

The authors of this study admitted that they were at a loss for the theoretical explanation of these results. Based on the expectancy theory, we can assume that the different results seen in two groups may be explained...
by the difference in the magnitude of the expectancy and, as a result, by different placebo responses that both settings produced. Subjects in a double-blind research setting have less expectation that they will receive the treatment. For example, in this study subjects assigned in the “double-blind administration” knew that they had a 50% chance of receiving coffee. In contrast, subjects in the “real-life” setting have full expectations that they are going to receive the treatment offered. For example, in this study subjects assigned to “deceptive administration” group were almost 100% sure that they were going to receive coffee. In this study, the researchers further divided the “deceptive administration” group in subgroups according to the degree of expectations they developed. Participants who had higher expectations that they are going to consume coffee showed more increase in alertness, better reaction time, and higher blood pressure and heart rate response compared to those who had lower expectations. Based on Moerman’s definition of “meaning response,” the differences could be explained by “meanings” in the experiment (100% means more than 50%) and the knowledge that one may or may not receive the treatment. It is the meaning of the treatment that increases expectations or, as Benedetti calls them, the “meaning-induced expectations.”

From Double-Blind to Open-Hidden Paradigm

The gold standard in clinical trial design is the double-blind placebo-controlled trial with two arms: an active group and a placebo group. In order to conclude that a treatment is effective, the outcome must be better than placebo. Is this design appropriate to enable us to conclude that a therapy is effective? To study the placebo effect, an interesting model has been developed, namely the “open-hidden” paradigm. As previously mentioned, any medical treatment has two components: the specific effect of the treatment and the context effect (or meaning response). To study the placebo effect, researchers usually eliminate the specific effect of the treatment by using a dummy treatment. In an open-hidden paradigm, the experiment is reversed. The specific effect of the treatment is maintained but the context of the treatment is eliminated by using a preprogrammed computer-controlled infusion pump to administer the intravenous drug infusions. The pump is hidden from the patient and there are no doctors or nurses in the room. The key here is that the patient does not know when he or she is receiving the treatment. By eliminating the context of the treatment, it is believed that most of clinical response (e.g., pain relief) that the participants experience is attributed to the specific effect of the drug and not to the placebo effect. In contrast, open injections are given by a doctor or nurse in full view of the patient. Clinical changes experienced here are believed to be the result of both the specific effect of the drug and the context effect. Therefore, the difference between open and hidden may be taken as a measure the context effect.

In 1995, Benedetti et al. ran a classical double-blind randomized trial that showed that: (1) the cholecystokinin antagonist proglumide was better than placebo, and (2) placebo was better than no treatment, for relieving pain in a group of 93 post-thoracotomy patients. According to the classical clinical trial methodology, the conclusion that can be drawn is that proglumide is an effective analgesic acting on pain pathways. However, this conclusion was proved to be wrong when the authors repeated the experiment by using the open-hidden paradigm. It was shown that the hidden injection of proglumide (the context and the resultant placebo effect are eliminated) produced no analgesic effect at all. The whole effect that proglumide produced in the classical trial was placebo effect. Obviously, proglumide acts only in expectation pathways, not in pain pathways. Colloca and Benedetti calls this the “uncertainty principle” in clinical trials, a term borrowed from Heisenberg’s uncertainty principles of physics. In physics, dynamic disturbances induced in the system by the act of measurement make the absolute value of the variable measured “uncertain” for any specific point in space-time. In clinical trials, a drug may act on expectation pathways rather than pain pathways, making it difficult to interpret the data.

This trial is the best example of the need to understand the neurobiology of placebo response and apply it to clinical research. This uncertainty in clinical trials cannot be resolved by using the classical trial design. The open-hidden paradigm may offer a way to address the uncertainty by eliminating the context (meaning) of a treatment, hence rendering the expectation pathways silent. To overcome the ethical problems, the design may consist of unknown temporal sequences of drug administration where the subject knows that a pain-killer will be administered but does not know when. If a drug is really effective, pain reduction will correlate with the time that the drug is administered. This paradigm offers a way to assess context effect without using placebo groups at all thus solving the debate on the use of placebo in clinical trials. It would provide an excellent alternative to placebo-controlled trials.
and would be consistent with the World Medical Association’s Declaration of Helsinki Ethical Guidelines. The hidden procedure is easy to carry out in the post-operative phase in which the patient is connected to several intravenous lines such as for antibiotic therapy or blood transfusion.

Although seen as the “gold standard” in studying the efficacy of a drug, double-blind clinical trials have a number of flaws. The “balanced placebo” design is a $2 \times 2$ design in which participants are told that they are or are not receiving an active treatment and, in fact, either do or do not receive it. Although the “balanced placebo” design overcomes some of these problems, it entails deception. Hidden-open design may offer an alternative to this design too. In fact, two groups in the hidden-open design (told drug/get drug and told no drug/get drug) are comparable to the balanced-placebo design groups. Moreover, adding a “natural history” group to the open-hidden paradigm produces information on the efficacy of a treatment that cannot be derived from conventional clinical trials.

In summary, open-hidden approach might be a valid complement to the classic placebo-controlled studies and provides an excellent way of investigating the placebo component of treatment.

Interpretation of Placebo

Moerman’s notion of “meaning effect” has implications for the design and interpretation of research studies. Moerman explains that the therapeutic consequences of being in the control group are not placebo effects because placebos have no effects. They are more likely the consequence of the meaning that the treatment has (the meaning response). Drugs (active or not), surgical procedures, diagnoses, and so on can be seen as meaning delivery systems. Meaning responses are inevitable in medicine and one cannot avoid meaning while engaging human beings. Studies mentioned here showed that meaning can have considerable physiologic action. For example, placebo analgesia can elicit the production of endogenous opioids leading to pain relief. Therefore, placebo is not the equivalent of “no therapy.” As a result, to say that a treatment is not better than placebo does not mean that it does nothing. It simply means that the effectiveness of that drug was not better than the effect of the context in which the treatment was given (or the effect of meaning that this drug carried during the study). The meaning of the treatment depends on biological, social, and cultural factors that are very difficult to account for in a research study.

A final comment that we would like to make relates to the use of the word “deception.” Although the reader will encounter this word numerous times in this article, we would like to clarify that it is used in quotation from other articles. In the light of Moerman’s new definition of “placebo response” and “meaning response” and Di Blasi’s definition of “context effect,” we advise caution in the use of this word because the elements that are included in the context of the treatment such as doctors, nurses, hospitals, pills, and so forth are not a deception.

IMPLICATIONS FOR CLINICAL PRACTICE

Meaning of Placebo Response

Newly acquired knowledge as to the mechanisms of placebo response has a number of important implications at a clinical level. First, it suggests that we have been looking in the wrong place for placebo responders. After a long search for personality or demographic characteristics, the most recent literature suggests that no such person exists and, in the right circumstances, anyone may respond to placebo. The expectancy theory suggests that placebo response (or the better term, the “meaning response” or “context effect”) depends on the individual’s learning history, also called the “response generalization.” As a result, the ability to respond to placebo is not associated with any specific psychological profile or personality trait. The literature also shows that a given subject’s response to placebo is not constant. For example, a subject can respond in a given situation but can become a nonresponder in a different situation. Consequently, placebo response cannot and should not be used as a diagnostic tool to detect if a patient’s pain is organic or psychogenic. It cannot detect individuals who are malingering or exaggerating their pain complaints. Claims that placebo works only in hystericis and hallucinators seem to be a myth.

The conditioning model suggests that patients’ expectations (faith or hope) are largely learned through patients’ past contact with the medical system. This theory places the responsibility for placebo response not with the patient but with the medical system, with its success or failure to treat the patient. Each time an individual encounters the medical system, the placebo response (or the better term, the “meaning response” or “context effect”) is being shaped. Note how the use of the term “meaning response” or “context effect” further clarifies this misconception.
Conditioning theory suggests that nocebo effect can also be conditioned through the association of neutral stimuli with aversive stimuli. For example, in patients with chronic pain, the negative conditioned response from ineffective therapy may generalize, thus weakening even potent unconditioned stimuli when they are administered. Consequently, a patient's meaning may extinguish, not just to the physician who has used the ineffective therapy, but to all subsequent physicians, creating a nocebo for any subsequent treatment that may be suggested in the future. Wickramasekera calls this phenomenon the “placebo sag.” Therefore, it is important for medical practitioners to refrain from administering treatments with doubtful efficacy or “pure placebo” treatment. For example, to increase the chance of success, practitioners inexperienced in the treatment of chronic pain are advised to refer them early to pain specialist and rehabilitation programs for chronic pain.

Using the above-mentioned open-hidden paradigm, Benedetti et al. in 2003 randomized 42 post-thoracotomy patients in two groups. One group of 21 patients received open infusions of morphine administered by a physician who told the patients that they were taking a potent painkiller (open administration). Another 21 patients in the second group received a hidden infusion of morphine administered by a computer-controlled infusion pump without any physician or nurse in the room (hidden administration). Both groups rated their pain on a numeric rating scale from 0 to 10 at 30 and 60 minutes after infusion. Patients in the hidden injection group reported less pain relief from morphine than patients in the open injection group. Although both groups took the same drug at same dose and at same infusion rate, the efficacy of treatment decreased in the hidden administration group because the context of the treatment was eliminated. Subjects were not aware of the treatment and as a result, they had no expectation of treatment outcome.

There are many important conclusions to draw from the results of this study. First, the comparison between open and hidden treatment used in this study is the best proof of the importance of context in the outcome of treatment. Second, the results strongly suggest that expectations are possible mechanism of placebo effect (likely by activation the opioid system leading to additional release of endogenous opioids). Third, from the clinical practice point of view, by increasing subjects’ expectations, it was possible to further enhance the efficacy of a very effective analgesic drug such as morphine. This study strongly suggests that context effect (or meaning response) could be used as a therapeutic tool to enhance the effect of a proven treatment.

The fourth conclusion that can be drawn from this study relates the definition of placebo. This study is another example that illustrates the above-mentioned paradox with the current definitions of “placebo” and “placebo response.” We cannot use the term “placebo” or “placebo effect” to explain the results of this study as no placebo (no inactive substance or treatment) was given at all. Participants of this study received morphine, which is one of the best analgesics that we have. By using the term “meaning response” as suggested by Moerman, things start to make more sense. Every treatment, be it inactive (a sugar pill) or active (for example, morphine in our case), carries a meaning, and it was the effect of this meaning that influenced the outcome of treatment and increased the effectiveness of morphine in this study. Therefore, it might be time to limit the use of the term “placebo effect” only to those situations in which an inert treatment is given. One could even argue that the term “placebo effect” would be inappropriate even if a placebo (an inert substance) is given because it is the meaning (or the meaning induced-expectations) that leads to the effect, not the inert substance per se.

In 2004, McRae et al. performed a study to determine the effectiveness of transplantation of human embryonic dopamine neurons into the brains of patients with advanced Parkinson’s disease. Forty patients were randomly assigned to receive either the transplant or the sham surgery (placebo). The double-blind condition was maintained for 1 year, providing a unique opportunity to investigate the effect of placebo over time. Assessments of quality of life, physical function, emotional and social function were made at baseline and 4, 8, and 12 months after surgery. The study showed that the transplant group reported a modest improvement in quality of life and motor function compared to sham surgery group. Next, researchers compared the group of patients who believed they received transplant and the group that believed that they received sham surgery and found that the difference in quality of life and function was significantly better in the group of patients that thought they received transplant. The study concluded that the perceived assignment of treatment, either active treatment or sham surgery, had a more powerful impact on both quality of life and motor function than actual treatment. It did not matter whether patients received transplant or not. What mattered most was their expec-
tion (meaning) of treatment. What was more interesting, the improvement occurred not only in the subjective parameters such as perceived quality of life but also in motor functioning. Surprisingly, improvements in the group that believed they were getting transplant continued throughout the year that the double-blind condition was maintained. The results of this study have very recently been replicated by Bausell et al. in 2005, who found that the perceived assignment in a trial of acupuncture had a greater impact on the outcome (analgesia) than the actual treatment itself.\textsuperscript{116}

These findings have implications for both research and clinical practice. From the research perspective, an important question arises: When designing a double-blind trial, is the perceived assignment to an arm more important than the actual assignment? From clinical practice perspective, a crucial question arises: Given the substantial effect that the context of treatment has on the treatment outcome,\textsuperscript{29,30,32,35–37,39,41,42,116,117} is it ethical to ignore this effect?

**Ethical Implications**

The debate over the use of placebo in clinical practice is not a new one. In 1974, Sissela Bok published an article in *Scientific American* on the ethics of giving placebo.\textsuperscript{118} She concluded that the practice of placebo is the practice of deception and placebo should not be used in clinical practice. On the side of the debate, in a letter to the *Lancet* in 1973, a physician argued that, whenever pain can be relieved with two milliliters of saline, why should one inject an opiate? In April 2005, the American Pain Society issued a position statement on the use of placebos in pain medicine, stating that the deceptive (intentional) use of placebo is unethical.\textsuperscript{106,107}

The statement pointed out that the “beneficence” or “benevolent deception”—the notion that the end (patient’s welfare) justifies the means (patients deception)—violates the patients’ right to know the truth, to consent, or to refuse the treatment. The document further argued that, although telling the truth about placebo reduces expectations that are at the heart of the placebo effect, no study has demonstrated that patients’ outcomes are improved by placebo. As no further statement on the use of placebo was made in this document, by implication one must assume that the American Pain Society does not see any scientific rationale for the use of meaning response or context effect in clinical practice.

The argument that no study has demonstrated that patients’ outcomes are improved by placebo is not quite correct. The studies of McRae and Bausell mentioned above showed that the sham surgery (placebo) had a significant effect in patients’ quality of life, motor functioning, and pain level of the study participants.\textsuperscript{40,116}

The study of Benedetti in 2003 showed that placebo enhanced the effectiveness of a powerful analgesic such as morphine.\textsuperscript{109} Other studies have shown that maximizing patients’ expectations can lead to reduction of drug intake and maintenance of clinical effect.\textsuperscript{63,119} The statement of the American Pain Society addresses only one aspect of the use of placebo in clinical practice, namely the “deceptive” (intentional) use of placebo. As the intention of a physician is to help the patient and not to deceive, addressing the problem as “intentional” vs. “unintentional” seems to be unhelpful. It would be more useful to address the problem from another perspective: administration of “placebo” (use of a substance without any effect) vs. using the “meaning response” or the “context effect” to enhance the effect of an effective treatment. In the first case, literature has shown that the use of “pure placebo” is unethical and could potentially result in “placebo sag.” In the second case, it is probably unethical not to use the “meaning response” or the “context effect” to enhance the effectiveness of an active and proven treatment. Again, note how the use of the term “meaning response” helps to make this important distinction, thus liberating placebo phenomenon from the label “quackery.” Applying the new terminology seems to clarify some of the ethical problems related to the use of this phenomenon. Hopefully, it will encourage clinicians to make use of this powerful phenomenon for the benefit of their patients.

**Therapeutic Dialogue**

Placebo research not only emphasizes the crucial role of nonspecific effects of treatment (context) and expectations in the outcome of a treatment, but also offers a means as to how to make use of the nonspecific effects of treatment and expectations in order to increase the placebo response and the effect of therapy. There are a number of ways in which the expectancies could be increased. Wickramasekera showed that several aspects of medical setting such as the credibility of the therapist, the credibility of the therapeutic setting, the credibility of the treatment per se, the credibility of the administrative ritual, and the nature of the relationship between the patient and the therapist might affect what patient perceives as credible.\textsuperscript{54} The importance of a therapist’s reputation and the therapeutic setting has been shown in different studies.\textsuperscript{5,117,120} For instance, pain clinics and
their staff are likely to have superior face validity for patients with chronic pain. The importance of the credibility of treatment per se has been stressed by other authors.

Early research has shown that the most important expectancies are probably related to the nature of patient–physician relationship, physician’s attitudes and behaviors toward the patient, and the enthusiasm for the treatment being recommended. New research presented in this review has shed additional light on the neurobiology of the doctor–patient relationship and the mechanism on how the appropriate words could activate the endogenous opioids or dopamine systems thus improving the outcome of treatment. A close interaction between the physician and his or her patient is likely the best way to enhance the perception of the treatment that is being provided and improve the outcomes. Therefore, every effort should be made to inform patients as to what is going on and what to expect from the treatment.

The expectancy theory claims that expectations are individually shaped, suggesting that a thorough assessment of each patient’s past interaction with medical system and patient’s expectations of a specific treatment would help physicians to better tailor their treatment for that particular patient. Naturally, the maximization of expectations should fall within best evidence for the particular treatment to avoid extension of any ethical boundaries. Moreover, although physicians should strive to enhance the patient’s knowledge about a therapy, research has shown that this is advantageous only when the therapy is given. If the therapy has to be interrupted, it may have the opposite effect. For example, in one study, an open interruption of morphine produced a greater worsening of symptoms than a hidden interruption. One should keep in mind that the expectation of worsening of the symptoms may create a nocebo effect thus reducing the efficacy of treatment.

In summary, the context effect or meaning response can be very powerful and this phenomenon should not be ignored by modern medicine. To quote Biller-Andorno, “Given the considerable populations of patients that medicine cannot provide with a cure nor with sufficient symptom reduction like chronic pain patients, it may well be that medicine cannot afford to simply neglect the therapeutic potential of the placebo effect.” It was already mentioned here that the magnitude of placebo analgesic effect across all individuals is 2 out of 10 on a visual analog scale. As Price in 2001 put it “the pharmaceutical industry would go to the ends of the earth to make improvements of this magnitude.” All it might take for the physician would be to add one or two sentences to each proven treatment that he or she is prescribing. Telling the patient that the drug is known to produce a powerful pain relief would not be a lie and could enhance the placebo response among patients.

CONCLUSIONS

Ample research shows that the context of treatment plays an important role in the treatment outcome. Although placebo may be an inert substance per se, it is administered within this context and carries a meaning. Therefore, the potential for developing a “meaning response” or a “context effect” exists with any treatment given in this context. The magnitude and the duration of this response can be quite remarkable.

Conditioning theory suggests that placebo response represents a form of classical conditioning that is based on learning through association. Expectancy theory postulates that placebo response is related to patients’ expectations of improvement, which are connected to the changes that take place. While expectation is a conscious process, human conditioning is assumed not to involve cognition; therefore, it is inevitable and occurs without the individual knowing it. Both conditioning and expectancy are largely learned through patients’ past contact with the medical system.

From pain medicine, we have learned that endogenous opioid release is likely the biological mechanism by which conscious expectations are mediated. On the other hand, the expectation of reward seems to trigger a placebo response that, at least in part, is mediated by dopamine. It is likely that the opioid and dopamine system are interconnected and may work together in producing the analgesic effect.

With regard to the definitions related to placebo phenomenon, we believe that the use of terms “meaning response” and “context effect” are more appropriate and could clarify many misconceptions that surround the placebo phenomenon. We hope that the new terminology will encourage medical practitioners not to see this phenomenon as a “deceit” but as a powerful ally in enhancing the outcomes of their treatment. In this article, we have used these two terms interchangeably although we realize that they are not exactly the same. We will leave it up to future research to further define these terms.

Recent development in placebo theory and mechanism offers an excellent basis for new hypothesis gener-
eration and testing. It has implications for both research and clinical practice. From the research perspective, the new knowledge has cast doubts on the appropriateness of the double-blind placebo-controlled design in assessing efficacy of treatment. From the clinical perspective, recent research supports the idea that meaning response or context effect could be used as a therapeutic tool to enhance the effect of the treatment. We believe that medical practitioners, researchers, ethicists, and society itself need to reopen the discussion on the use of placebo in clinical practice. We hope that this review will stimulate such a discussion. It will be a challenge for the modern medicine to find ways to integrate the placebo concept and make constructive use of it in an ethically acceptable manner. In fact, this whole field of placebo research is a challenging one. Even so, placebo research represents an excellent model that could allow us to understand the amazing interaction of mind and body and is therefore a challenge worth the effort.

The results of the studies presented here show that practitioners’ words could have a powerful effect on the expectations and the meaning of a therapy leading to neurobiological changes in human body that could enhance the healing process. Therefore, ignoring this aspect of medical treatment is a scientific error. As Moerman stated in the 11th World Congress on Pain in 2005, “To withhold from our patients the healing powers of their own body is unethical. I contend that we cannot avoid manipulating meaning, and thereby inducing a ‘meaning response,’ so we had better understand it and get it right, rather than evade and avoid one of the most powerful forces in medicine.”

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