

# Chapter 11

## Importance of Placebo Effect in Pain Management

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### Introduction

The word placebo is derived from the Latin verb “to please” and, as early as 1811, appeared in the Hooper’s Medical Dictionary as a medical treatment aimed at pleasing – a placebo was defined as “an epithet given to any medication adopted more to please than to benefit the patient (Hooper 1817).” In the modern day era, Tilburt et al. refer to the placebo effect as “positive clinical outcomes caused by a treatment that is not attributable to its known physical properties or mechanism of action (Tilburt et al. 2008).”

Despite the lack of specific action of the placebo on the condition being treated, the placebo often provides benefit. In 1955, Henry Beecher, the first chairman of anesthesia at Massachusetts General Hospital, published a seminal article, “The Powerful Placebo,” in which he observed a high rate of response to placebo administration. In this article, he observed, “It is evident that placebos have a high degree of therapeutic effectiveness in treating subjective responses, decided improvement, interpreted under the unknown technique as a real therapeutic effect, being produced in  $35.2 \pm 2.2\%$  of cases (Beecher 1955).” Beecher observed this high degree of therapeutic effectiveness across a variety of clinical conditions, the breadth of which has been confirmed in subsequent scientific trials (Table 11.1). Since its publication, Beecher’s article has become one of the most cited analyses of the powerful therapeutic effect of the placebo.

In recent years, however, the magnitude of the placebo effect has been questioned. Even the results of Beecher’s landmark article have been criticized because none of the studies he referenced was properly controlled. In fact, recent reviewers have concluded that in fact no evidence of placebo effect could be found in any of the original studies cited by him (Kiene 1997). Nevertheless, the use of the placebo continues to be ubiquitous in clinical medicine today, both as a clinical intervention and as a research tool.

### Mechanism for the Placebo Effect

Several theories have been proposed for the mechanism of the placebo effect.

**Table 11.1** Partial list of conditions in which the placebo effect has been shown to be effective.

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ADHD  
 Anxiety  
 Asthma  
 BPH  
 Chronic fatigue  
 Crohn's disease  
 Depression  
 Epilepsy  
 Erectile dysfunction  
 Ulcers  
 Headache  
 CHF  
 Hypertension  
 Nausea  
 Pain  
 Parkinson's  
 Psoriatic arthritis  
 Reflux  
 Ulcerative colitis  
 Multiple sclerosis

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ADHD = attention-deficit hyperactivity disorder,  
 BPH = benign prostatic hyperplasia,  
 CHF = congestive heart failure.

### **Cognitive Theory (Expectation Theory)**

The cognitive theory states that patient expectations are critical in the placebo response. The administration of a placebo creates an expectation of a certain response, and the expectation of this response creates a biological effect. The mechanisms whereby expectancies might produce biological effects are many. They include (1) a reduction in anxiety which could aid immune system functioning, (2) changes in cognition or coping mechanisms, or (3) changes in behavior that would improve health outcomes (Stewart-Williams and Podd 2004). Patient expectations can be quite specific, and studies have shown that expectations of pain relief in particular body parts lead to the expected effect in that body part alone (Benedetti et al. 1999, Montgomery and Kirsch 1996).

### **Conditioning Theory**

The classic example of conditioning theory is the Pavlovian experiment on dogs, in which administration of food was paired with the ringing of a bell. Over time, the ringing of the bell alone would produce salivation in the dogs. In this experiment, a neutral stimulus (the bell) paired with an unconditional stimulus (food) elicited an unconditioned response (salivation). Over time, the neutral stimulus alone elicited a response similar to the unconditional response and became a conditioned stimulus capable of eliciting a conditioned response (salivation). With respect to the placebo effect, the placebo drug represents the conditioned stimulus, and the beneficial effect is the conditioned response.

The biological effects of conditioning can be profound and varied. For instance, in 1975, Ader and Cohen showed that a flavoring agent administered with an immunosuppressant produced profound immune suppression. After conditioning, the administration of the flavoring agent alone decreased the immune response (Ader and Cohen 1975). In 1973, Laska and Sunshine demonstrated a similar conditioning response to pain medication. In their study, patients were first given analgesics at different strengths, and subjects experienced pain relief in proportion to the strength of pain medication administered. Later, patients were instead given a placebo medication. Those patients who had experienced greater pain relief from the higher strength analgesic during the first arm of the study reported greater pain relief with the administration of the placebo. In effect, the patients' prior analgesic experience predicted the efficacy of the placebo (Laska and Sunshine 1973).

### Endogenous Opioids

The transmission of endogenous opioids may be responsible for placebo analgesia by fostering pain suppression. Using molecular imaging techniques, Zubieta et al. examined the activity of the endogenous opioid system in patients with chronic pain. They found that placebo agents could activate regional opioid neurotransmission, and this activation correlated with lower pain ratings (Zubieta et al. 2005). To further test this mechanism, Levine et al. examined whether an opioid antagonist, naloxone, could block placebo-induced pain relief. They found that among the subset of patients whose pain improved with placebo administration, the added administration of naloxone inhibited the pain relief (Levine et al. 1978). This suggests that placebo-induced analgesia was mediated by the release of endogenous opioids.

## Placebo Characteristics

### Active Agents and Specific Therapeutic Benefit

The specific therapeutic benefit of an active agent is the difference in efficacy between an active agent and a placebo. The overall clinical benefit of the active agent is therefore the sum of the benefit from the specific therapeutic effect of the active agent and the benefit from the placebo effect. Because of this, active agents will usually have an efficacy greater than that of a placebo.

### The Response to Placebo

In his landmark paper on the power of the placebo, Beecher found that the number of patients who responded to a placebo varied between 15 and 53% (Beecher 1955). Other investigators examining such various diseases as headaches, low back pain, and angina have even reported response rates higher than 50%. The oft-cited statement that the response rate to placebo is 30% likely derives from the average of Beecher's original observations.

These figures, however, represent the average of many individual placebo responses and do not indicate how each member of the group responds. One might imagine all members of the group responding equally well or in contrast, some members responding extremely well, and other members not responding at all, with a group response average of 30%. Levine et al. demonstrated this concept in a study of pain following tooth extraction. When given placebo medication, he found that 39% of the patients had some response to the placebo while 61% had no response at all (Levine et al. 1979). Thus, he was able to categorize individual patients as "placebo responders" or "placebo non-responders."

Predicting which individuals would respond to placebo administration becomes important, but this information is difficult to identify. Various studies have determined that intelligence or susceptibility poorly predicts the response to placebo. Furthermore, gender has been shown to be a poor predictor of placebo response, and there have been varied results in attempting to link personality traits with placebo response. In addition, people who respond to placebo in one setting may not respond in another setting (Oken 2008, Harrington 1997). However, adherence to a placebo regimen has been shown to be predictive of high placebo response (Horwitz et al. 1990).

### **Perceived Effects and True Effects from Placebo Agents**

In quantifying the placebo effect during a clinical trial, it is important to understand that this effect is composed of multiple components. To better understand these components, consider a clinical trial that compares three groups of patients: those treated with an active agent, those treated with a placebo agent, and those receiving no treatment. As discussed earlier, the specific therapeutic benefit of the active drug is the difference in efficacy between the active drug and the placebo. Similarly, the specific effect of the placebo is the difference in efficacy between the placebo group and the untreated group. This specific effect of the placebo itself is called the "true placebo effect." In contrast, the overall efficacy of the placebo is defined as the "perceived placebo effect (Ernst and Resch 1995)."

The increased efficacy seen in the perceived placebo effect compared to that measured in the true placebo effect results from several factors. First, the symptoms of a disease may change over time, so the natural history of the disease itself may contribute to the perceived placebo effect. For instance, it is well known that acute episodes of low back pain often significantly resolve within 4–6 weeks. A clinical trial comparing an active agent against a placebo during this time period would demonstrate a large perceived placebo effect, when in fact the improvement in clinical symptoms would likely be expected from understanding that acute low back pain is usually self-resolving.

A second contributor to the perceived placebo effect is the change over time in measured symptoms of a disease due to biologic fluctuation. In fact, many biologic variables such as temperature, blood pressure, and heart rate fluctuate around a mean value, and over time these values will show statistical regression to the mean value. Clinical trials will often enroll patients above a defined measured variable, such as a blood pressure. A certain percentage of patients with high blood pressure at the time of enrollment will often have mean blood pressures that are much lower than the cutoff, but are selected into the trial because of the biologic variability. Over time, the measured blood pressure will show regression to the mean and contribute to the perceived placebo benefit.

Finally, the perceived placebo benefit is potentially increased by any beneficial factor that would change over the course of the clinical trial. For instance, the skill of an individual doctor might increase over time in a way that lessens disease progression. Similarly, characteristics of the patient might change over time. For example, a patient with "white coat hypertension" might become more comfortable after repeated office visits over the course of a trial, with a subsequent decline in measured blood pressure. Each of these examples would contribute to the perceived placebo effect, but would not affect the true placebo effect (Ernst and Resch 1995).



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## Nocebo Effect

In addition to beneficial side effects from the placebo, patients may also experience unwanted side effects such as headache, fatigue, or drowsiness. These harmful effects are termed *nocebo* effects. In 2002, Barsky et al. conducted a literature search of articles related to non-specific medication side effects, and they identified several factors associated with increased *nocebo* effect. These factors included patient expectation of adverse effects before beginning therapy, prior experiences of medication consumption leading to adverse symptoms, psychological co-morbidity such as depression or anxiety, and other situational factors. Patients who suffer from chronic pain are often characterized by several of these factors and are thereby at increased risk for *nocebo* effects (Barsky et al. 2002).

## Placebo Sag

After patients have experienced numerous treatment failures, they often exhibit a decrease in placebo response rate. This phenomenon is termed *placebo sag* and is frequently seen in chronic pain patients who have failed numerous therapies. Conversely, in patients who have had treatment successes, the placebo effect may be enhanced with further intervention. Over time, the placebo sag often proves particularly problematic in chronic pain patients because the overall effect of therapeutic medicines declines when the non-specific placebo component of the therapy inevitably sags.

## Placebos and Procedures

The placebo response can also be evident with procedures and medical devices. A particularly powerful example of the effect of placebo was published in the *New England Journal of Medicine* in 1959. For the 20 years prior to this article, angina had been treated by ligation of the internal mammary artery, under the assumption that blood flow to the myocardium could be increased. However, Cobb et al. showed that patients who were anesthetized and received sham incisions fared just as well as those with the real procedure. In fact, studies showed that both interventions could produce significant (70%) decrease in angina and increase in exercise tolerance (Cobb et al. 1959). This study conclusively demonstrated that procedures could have a powerful placebo effect.

On occasion, the placebo effect from an invasive procedure can be even more powerful than the placebo effect from medication. In 2006, Kaptchuk et al. examined the effects of sham acupuncture compared to a sham pill on patients with arm pain due to repetitive stress injury. They found that over the course of the trial, improvement in pain score and symptom severity scale increased in the group receiving sham acupuncture more than in the group receiving the sham pill (Kaptchuk et al. 2006).

## Active Placebo

Although placebo agents are often chosen in blinded clinical trials because they do not have clinical effects, patients may be able to differentiate placebo from active drug and thereby unblind the study. To make this awareness difficult, active placebos may be used. An active placebo is a drug that has no effect on the condition being treated but does simulate medical therapy, often through other side effects. For instance, consider a trial investigating chemotherapeutic agents, which often have known side effects of nausea and vomiting. An

active agent would have no specific therapeutic effect on the patient's cancer, but would provoke nausea and vomiting.

### The Placebo as a Therapeutic Intervention

Employing the placebo effect as a therapeutic intervention is controversial. Some clinicians argue that the benefits of the placebo effect might be quite useful in treating patients with conditions that are refractory to standard medical therapy. Others argue that the use of a placebo in the guise of therapy is deceptive, unethical practice and undermines the physician-patient relationship of trust.

Nevertheless, it appears that nationwide the practice of prescribing placebo treatments is quite pervasive. In 2009, Tilburt et al. published the results of a survey of 1200 internists and rheumatologists in the United States regarding their attitudes toward placebo therapy (Tilburt et al. 2008). Over 60% of respondents agreed that it is permissible to prescribe placebo therapy primarily to promote patients' expectations. When then queried if this permissive attitude toward prescribing placebo treatment applied to clinical practice, almost half of all respondents stated that they had recommended placebo treatment for patients at least once in the past year. Moreover, when placebo treatments were prescribed, 68% of prescribers described the proposed therapy as "medicine not typically used for your condition but might benefit you."

Interestingly, the authors found that the type of placebo prescribed was varied, but that purely inert substances such as sugar pills or saline were prescribed less than 5% of the time. The most frequently prescribed placebo treatments included multivitamins and over-the-counter analgesics. Alarming, more than one-quarter of prescribed placebo treatments were sedatives or antibiotics – medicines with potentially deleterious effects. Thus, practice patterns alone suggest that using the placebo effect as a therapeutic intervention is quite widespread.

Given the ubiquitous nature of placebo treatment in clinical practice, determining the beneficial effect of this form of therapy is paramount. Clearly this task is difficult. As noted earlier, since the publication of Beecher's landmark article, "The Powerful Placebo," the placebo effect has been reported to be effective in 30–40% of cases. However, differentiating the improvement in a clinical condition due to the placebo itself, as opposed to improvement due to the natural course of the disease or other factors, is challenging.

In 2001, Hróbjartsson et al. attempted to answer the question of whether placebo treatment conferred therapeutic benefit by systematically reviewing 130 clinical trials in which patients were assigned to either placebo or no treatment. They looked at the difference in outcome between the placebo and the no-treatment groups, rather than looking at the effect of the intervention arm of each trial. The underlying disease processes in each trial were diverse and involved 40 clinical conditions, such as asthma, schizophrenia, and chronic pain syndromes. In their analysis, they found no significant placebo effect in trials with binary outcomes, either subjective or objectively measured, nor in trials with continuous, objective outcomes. However, they did find a significant difference in trials with continuous subjective outcomes and in trials where pain was investigated (Hróbjartsson and Gøtzsche 2001). The authors acknowledged several limitations to their study, including the inability to blind the untreated group, the effects of reporting bias, and the inability to assess the effects of the physician-patient relationship independent from the placebo itself. Moreover, critics contend

The second school of thought argues that the current therapy for a particular condition must always act as the control group in a clinical trial if it is effective. Furthermore, they argue that withholding active treatment from the control group is unethical. Using this logic, new drugs would be tested only compared to standard therapies, not to placebo. This school of thought is supported by language within the Declaration of Helsinki, a set of ethical principles for human experimentation developed by the World Medical Association. Within this document it states, "The benefits, risks, burdens, and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of the placebo, or no treatment, in studies where no proven prophylactic, diagnostic, or therapeutic method exists (World Medical Association Declaration 2000)."

However, Emanuel et al. highlight several problems with the mandated use of active controls in every clinical trial. In some cases, the discomfort or harm suffered by a patient is relatively minor and an inert placebo would cause little harm, and so forcing a clinical trial using standard therapy would not be ethically necessary. For instance, the use of a sugar pill as the control instead of celecoxib in a trial exploring treatments for chronic low back pain would not cause undue and irreparable harm. Furthermore, patients receiving placebo therapy do receive clinical attention, and this may lead to clinical improvement irrespective of the efficacy of any pharmacologic intervention. Finally, they argue that clinical trials comparing an investigational drug against standard therapy require a larger number of participants than trials using placebo. This arises because the difference in clinical effect is likely larger in the placebo-controlled trial, so researchers need a fewer number of patients in order to demonstrate a difference. In effect, a greater number of patients would be exposed to known or unknown harmful side effects of a drug in a trial using standard therapy as a control.

Consequently, an emerging consensus opinion suggests that placebo-controlled trials may be conducted ethically with certain caveats and protections in place – such as rigorous oversight and observation, exclusion of patients at increased risk for harm, limitation of the placebo period to the minimum required, and clear disclosure to the participants. In spite of this, Huston et al. feel that proponents of the policy proposed by the Helsinki Document have trouble accepting these arguments altogether or any ethical justifications for placebo-controlled trials (Huston et al. 2001). However, they also concede that proven treatment would be withheld in both placebo arms and investigational drug arms, and sometimes patients in placebo arms fare better than those patients who did not enroll in the trial at all.

In evaluating the ethics of placebo-controlled trials, placebo surgery deserves special consideration. In 1959, Cobb et al. showed no improvement in angina symptoms from ligation of the internal mammary artery when compared to sham operations. Since then, ethicists have debated whether the risks of placebo surgery outweigh the benefits. In a 2002 article in the *New England Journal of Medicine*, Horng et al. argue that trials involving placebo-controlled surgery can and must fulfill three criteria in order to be considered ethical: the trials must minimize the risk of the procedure and demonstrate that the control for the placebo surgery is necessary for validity of the test; the trials must justify the risks by showing that the risks of the placebo arm are minimal; finally, the trials must demonstrate that adequate informed consent has been obtained (Horng et al. 2002). Placebo-controlled surgeries have met and continue to meet these criteria.



therapy for a particular condition is effective. Furthermore, they argue it is unethical. Using this logic, new medicines, not to placebo. This school of thought is from Helsinki, a set of ethical principles from the World Medical Association. Within this school, the effectiveness of a new method should be evaluated against known, diagnostic, and therapeutic methods. However, in studies where no proven procedure exists, the World Medical Association Declaration

prohibits the mandated use of active control or harm suffered by a patient in a clinical trial, and so forcing a clinical trial on a patient is unethical. For instance, the use of a sugar pill as a placebo for chronic low back pain is unethical. In patients receiving placebo, there is no therapeutic improvement irrespective of the placebo effect. They argue that clinical trials comparing a larger number of participants to a smaller number of patients in order to achieve statistical significance would be exposed to known standard therapy as a control.

They also argue that placebo-controlled trials are unethical in place – such as rigorous monitoring, increased risk for harm, limitation on disclosure to the participants. A policy proposed by the Helsinki Declaration is that any ethical justifications for using placebo also concede that proven treatments exist, and sometimes patients who did not enroll in the trial at all. Therefore, placebo surgery deserves special consideration. Angina symptoms from ligation of coronary arteries. Since then, ethicists have argued for the benefits. In a 2002 article in the *New England Journal of Medicine*, the authors considered ethical: the trials must be controlled for the placebo surgery by showing that the risks of the placebo surgery are not greater than the risks of the controlled surgeries have met and

## Conclusion

The placebo effect can be profound. As a clinician, it is important to recognize the power of this effect, both in clinical practice and as a comparison group in controlled trials. The fiduciary trust that connects patients to their doctors demands that all clinicians consider placebo in a way that furthers the well-being of each individual patient.

## Case Scenario

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After injuring his back from lifting a piece of furniture, James, a 42-year-old man, is urged to take a multivitamin by his primary care doctor following a clinic appointment. Although the patient does not believe that the multivitamin will help, he reports a 50% pain relief in his follow-up visit 4 weeks later. The patient attributes this reduction to the multivitamin.

*What could be the best possible explanation for the pain reduction?*

The decrease in pain was likely due to the natural history of lower back pain: within 4–6 weeks, the symptoms from acute-onset back pain often resolve spontaneously. The perceived “placebo effect” accounts for improvements due to the natural history of the disease. The true placebo effect is the specific difference in effect observed in a trial of multivitamins for back pain patients, with some patients taking no medication and some patients taking multivitamins. This would control for any resolution of symptoms due to disease improvement. The specific therapeutic effect of the drug did not account for the observed degree of pain relief, since there is little evidence or biologic plausibility that vitamins could decrease back pain in such a short time.

*Which theory of placebo action would best explain any pain relief that he experiences due to the placebo effect?*

The cognitive theory of the placebo effect states that the expectations of the patient play an important role in the efficacy of the placebo, which is applicable to James. The conditioning theory would be applicable if he had previously experienced success with neuraxial blocks and subsequently responded favorably to the current procedure because of his previous successes. The endogenous opioid theory could explain his pain relief, but it is not the best answer.

Several weeks later, James develops postherpetic neuralgia and is prescribed a lidocaine patch. He is now complaining of nausea and vomiting, in addition to a moderate fatigue.

*Which effect would best describe his symptoms?*

The patient is suffering from a nocebo effect from the lidocaine patch: these symptoms are probably not related to the specific pharmaceutical action of the lidocaine



**patch itself.** If these effects helped to decrease his pain, the effects would be considered specific therapeutic drug effects or placebo effects. However, since the effects are undesirable, they are either side effects from the medication (not a choice) or nocebo effects.

Ten years later, James develops hypertension and stable angina which are well controlled with lisinopril and metoprolol and sees you regularly to manage his conditions. He would like you to consider him for a placebo-controlled clinical trial for angina. When he is not compliant with his medication regimen, his anginal symptoms escalate. As part of the trial, he would need to stop his current medication regimen.

*Which consideration would make it unethical for James to participate in the trial?*

**When conducting a placebo-controlled trial, it is important to ensure that several ethical considerations are fulfilled.** In this case, the patient suffers from unstable angina when his medications are discontinued. **Therefore, the risk to the patient would be high, and enrolling him in placebo-controlled trial and discontinuing his medications would not be ethical.** Clearly, there is a scientific rationale for improving the care of angina, and there is nothing in the vignette to suggest that the patient could not be monitored closely or would not be able to give informed consent.

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