The Importance of Placebo Effects in Pain Treatment and Research

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Objective.—To estimate the importance and implications of placebo effects in pain treatment and research from the existing literature, with emphasis on their magnitude and duration, the conditions influencing them, and proposed explanations.

Data Sources.—English-language articles and books identified through MEDLINE (1980 through 1993) and PsycLIT (1967 through 1993) database searching, bibliography review, and expert consultation.

Study Selection.—Articles were included if they pertained to the review objectives.

Results.—Placebo response rates vary greatly and are frequently much higher than the often-cited one third. Placebos have time-effect curves, and peak, cumulative, and carryover effects similar to those of active medications. As with medication, surgery can produce substantial placebo effects, and this possibility is commonly overlooked in case series reports on back surgery. Individuals are not consistent in their placebo responses, and a placebo-responder personality has not been identified. Models advanced to explain placebo effects emphasize the role of anxiety, expectations, and learning.

Conclusions.—Placebo effects influence patient outcomes after any treatment, including surgery, that the clinician and patient believe is effective. Placebo effects plus disease natural history and regression to the mean can result in high rates of good outcomes, which may be misattributed to specific treatment effects. The true causes of improvements in pain after treatment remain unknown in the absence of independently evaluated randomized controlled trials.

(*JAMA*. 1994;271:1609-1614)

TWO questions are of major interest to clinicians and researchers with respect to pain treatments: What is the efficacy of a specific treatment (under what conditions and for what patients will it improve certain dimensions of outcome), and why do patients improve with it (what is the mechanism)? There are three general reasons for clinical improvement in a patient's condition.

1. Natural history and regression to the mean. Most acute and some chronic pain problems resolve on their own irrespective of treatment.[1] Many individuals have recurrent episodes of pain such as headache or low back pain, interspersed with no or minimal pain. Patients with chronic conditions typically have fluctuating symptoms and seek medical care (and enroll in research studies) when symptoms are at their worst. Thus, the next change is likely to be an improvement. This tendency of extreme symptoms or findings to return toward the individual's more typical state is known as regression to the mean.[2] Apparent improvement may also reflect measurement error or random variation in patient symptoms over time.[2]

2. Specific effects of treatment, attributable to the characteristic content of the intervention.

3. Nonspecific effects of treatment, attributable to factors other than specific active components. These include physician attention, interest, and concern in a healing setting; patient and physician expectations of treatment effects; the reputation, expense, and impressiveness of the treatment; and characteristics of the setting that influence patients to report improvement. The term *placebo effect* is often used synonymously with *nonspecific effects*.

It is helpful for clinicians to know the contributions of each of these processes to treatment effects in order to make optimal treatment decisions. It is also essential for investigators to understand the extent to which placebo effects can account for improvements observed in clinical studies. The purpose of this article is to review the literature on placebo effects, with an emphasis on their magnitude and duration, the conditions influencing them, proposed explanations, and their implications for pain treatment research. Although this article pertains to pain problems in general, low back pain is used frequently as a specific example because it is highly prevalent, costly, and a leading reason for seeking health care.

METHODS

To identify relevant English-language articles for this review, the MEDLINE

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bibliographic database (1980 through 1993) and the PsycLIT database (1967 through 1993) were searched using the term *placebo effect*. The MEDLINE search yielded 163 articles, and the PsycLIT search yielded 41 articles (nine of which were also found in MEDLINE). Additional articles and books were identified from personal files, bibliography reviews, and requests to professionals with expertise in the area. Three books and 75 articles were read for this review.

RESULTS

Definitions

A placebo is an intervention designed to simulate medical therapy, but not believed (by the investigator or clinician) to be a specific therapy for the target condition.[3] It is used either for its psychological effect or to eliminate observer bias in an experimental setting.[3] Alternatively, it could be a treatment now believed to be inefficacious, though believed efficacious at the time of use.[3] A placebo effect is a change in a patient's illness attributable to the symbolic import of a treatment rather than a specific pharmacologic or physiological property.[3] Thus, a placebo effect does not require a placebo. A placebo response refers to any change in patient behavior or condition following the administration of a placebo.[4] The literature does not always use these distinctions, and there are many misconceptions, including the following beliefs: (1) about one third of patients will have a placebo response in any clinical trial; (2) placebo effects are necessarily brief; (3) certain personality types are more likely to be placebo responders; (4) placebo responders had nothing wrong with them to begin with; and (5) giving a placebo is the same as doing nothing.

Placebo Effects of Medical Treatments

The widely accepted one-third placebo response rate is based on the classic article by Beecher.[5] This was a review of 15 studies of patients suffering a variety of conditions (postoperative pain, cough, angina pectoris, headache, drug-induced mood changes, seasickness, anxiety and tension, and common cold). On average, symptoms were "satisfactorily relieved" by the placebo in 35% of patients in these studies, but the placebo response rate ranged from 15% to 58%. Wide variation in placebo response rates has since been observed in other settings as well. The Table shows examples of response rates after sham treatments for painful conditions and in studies of treatments initially considered efficacious but later shown to be no better than placebo. The combined results for the treatments reviewed by Roberts et al[6] that were originally believed efficacious but later abandoned averaged 70% excellent or good outcomes, presumably reflecting placebo and natural history effects. Sham treatments can also produce excellent results. For example, 64% of patients who underwent a sham tooth-grinding procedure for myofascial pain dysfunction (temporomandibular disorder) reported total or near-total symptom remission.[9]

In sum, rates of good patient outcomes after treatments that have no specific therapeutic effects vary considerably across studies, but are strikingly high on average. Even patients with a long history of back pain show clinically and statistically significant improvement with placebo. Deyo et al[10,11] found that scores on measures of pain severity, pain frequency, and functional status improved, on average, 20% to 40% after patients with back pain received sham transcutaneous electrical nerve stimulation plus hot packs, despite the chronicity of their pain (average duration, 4 years).

Placebo Effects of Surgery

Beecher[12] emphasized that surgery could evoke a placebo effect and urged caution in interpreting the benefit of new operations. Similarly, Spiro[13(p42)] wrote that "skeptics have long noted that an operation, particularly a new one, seems to bring benefit for several years until it is reevaluated and then often abandoned." He noted that new operations are often associated with a new diagnostic device yielding information that is interpreted as explaining a pain problem. Attempts are then made to correct the problem by operations or drugs. Spiro suggested that the experience of surgery and the symbol of the scar must themselves be important sources of pain relief.

In the 1950s, there were two double-blind randomized trials of internal mammary artery ligation vs skin incision (with vessel exposure but no ligation) for patients with angina pectoris.[7,8] At the time, internal mammary artery ligation was believed to help angina pectoris by increasing coronary artery blood flow through increased collateral circulation. As summarized in the Table, these studies demonstrated substantial and sustained improvement in angina after skin incision alone.

Placebo effects of back surgery are suggested by Spangfort's[14] review of long-term outcomes of 2504 diskectomies for lumbar disk disease. Complete relief of sciatica was noted in 37% and complete relief of back pain in 43% of patients who had no disk herniation (negative surgical exploration). There is no known therapeutic effect of surgical exploration of the lumbar spine; changes in patient status were most likely attributable to placebo effect and natural history.

The success rates after sham or discredited procedures may be compared to the success rates in spine surgery case series. Across 74 studies of surgery for lumbar spinal stenosis, an average of 64% of patients had good or excellent outcomes.[15] Similarly, 68% of patients had good or excellent results among 47 studies of lumbar spinal fusion.[16] These figures reflect outcomes reported at long-term follow-up; the absence of randomized controlled trials precludes the interpretation of the outcomes as resulting from specific surgery effects as opposed to placebo effects plus natural history. However, the figures are similar to the average 70% excellent or good outcomes for several abandoned medical and surgical therapies.[6]

In sum, nonspecific influences plus natural history and regression to the mean play an important role in pain relief after surgery. Important nonspecific influences likely include subjects' and surgeons' expectations of improvement. This situation with respect to low back surgery is highlighted further by the weak association between imaging test results and symptoms,[1,17-21] and between technical success of surgery (eg, solid fusion) and symptom improvement.[22,23]

Pharmacokinetics of Placebo Response

Placebos have demonstrable time-effect curves and peak, cumulative (greater effects with repeated administrations), and carryover effects after cessation of treatment, which mimic those of active medications.[24] When varying doses of analgesic followed by a placebo are administered, patients' placebo responses correspond in degree of pain relief over time to their original dosage of analgesic.[25] Dose-response effects have also been demonstrated; for example, two placebo capsules were shown to have more pronounced effects than one.[26]

Placebos are associated with side effects, especially drowsiness, headaches, nervousness, insomnia, nausea, and constipation.[27] Perceptual characteristics of drug preparations play a role in individuals' responses. Larger capsules tend to be viewed as stronger, yellow capsules tend to be perceived as stimulants or antidepressants, and white capsules tend to be perceived as analgesics or narcotics.[28] Injections may produce larger effects than do pills.[26]

The duration of response to placebos has not been studied extensively. Patients with painful diabetic neuropathy who re-

Placebo Effects in Studies of Medical and Surgical Treatments for Painful Conditions

Source	Condition	Treatment(s)	% Improved	Comments
Roberts et al[6] (review of treatments originally believed efficacious but later found to be ineffective)	Herpes simplex virus infections	Levamisole*	85% excellent or good	Average across uncontrolled trials that asserted the efficacy of levamisole
		Photodynamic inactivation treatment*	85%-100% excellent or good	Average across 5 uncontrolled trials
		Topical application of organic solvents*	83% excellent or good	Average across 5 uncontrolled trials
	Duodenal ulcers	Gastric freezing*	98%-100% marked or complete relief	Results in initial studies
			65% good/excellent	Average across 8 studies that asserted the efficacy of gastric freezing
Cobb et al[7]	Angina pectoris	Internal mammary artery ligation	63% significant improvement, 34% decrease in nitroglycerine use	During first 6 mo after surgery
		Skin incision only	56% significant improvement, 42% decrease in nitroglycerine use	
Dimond et al[8]	Angina pectoris	Internal mammary artery ligation	After surgery, 100% improved	During year after surgery, 69% reported over 50% improvement in angina
		Skin incision only	After surgery, 100% improved in exercise tolerance, nitroglycerine use, and angina	During year after surgery, 100% reported over 50% improvement in angina
Goodman et al[9]	Myofascial pain dysfunction (temporomandibular disorder)	Sham tooth-grinding	64% total or near-total symptom remission	

*Treatment subsequently found to be no better than placebo in controlled trials.

ceived a placebo reported a decrease in pain intensity for the first 3 weeks, followed by a partial return toward baseline levels during the next 3 weeks.[29] Clinically significant improvement in angina symptoms was maintained as long as 1 year after sham surgery.[8] These studies do not allow for a separation of placebo from natural history effects.

Nocebo Effects

Nonspecific influences of treatments may produce adverse effects, sometimes referred to as "nocebo effects." The overall incidence of adverse events in healthy volunteers during placebo administration was 19% in a review of 109 double-blind drug trials.[30] Placebos can also make preexisting symptoms worse. For example, in a double-blind study[31] of a magnetic device for which pain-relieving qualities were claimed, 13 of 58 pain patient subjects discontinued treatment after one or two treatments because their pain was worse. Six months later, three of these patients believed the treatment made their pain permanently worse. Placebos can also produce pain in normal subjects. Headaches were reported by 70% of students told that a (nonexistent) electric current was passing through their heads.[32]

Very little research has focused on negative nonspecific influences in medicine. One general practitioner randomly assigned his patients who had symptoms but no abnormal signs and in whom no definite diagnosis could be made to a positive or a negative encounter with him.[33] In the positive encounter, patients were given a diagnosis and told they would be better in a few days. In the negative encounter, the doctor told patients he was not certain what was the matter with them. Two weeks later, 64% of the positive group, but only 39% of the negative group, reported that they had gotten better (P=.001). The author speculated that these minor illnesses would be expected to resolve spontaneously by 2 weeks in the majority of patients, and that the 61% nonimprovement rate in the negative encounter group reflected adverse effects of the encounter.

FACTORS INFLUENCING PLACEBO RESPONSES

Patient Factors

Efforts to identify personality, demographic, and other characteristics that predict placebo responses have had little success.[34] In fact, individuals tend not to be consistent about showing placebo responses across placebo administrations.[35,36] However, patient expectations of treatment effects clearly influence their responses. For example, when subjects were given a pill containing only a magnet to measure stomach contractions, the contractions increased, decreased, or did not change according to the effects they were told the pill would cause.[37] In asthmatic patients, isotonic saline produced increases or decreases in airway resistance according to what patients were told to expect.[38] Further, when patients were given a true bronchodilator, its effects were about twice as great if patients were told it would produce this effect than if they were told it would produce the opposite effect. The patient's positive attitude toward the provider and toward the treatment have been shown to predict improvement in studies of psychiatric outpatients treated with placebo, psychotropic drugs, or psychotherapy.[34] There is also some evidence that highly anxious subjects show the greatest placebo responses.[34]

Highly compliant patients may have better outcomes than noncompliant patients, even when complying with a placebo. In a randomized trial to evaluate the efficacy of lipid-lowering drugs in the therapy of coronary heart disease, patients in the placebo arm were divided between those who were highly compliant (took at least 80% of placebo capsules) and those who were less compliant (took less than 80% of capsules).[39] Even after controlling for 40 known or suspected coronary risk factors, the placebo noncompliers had a 5-year mortality rate 57% higher than that of the compliers. We may hypothesize that placebo effects had some effect on mortality, or that patient compliance related to other characteristics associated with mortality, but not assessed in the study.

Provider Factors

The provider's warmth, friendliness, interest, sympathy, empathy, prestige, and positive attitude toward the patient and toward the treatment are associated with positive effects of placebos as well as of active treatments.[34] The importance of provider expectations was illustrated in a study of a new antihypertensive drug.[40] In the middle of this double-blind study, partners of the enthusiastic physician administering the drug broke the code. Without telling him which pills were the placebo and which were the drug, they told him that the drug, though effective, appeared similar to existing

drugs. Although less enthusiastic, they decided to complete the study. The difference between the drug and placebo was maintained, but there was an immediate and marked increase in the blood pressures of both groups.

In a double-blind study of dental extractions,[41] placebo responses were compared for patients in two groups: those whose clinicians knew they would administer a narcotic analgesic, a placebo, or a narcotic antagonist vs those whose clinicians knew they would administer only a placebo or narcotic antagonist. Placebo patients in the first group had significantly less pain. Because the two placebo groups differed only in the clinicians' knowledge of the range of possible treatments, this knowledge seems to have resulted in subtle behaviors that influenced patient responses.

EXPLANATIONS FOR PLACEBO EFFECTS

Decreased Anxiety

Stress and anxiety adversely affect several physiological processes and increase symptom reporting. Placebos seem to be most effective for highly anxious subjects, and placebo effects are often attributed to anxiety reduction and associated decreased suffering.[42] Placebos have been shown to decrease anticipatory anxiety.[43] However, it is not clear whether anxiety reduction is a cause of the placebo effect, or a component of it.[44]

Expectations

There are several possible explanations for how subject and researcher or clinician expectancies influence placebo effects. A patient's expectation that treatment will relieve symptoms may reduce anxiety and thus ameliorate symptoms. Expectancy of improvement may result in the patient's viewing the pain problem more positively and as more controllable. Thus, patients may be more likely to notice small improvements, to disregard negative events, and to interpret ambiguous stimuli favorably.[45] Changes in appraisals and expectancies may lead to beneficial behavior changes. For example, a low back pain patient may resume physical and functional activities he or she had avoided because of fear of pain or harm.

Learning

Treatment may have a positive effect because of its association with effective treatments the patient has had before (this learning process is referred to as conditioning). Thus, inert or neutral drugs, procedures, people, and places can come to function as conditioned stimuli or discriminative stimuli for the alleviation of symptoms, if they have been associated repeatedly with powerful unconditioned stimuli (eg, penicillin, nitroglycerine, analgesics) that reliably relieve symptoms.[46] Further, neutral stimuli (eg, the physician, the physical examination, and medication prescription) associated with the reduction of unpleasant symptoms may acquire positive conditioned properties for healing and anxiety reduction.

Experiments have demonstrated that placebo responses can be conditioned.[47] Furthermore, the direct experience of conditioning appears to be more powerful than expectancy formed through verbal persuasion.[48] Past treatment responses may influence a patient's responses to subsequent treatments in a positive or negative manner, depending on the prior history. This raises one possible explanation of why repeated back surgery yields progressively poorer results and sometimes makes patients worse rather than better.[49]

Endorphin Effects

It has been suggested that placebo responses may be mediated by endogenous opiate release in the central nervous system.[50] However, subsequent studies have yielded contradictory results, and the role of endogenous opiate processes is unclear at present.[42,51,52]

Conclusions

These models are not mutually exclusive, and each of these factors may play a role in placebo effects. In fact, Roberts[53] has argued persuasively for dropping the term *placebo* altogether. The understanding of placebo effects may be advanced by studies undertaken to examine the variety of potential influences other than specific treatment effects on patient outcomes, including natural history, regression to the mean, patient expectations, provider expectations, characteristics of the treatment situation that influence patients and physicians to behave in certain ways (eg, to report improvement), conditioning, and psychophysiological states such as anxiety and relaxation.[53]

IMPLICATIONS FOR RESEARCH DESIGN

Placebo effects are found with drugs, medical treatments, surgery, biofeedback, psychotherapy, and even diagnostic tests.[46,54] Thus, placebo effects can play a role in all interactions between provider and patient. Only independently evaluated (ie, not by the treating clinicians, and preferably by observers unaware of the treatment assignment) randomized controlled trials can establish an effect of a treatment above and beyond natural history of the condition and nonspecific effects. Random assignment of patients to treatment and control conditions is essential to reduce systematic bias in group membership, which may lead to differential improvement attributable to differences in patient characteristics rather than in the treatment. However, even in randomized controlled trials, physician and patient know there is a sham treatment and a real treatment, and outcomes are influenced by their expectancies and beliefs about which treatment the patient received. If either or both can guess (eg, by side effects) which treatment the patient received, or if one treatment is more credible, this may bias the study results. To the extent that the patient or clinician believes a treatment may be ineffective, the power of nonspecific effects will be reduced or underestimated.

Therefore, the control treatment in a trial should be as similar as possible to the active treatment, to create similar expectations. Patients receiving sham therapy should have visit frequency, contact, and support equivalent to that in the active therapy condition. It can be difficult to create placebo controls that appear to be active treatments, but creative placebos have been devised (eg, sham transcutaneous electrical nerve stimulation, the use of misplaced needling as a control for acupuncture, the use of subtherapeutic weight as a control for traction, and the use of massage as a control for spinal manipulation). Trials in which control treatments mimic the active intervention typically have found less advantage of the active treatment over the control than have trials with obviously different types of therapy or with inert placebo controls.[55,56]

A completely untreated group (eg, waiting list) is not the same as a placebo-treated group. A waiting list condition controls for the effects of the passage of time, but not for patient expectations. However, an untreated group condition in addition to a placebo group can help distinguish nonspecific effects from natural history. For chronic conditions, long baselines with multiple measures of the outcome variable before treatment can reveal changes in the absence of treatment and thereby help to estimate the magnitude of regression to the mean as a source of within-patient change.[57,58]

Ethical and practical factors make it difficult to conduct surgery trials with sham controls. For situations in which it is not possible to have a sham surgery control condition, randomized trials of surgery vs credible alternative nonsurgical therapies may be feasible, as has been done with coronary artery bypass surgery[59] and diskectomy.[60]

IMPLICATIONS FOR CLINICIANS

The administration of any treatment, including surgery, has physiological and psychological effects on the patient, and these are interrelated. There are placebo effects whenever the patient and the clinician perceive the treatment as effective. These effects can be potent and can lead to erroneous claims of efficacy for any type of treatment. These effects are likely to be strongest when the patient is anxious, the physician is perceived as having great expertise, the patient and physician believe the treatment is powerful, and the treatment is impressive and expensive. Placebo effects act synergistically with active treatment effects and natural history to influence patient outcomes. Physicians should use these nonspecific effects to their (and their patients') advantage. However, it is a gross error to use a placebo to assess whether a patient's pain or disease is "real," and to dismiss or delegitimize the complaint on the basis of a placebo response.

Physicians who use inactive treatments in the hopes of producing positive placebo effects run several risks. Patients may feel deceived if they discover they have been treated with a placebo. The placebo can produce adverse reactions. Failure to improve as expected may cause the patient to view his or her problem as more serious, and the patient may consequently become more concerned about it.[45] Failure to improve may also increase the risk of not improving with subsequent treatments.

Some patients with chronic pain may fail to respond to a treatment that is effective for other patients. This may be especially likely, due to previous learning experiences, if the patient previously responded poorly to different treatments, including those that were, unknown to the physician, no more than placebos. These patients may also be influenced by psychosocial, economic, and other factors that cause them to continue to fail additional treatments.

CONCLUSIONS

In most pain treatment and research situations, nonspecific effects of treatment are underestimated, and patient improvement is likely regardless of treatment. Nonspecific effects, natural history, and regression to the mean must be distinguished from specific effects when medical and surgical treatments are evaluated. It cannot be assumed that a treatment whose response rate is more than one third is better than placebo. The extent to which patient outcomes after a medical or surgical treatment reflect nonspecific effects, regression to the mean, natural history, or specific treatment effects is unclear in the absence of randomized controlled trials with outcomes assessed by persons blind to the patient's treatment. Our reviews[15,16,61] of the published literature on the treatment of low back pain have repeatedly found that few, if any, of the articles suggest that outcomes could be attributable to natural history or nonspecific effects. These effects are likely to be substantial, may be sustained over long periods of time, and may explain some or all of the benefits attributed to treatment. There are important implications for research and clinical training in all areas of medicine. The quality of the interaction between the physician and patient can be extremely influential in patient outcomes, and, in some (perhaps many) cases, patient and provider expectations and interactions may be more important than specific treatments.

Analysis and interpretation of placebo-related findings brings us to consider the nature of illness and disease and the relationships between body processes and the environment. Confusion and uncertainty among physicians and other health care professionals about placebo effects suggest an inadequate appreciation of the interaction of body processes with past experience, anticipated events, and immediate environmental influences. Further, the body's capacity to modulate symptoms and suffering involves more than simply "psychological factors," where those are seen as traits or personality characteristics. Symptoms, illness, and their changes over time reflect complex interactions between anatomical and neurophysiological processes, on the one hand, and cognitive-behavioral and environmental factors on the other. The findings reviewed herein support the thesis that these factors are inextricably intertwined.

This project was supported by grant HS 06344 from the Agency for Health Care Policy and Research (the Back Pain Outcome Assessment Team) and the Health Services Research and Development Field Program, Seattle (Wash) Veterans Affairs Medical Center.

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