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The placebo effect: Why we should care

Francisco Tausk, MD[a,b,*], Robert Ader, PhD[b], Nana Duffy (Smith), MD, MSCE[a]

[a]*Department of Dermatology University of Rochester School of Medicine and Dentistry, Box 697, Rochester, NY 14642, USA*
[b]*Department Psychiatry, University of Rochester School of Medicine and Dentistry, 601 Elmwood Av, Rochester, NY 14642, USA*

Abstract Contrary to its definition, a placebo is far from an inert substance but carries meaningful responses that can mediate significant outcome results in pharmacotherapeutic studies. The advent of detailed studies and modern imaging techniques have provided the basis to understand the underlying mechanisms of the placebo effect, as well as its localization to determined brain centers. Designing clinical trials using principles of classical conditioning to mediate placebo effects may enhance treatment outcomes and provide novel pharmacotherapeutic modalities.

Introduction

Medical therapeutics until the late 1800s have been mostly the history of placebos; that is, interventions that have no specific therapeutic effect for a given disease. Voltaire summed it up as: "The art of medicine consists of amusing the patient while nature cures the disease." The definition of a *placebo effect* is the improvement of a disease after the administration of an "inert" intervention.

Since Beecher's landmark report of a 30% placebo effect in clinical trials,[1] this concept became generalized in popular and academic beliefs. Subsequently, a number of studies have shown that this effect may vary between 0% and 100%. The incorporation of placebo arms in pharmacotherapeutic studies appeared to validate the concept that nonspecific effects could modify the outcome of medical interventions. If the placebo arm merely measures the natural course of a disease, regression to the mean, washout of previous treatments, or the patient's feeling of being cared for, a no-treatment attention arm would suffice.

Unfortunately, the medical field has been reluctant to accept the notion that a placebo is more than an inert substance, relegating it to mere anecdotal observations and discussions, despite being a required clinical trial arm to obtain U.S. Food and Drug Administration approval for a novel drug. The last decade has seen a significant increase in studies directed at the understanding of the nature of its effects and the brain centers involved in placebos, as well as their putative application in pharmacotherapeutics and the every day practice of medicine.

The current theoretic explanations underlying this phenomenon include expectancy, classical conditioning, and meaning response. Although these three aspects are presented separately, all three overlap significantly.

Expectancy

This term describes the belief or "expectation" that a given treatment will be effective. We need to differentiate the effects of a placebo in clinical research, where research subjects are informed that they may receive "real" or "sham" treatment from what occurs during a therapeutic intervention, where patients are told that they are receiving the appropriate therapy for their ailments, because the conditions of their expectations will differ significantly.

The belief and expectation of the health provider are also very different in these two situations. How much of the beneficial effect of a drug is due to its pharmacologic

* Corresponding author.
E-mail address: francisco_tausk@URMC.Rochetser.edu (F. Tausk).

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effects and how much to a placebo response is difficult to measure. A number of studies have attempted to address this issue. One contribution[2] examined the outcome of published studies that reported the effects of interventions that were deemed to be significantly beneficial by patients and physicians at the time they were used. For example, of 6931 individuals treated with glomectomies for asthma or photodynamic therapy for herpetic infections, approximately 70% had good-to-excellent results. When subsequent controlled trials showed these treatments to have no benefit, they were rapidly abandoned. This suggests that when doctors and patients believed that these interventions were beneficial, they were effective.

In the 1950s, angina pectoris was significantly improved by ligation of the internal mammary artery (supposedly increasing the blood supply to the heart) or the implantation of this artery into the myocardium.[3] Thousands of patients were operated on with success rates of up to 91%.[4] This result suggested high treatment efficiency, but these interventions were discontinued when a sham incision without ligation was shown to result in identical improvement.[5,6]

In other examples, postoperative patients required significantly less administration of the analgesic buprenorphine when they were deceptively informed that they were receiving a very powerful pain killer compared with patients who were administered the same drug but were not given any specific information.[7] A similar study showed that patients who purposely were shown analgesics being administered required significantly less medication than those that did not see it being delivered.[8]

In a study that examined hypnosis as a treatment for psoriasis, highly hypnotizable participants were given general suggestions of well-being or specific suggestions that they were receiving a treatment that each individual believed would resolve the psoriasis. Only the latter group experienced a significant improvement.[9]

The explanation of the placebo effect goes beyond the mere expectation of patients but seems to also involve expectations of the providers.

In an elegant study, 60 patients were scheduled for molar extractions.[10] Patients were given postoperative intravenous saline, and all received the information that they were being administered fentanyl, naloxone, or placebo These agents would respectively alleviate, exacerbate, or have no effect on their postoperative pain. The clinicians that administered the pain questionnaire and the medication were misled to believe that one group of patients was being administered naloxone or placebo and no fentanyl analgesia; they were told that the second cohort of patients was additionally randomized to also receive fentanyl or the other two interventions. Those in the first group rated the pain suffered as significantly higher than those in the second group. Of interest is that the only difference between the two groups of patients was not *their* expectations, which were identical, but the expectations of the health providers. The authors concluded, "the knowledge of the clinicians may result in subtle behaviors that influence patient responsiveness to a possible analgesic manipulation."[10]

Classical conditioning

In 1927, Pavlov[11] described how physiologic responses could be elicited after a period of conditioning. In this case, he paired repeatedly an unconditioned stimulus (food) with a conditioned stimulus (sound) until the latter evoked the same physiologic response (salivation). He also noticed that without the unconditioned stimulus, the conditioned stimulus elicited less and less salivation, leading to the concept of "extinction"; however, this could be reversed if the animals were re-exposed to the unconditioned stimulus. Investigators from Pavlov's laboratory subsequently showed that this paradigm could be used to modify a variety of immune responses. Translated to the clinical environment, a drug (unconditioned stimulus) is administered within the environmental context of the rituals surrounding its administration; these could be the place where the medication is administered and by whom, the color, shape, scent, and taste of the drug (conditioned stimuli).

Repeated pairing of the unconditioned stimulus (drug) and the conditioned (sensorial) stimuli eventually enables the conditioned stimulus to elicit a conditioned response, that is, a physiologic response that approximates the one elicited by the unconditioned stimulus. Thus, the response to an inert or therapeutically irrelevant substance or placebo becomes a conditioned response. The entire ritual surrounding drug treatment can become a conditioned stimulus by virtue of the repeated association of such neutral cues with active drug administration throughout the patient's life.

Pharmacologic clinical trials are designed basically with only two arms: the experimental one, in which participants are administered an active drug, and a control arm, where patients receive a placebo consisting of a similar intervention except that the active ingredient is substituted by an inert substance.[12] No matter how the dose, route of administration, frequency, or duration of treatment may vary, experimental subjects receive medication that is invariably followed (reinforced) by the unconditioned effects of the drug (a continuous or 100% reinforcement schedule). In contrast, control subjects who engage in the same behaviors under the same environmental conditions and receive placebo medication are never therapeutically reinforced; they are on a 0% reinforcement schedule. As a result, the placebo effect is reinforced in subjects in the active drug arm every time they take the drug, and this effect is absent in those randomized to the placebo group (receiving only an inert substance). Only a few studies have evaluated placebo effects by introducing varying reinforcement schedules such as interspersing placebo with active drug.[13,14]

Although numerous animal studies have corroborated the notion of placebo as a learned pharmacologic response,

very few human studies have been conducted in this area. More than 35 years ago,[15] the therapeutic response to placebo or aspirin was shown to be a function of the order in which they were administered. The pain-alleviating response to aspirin was seen in approximately 63% of subjects, whereas it occurred in approximately 21% of those who received placebo. After a *first* dose of aspirin (unconditioned stimulus), 41% of participants who subsequently were treated with placebo (conditioned stimulus) had an analgesic response. This study suggested that when individuals were exposed to the active drug first, a conditioning effect occurred, such that when exposed to subsequent inert pills, many of them responded as if they were receiving active drug.

More recently, volunteers who were administered cyclosporine in association with gustatory, olfactory, and visual cues by taking the drug with a distinctly flavored drink showed a significant reduction of interferon-γ and interleukin-2 messenger RNA as well as protein secretion. After a washout period during which the values returned to normal, the participants were given a placebo combined with the distinctly flavored drink, and the messenger RNA and protein values of interferon-γ and interleukin-2 decreased to the same levels as seen when they were administered cyclosporine.[16] Similar results in human studies have been reported for conditioned cyclophosphamide-induced leukopenia,[17] allergic reactions[18] conditioning of the effects of antihistamines,[19] and behaviorally conditioned secretion of cortisol and growth hormone.[20]

The effects of classical conditioning in the pharmacotherapy of psoriasis were recently studied using a colored and odoriferous ointment containing active steroid or vehicle.[14] All participants received the active drug until the target plaque cleared. Subsequently, they were randomized to continue receiving the active drug, the active drug interspersed with placebo 25% of the time, or receive continuously 25% of active drug (the control group). Those in the first two groups remained free of lesions, whereas those in the latter group relapsed. Another study of placebo and pain showed that four exposures to the conditioning paradigm (pairing unconditioned with conditioned stimuli) were sufficient to induce a long-lasting placebo effect.[21]

In summary, a number of studies have shown that applying classical conditioning to the dosing of medications can mimic the effects of continuous, active drug administration; however, this principle only applies to interventions that somehow engage the central or peripheral nervous system, alone or in interactions with the immune or endocrine systems. In diseases that require replacement therapy, such as type 1 diabetes or drugs that have direct toxicity on a cell or microorganism, one would not expect learned placebo response. Animal[22] and human[23] studies have identified neurobiologic mechanisms and brain structures that are involved in mediating such effects.

Meaning response

A placebo is, by definition, inert and by itself should not have any beneficial effect for any disease. Its use in clinical studies should not provide any additional benefit over a no-treatment arm where the patients are given the same health provider attention as in the active arm, but withholding any medical intervention. In this scenario, the natural evolution of the disease, regression to the mean, washout of prior treatments, and beneficial effects of physician attention should be evenly distributed across treatment and control groups. Unfortunately, the administration of a placebo adds a different dimension, converting an inert intervention into one that is surrounded by various environmental, sensory, cultural, psychologic, and anamnesis qualities that are individual to each participant.

The physical environment where the treatment is administered; the smell, taste, form, and color of a tablet; the core beliefs of a participant's conception of a treatment; the cultural background of an individual; and the conscious or unconscious memory of prior interventions begin to exert a strong influence on the effects of a given medical intervention. It is the meaning that a patient experiences surrounding a treatment that will result in the size of placebo effects. For example, a meta-analysis of 117 double-blinded placebo-controlled clinical trials performed in various countries evaluating the effects of ranitidine and cimetidine showed that the effect of the placebo arm varied between 0% and almost 100%.[15]

In Chinese culture, the year of birth is associated with one of five phases, and each of these influences different organs in such a manner that it is believed that a Chinese person is more likely to die of a specific organ/disease, according to the year of birth. The causes of deaths of 28,169 Chinese Americans with 412,632 whites were compared.[24] The Chinese Americans with a disease that was associated to their birth year actually died significantly earlier from that disease than Chinese Americans who were born in a different year or to white individuals. Interestingly, higher effects were found in those individuals who had been born in China, which led the authors to infer that they probably had more knowledge and belief in Chinese astrology. If one could parse out those that had no knowledge of these customs, the effects might have been even more significant. "These differences in longevity (up to 6% or 7% difference in length of life) are not due to having Chinese genes but to having Chinese ideas, to knowing the world in Chinese ways. The effects of meaning on health and disease are not restricted to placebos . . . but permeate life." Other studies[25] also support the notion of the *meaning response.*

The placebo effect as a neurobiologic phenomenon

The advent of sensitive neural imaging instruments has allowed researchers to visualize for the first time cerebral

blood flow and neurotransmitter release during the administration of placebos. The first studies that shed light into this phenomenon were those that examined brain imaging, mostly in the form of positron emission tomography (scanning and functional magnetic resonance imaging to evaluate the activation of brain centers in response to the administration of placebos in the study of pain and Parkinson disease.

Individuals receiving opioids or placebo showed evidence of the activation of identical brain centers in the anterior cingulate cortex, orbitofrontal cortex, anterior insula, nucleus accumbens, and amygdala.[26] In another report,[27] a placebo intervention not only activated specific areas of the central nervous system but also led to the release of endogenous opioids. In an additional study,[28] patients with Parkinson disease were administered a placebo, and positron-emission tomography scanning showed significant amounts of dopamine had been secreted from the striatal area of the brain in those who responded to the intervention. More recently, this response has been shown to be directly proportional to the patient's expectation and beliefs in the success of the treatment.[29]

Patients with Alzheimer disease lose the capacity to respond to placebo interventions, supporting the notion that the cognitive damage impairs the placebo mechanism.[30] Intact prefrontal cerebral functioning is necessary for placebo effects to take place.

Discussion

Reviewing placebo phenomena raises a number of questions that need to be addressed to move the field forward.

First: *Does the placebo effect really exist?* In view of the literature, this question may seem out of place; however, many in the medical sciences seriously believe that placebos play no role whatsoever in pharmacotherapy and dismiss it as a quasi New Age stigma supported by those who wish to psychologize the biologic nature of human diseases with a mind–body discourse. The evidence that supports the notion that the placebo effect does not exist mostly relies on a landmark study,[31] "Is the Placebo Powerless?—An Analysis of Clinical Trials Comparing Placebo with No Treatment," in which the authors analyzed the data of 114 trials where there was an active arm, a placebo arm, and a no-treatment arm. The meticulous statistical analysis showed that there were no significant differences between placebo interventions and no treatments, thus finally debunking the "placebo myth." These findings have been reproduced and editorialized in many journals.[32]

Despite immaculate statistical analysis, the authors, unfortunately, omitted reporting in the published manuscript any information regarding the specific details of the studies on which their conclusions were based but chose to add them as appendixes accessible only through the Web site of The *New England Journal of Medicine.* Most of the studies they reviewed were of psychologic interventions in which placebo controls are difficult to implement, such as attention control, and leisure reading, compared with the active intervention. The authors only compared the results of outcome measures between placebo and no-treatment arms, but what they failed to note was that in most of those studies, *the active intervention was also unsuccessful.* If a therapeutic intervention does not have positive results, how can one expect them from the placebo control arm? This meta-analysis included many trials of patients with diseases such as orgasmic difficulties, enuresis, poor oral hygiene, infertility, marital strife, or even no particular diagnosis, all of which were combined.

Second: *Are placebos used appropriately in pharmacotherapeutic clinical trials?* For many years, the Food and Drug Administration required that new drugs be compared with a placebo arm (although this is currently being somewhat modified following the conclusions of the latest Helsinki accords). In crossover studies, the patients who originally receive placebo are later administered the active drug and vice versa; however, this kind of design is rarely used in dermatologic trials. For example, in randomized clinical trials of psoriasis published between 1977 and 2000, only three (1.2%) had a crossover design,[33] and current studies of biologicals only have a partial cross from placebo to active drug; furthermore, in current crossover designs, participants are made aware of the sequence of events (ie, active drug or placebo-washout-crossover). If one would want to measure the real placebo effect of an intervention, subjects would need to be started with active drug, and without their knowledge, be seamlessly transitioned to washout and crossed to a placebo arm.

This concept has been highlighted by a recent report[34] that showed that only those participants exposed first to an active intervention would subsequently respond to a placebo, therefore the sequence is critical in determining the outcome of an intervention. By avoiding the underlying *conditioned* mechanism of placebos, clinical trials can understate the effects of the placebo, and overstate the effects of the active intervention. If patients received *first* the active medication, and associated its effects to the rituals surrounding a medical intervention, and after sufficient exposures, subsequently received a placebo under identical conditions, the outcome measures of the placebo arm could be much higher than a no treatment arm, and approximate the effects of the active drug.

Pharmaceutical companies rarely disclose the contents of the placebo they use. A recently published analysis showed that only 9.3% of trials using orally administered placebos disclosed their composition,[35] and that the content of the placebo (supposedly inert by definition) in many instances contained substances that could alter the results of outcome measures in a positive or negative manner. On occasions, oral solutions of drugs have a very different distinct taste when compared with the placebo solution provided by the

pharmaceutical manufacturer for the purpose of a clinical trial (unpublished observation).

In addition, the placebo effect in a clinical trial environment, in which participants are informed that they may receive the active drug that may or may not help them or a "dummy pill," is very different from the clinical setting, in which a patient is prescribed a drug presented in a positive manner by the physician. One would expect a much higher placebo effect in the latter situation, but demonstrating this would entail an ethical dilemma. As discussed subsequently, one would have to design a study in which patients are first exposed to the active drug, and then crossed over to placebo *without* disclosing this change to the patient until the trial has concluded.

To evaluate conditioning effects, one needs to account for the "extinction" aspect of classical (Pavlovian) conditioning. After a number of exposures to the placebo, in the absence of active intervention, a person will stop responding, unless he or she is re-exposed to the active drug. That is, the learned effect of pairing an active intervention with sensorial (conditioned) stimulus is lost unless it is reinforced by reintroducing the active intervention.[21] Translated to the clinical therapeutic setting, this would mean that patients could be treated with active drug (of a determined color, odor, and taste) until they showed improvement of their disease. At that point, having established the learning (ie, pairing) period, they could be introduced to receiving a placebo as long as the placebo effect was reinforced by periodic exposure to the active drug. For example, a patient could at this point receive a bottle (in the case of tablets) of which 25% of tablets contain the active drug and 75% of identical-appearing tablets are the placebo.

Third: *What role does expectancy play in clinical trials?* We have discussed previously the *meaning response* and how cultural environment and beliefs may influence clinical responses. A study[36] examined the role of expectancy by enrolling 864 patients in a randomized controlled trial of acupuncture compared with sham acupuncture for ameliorating pain. They observed that participants who believed in acupuncture and had high expectations regarding the intervention had significant improvement compared with those who had low expectations, regardless of being assigned to the active or sham intervention. These results support the numerous reports suggesting that the perception of being in an active or placebo experimental arm correlate better with outcome measures than the actual assignment itself,[7,37-40] even in studies evaluating surgical interventions.[41]

Should we care?

If our role as physicians is to heal our patients, we should learn to harness the power of the placebo effect, because there is no more effective placebo than the health provider himself or herself. We practice it every day in our choice of words, the tone of voice, the demeanor, and the power of modifying the perceptions of patients who find themselves in a relatively helpless position. For example, a study compared the perception of patients regarding the length of the interaction when their doctors remained standing or sat down during the visit. Although all physicians spent the same allotted time in the room with the patients, the latter believed that when the doctors sat down, they had spent significantly more time with them.[42]

Investigators in a recent study administered pain-provoking heat to volunteers, who rated the pain level. Subsequently, unbeknownst to the subjects, they administered a rapid acting opioid that decreased their discomfort. When the participants were then told that the analgesic was going to be started, their pain perception decreased significantly more. Although the analgesic was administered continuously, when the investigators subsequently deceptively informed the subjects that it had been stopped, their pain ratings increased markedly, almost canceling the effect of the opioid.

Brain imaging has also showed that the expectation of increased pain activated centers associated with mood and anxiety.[43] This report lends further support to the power of physicians' words, as summarized in the accompanying editorial:

> These clues about how our beliefs can affect the way we experience medical treatment for pain can improve the practice of medicine. A drug with a true biological effect may appear to be ineffective to a patient conditioned to expect failure, whether the patient is enrolled in a clinical trial or treated in a physician's office. Patient education about treatments can help counteract this problem by shaping beliefs to maximize drug effectiveness.[44]

Conclusions

Beyond the physician's role, is there a place for pharmacologic placebo interventions in the modern medical armamentarium? Animal studies definitely support this notion, where, capitalizing on classical conditioning, active drugs can be interspersed with placebos, reducing side effects and resulting in the same outcome as those receiving full active medication.[13] Now that the neurobiologic pathways of placebo effects have been uncovered, it is time to investigate their application to human diseases,[12,45] as well as to design clinical pharmacotherapeutic trials that reflect more appropriately the outcomes of a placebo intervention instead of attempting to minimize it. Further research on the placebo effect is needed to better understand this tool so that it can be used for the benefit of our patients.

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