

The Power of the Placebo

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The placebo is much more than a control medicine in a clinical trial. The placebo response is the largest component of any allergy treatment and consists of two components: nonspecific effects (eg, natural recovery) and a “true placebo effect” that is the psychological therapeutic effect of the treatment. Belief in the beneficial nature of the treatment is a key component of the true placebo effect, and can be enhanced by factors such as interaction with the physician and the sensory impact of the treatment. Negative beliefs can generate a nocebo effect that may explain some psychogenic illnesses; this is the basis of much research in psychoneuroimmunology. An understanding of the placebo and nocebo effects is important for general allergy practice, and harnessing the power of the true placebo effect is a major challenge to modern medicine.

Introduction

If a placebo treatment consists of an inert tablet, how is it possible for it to have any effect on the patient? The idea of a “placebo effect” seems illogical. The term “placebo” has a special meaning in clinical trials because it refers to an inert tablet or sham treatment that is used as a control for comparison with an “active” treatment that is under investigation, or in a wider sense the therapeutic effect of any form of treatment that depends on the patient’s belief in the treatment rather than on any physical or pharmacological properties of the treatment (eg, faith healing, prayer). The use of the term “placebo” for a medicine that “pleases” the patient relates to an older Latin word meaning “to please.”

The placebo-controlled clinical trial was first used in the latter half of the 20th century as a means of demonstrating the efficacy of medicines in the treatment of disease. Before the introduction of placebo-controlled clinical trials, physicians judged the efficacy of medicines solely on the basis that the treatments made their patients

better. This was a problem! Virtually any medicine could be shown to make the patient feel better; moreover, because the severity of disease often declined spontaneously due to natural healing, it was impossible to separate medicines with specific immunological or pharmacological effects from those with only nonspecific effects unrelated to the disease under treatment.

Patients felt better after seeing a physician, and they often felt much better after receiving some form of medicine or treatment. Physicians who prescribed powerful medicines or treatments were in demand. In the 18th and 19th centuries most of the treatments (eg, bleeding, cupping, and the administration of emetics and purgatives) had positive nonspecific effects on the patient, but little if any specific effect on the course of the disease. Fortunately, many patients returned to health after seeing a physician, and the physician could claim responsibility for a “cure” and demand a fee. The 1899 edition of *Merck’s Manual of the Materia Medica* lists 92 treatments for asthma, including ammonia vapor, antimony, cannabis, chloroform, creosote, and hyoscine. The sensory impact of the medicine (eg, its foul taste, or psychopharmacological effect) may be important for its placebo effect rather than any specific effect on the airway. In the long list of early treatments, only the anticholinergics are used today for treatment of asthma. With advances in organic chemistry, immunology, and pharmacology at the start of the 20th century, new medicines began to replace the herbal medicines, folk remedies, and patent medicines that had evolved over hundreds of years. The placebo-controlled clinical trial was used to demonstrate the clinical efficacy of these new medicines and the lack of efficacy of numerous old remedies that were no more effective than a placebo.

The placebo effect has now become an active area of research, rather than simply a control treatment, and there is much interest in harnessing the placebo effect for the treatment of disease, rather than viewing the placebo effect as a nuisance in clinical trials [1]. The number of publications on the placebo effect has increased fivefold in the last 20 years, and there are several mainstream medical text books on this topic [2–5]. The pendulum of scientific opinion has now swung from denigrating the placebo and the problematic placebo effect, to praising the placebo effect, and this has led to an increased interest in many forms of complementary therapy, such as acupuncture, aromatherapy, and homeopathy, and in treatments that

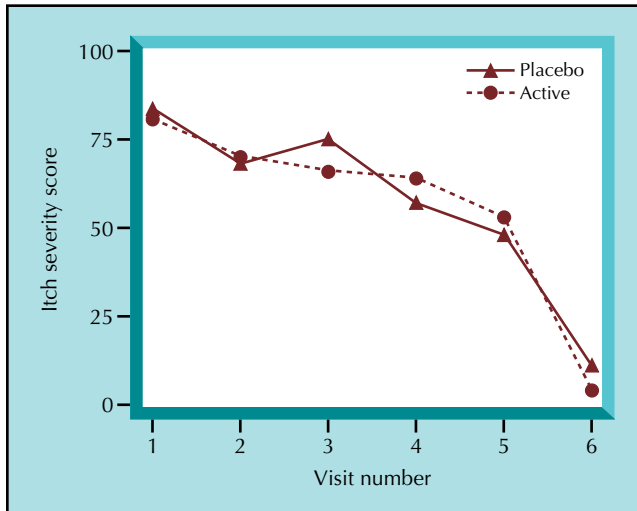


Figure 1. Mean itch severity scores after hyposensitization therapy to house dust mite showing no significant difference between active and placebo groups after six visits over 8 months. (Adapted from Glover and Atherton [7].)

rely solely on belief rather than any medical intervention, such as prayer [5].

This review discusses the effects of placebo treatment in the field of allergy, and demonstrates that every treatment provides some of its benefit by a placebo effect, which is often more powerful than any pharmacological effect of a medicine.

Placebo Response in Allergy

The treatment of allergic disease is a good field for the study of the effects of placebo treatments. In a paper in 1965 the occasional patient is described as enjoying coming in for a regular injection of allergy extract even though the physician believes this is solely a placebo treatment [6]. The powerful placebo effect of hyposensitization treatments using injections of small quantities of allergen still persists today and can be easily demonstrated in clinical trials. In a double-blind placebo-controlled trial of hyposensitization to house dust mite on 24 children with atopic eczema and immediate hypersensitivity to *Dermaphagoides pteronyssius*, a dramatic effect of placebo therapy was reported [7]. The mean itch severity scores for the study (Fig. 1) show that itching was almost abolished in both the active treatment group and the placebo group after six visits over an 8-month period. The investigators report that “a striking feature of our study was the magnitude of benefit seen in patients treated with placebo. There can be little question that this response was great enough to have concealed most of the additional therapeutic effect that might have resulted from active treatment.” They explain that the placebo effect may “be related to the physically unpleasant nature of the treatment and the rather ritualistic procedures involved in its administration, for example, the preparation of adrenaline, checking

of resuscitation equipment, and the close observation for the subsequent 2 hours.” It is interesting that only one child suffered an adverse reaction, with faintness and dizziness that was thought to be a systemic reaction to the injection; however, on emergency unblinding of the treatment it was found that the patient was being treated with placebo! Another interesting finding was that six patients in the placebo group and six in the active treatment group suffered redness, swelling, and local discomfort at the injection site for 1 or 2 days after each injection, demonstrating that the placebo can have physical as well as psychological effects.

The placebo response is not limited to injections, as it is usually a large component of any relatively innocuous therapy, such as antihistamine tablets. Figure 2 shows the changes in the rhinoconjunctivitis quality-of-life scores for patients with seasonal allergic rhinitis before and after 14 days of treatment with antihistamine (fexofenadine 120 mg or loratadine 10 mg) or placebo [8]. All three treatments caused a highly significant improvement in quality-of-life scores ($P < 0.0001$) when comparing baseline scores with the scores after 14 days. The important point to note from the figure is the magnitude of the placebo response and the small additional benefit provided by treatment with antihistamines. The mean change in the scores observed in the placebo group of 0.93 is well above a change of 0.5, which is considered of clinical importance and which would justify a change in the patient’s treatment in the absence of troublesome side effects or excessive cost [9]!

Components of the Placebo Response

To understand the nature of the placebo response, it must be first understood that even the active treatment effects shown in Figures 1 and 2 also include a placebo response. This is the basis of placebo control. If the change in symptom score associated with the placebo response is subtracted from the change in symptom score associated with the active treatment, then we are left with the “specific immunological or pharmacological effect” of the medicine. In the two examples shown, the immunological and pharmacological effects are minimal and the placebo effect is the major component of the treatment.

The overall response caused by the placebo is often termed the “perceived placebo effect” and this can be divided into two components: nonspecific effects and a “true placebo effect” [10,11]. Thus, any treatment such as injection with an allergen or oral antihistamine can be considered as consisting of three components: a specific immunological or pharmacological effect, nonspecific effects, and a true placebo effect.

Immunological or pharmacological effect

The immunological or pharmacological effect of treatment is related to the active ingredient of the medicine, such as allergen or antihistamine. The active ingredient

has a high affinity for a specific immunological or pharmacological receptor. Slight changes in the molecular structure of the active ingredient may have marked effects on its affinity with the receptor and its biological activity.

In clinical trials of allergy medicines, the immunological or pharmacological effect of the medicine is under investigation, and any other effects of the treatment are controlled by comparison with the effects of a placebo medication that is identical in appearance, color, taste, and so forth with the active medication but does not contain the active ingredient.

Nonspecific effects

“Sick people often get better.” Natural recovery from a disease may occur, and may be unrelated to any effect of the treatment. Spontaneous recovery may form a major component of the perceived placebo effect.

Patients recruited to a clinical trial to determine the efficacy of a treatment for allergic disease are screened to determine the severity of the allergic response, and only those patients with a high subjective score, and/or objective measure of allergy, are recruited for the study. By recruiting only those patients with severe or troublesome disease and excluding those patients with mild disease, the population of patients on the trial is skewed towards those with severe symptoms. In these circumstances, the symptom severity of the patients on the trial is unlikely to increase during the study, and it is more likely that the symptom severity will decrease due to the process of natural recovery. The mean measure of symptom severity is likely to decline during the course of the clinical trial and this statistical effect is often referred to as “regression to mean” [12].

True placebo effect

The true placebo effect is a component of the perceived placebo effect and refers to the psychological therapeutic effect of the treatment [10]. This will depend on many factors, such as the belief in the effectiveness of the treatment and the attitude of the patient towards the therapist. It is not possible to control for the effects of rest and spontaneous recovery in controlled clinical trials that involve only placebo and active treatment groups, as both these treatment groups will be affected by rest and recovery. However, if a “no-treatment” group is included in the trial design, then this will allow direct comparison with the placebo treatment group and any effect of placebo above the effect of no treatment can be deemed to be a “true placebo effect.” Very few clinical trials include a no-treatment group and the magnitude of the true placebo effect has rarely been measured [10,13].

The psychological therapeutic effect attributed to the true placebo effect of treatment is related to the patient’s belief about the efficacy of the medicine [5]. The true placebo effect may be explained in terms of interaction between nervous and immune systems with

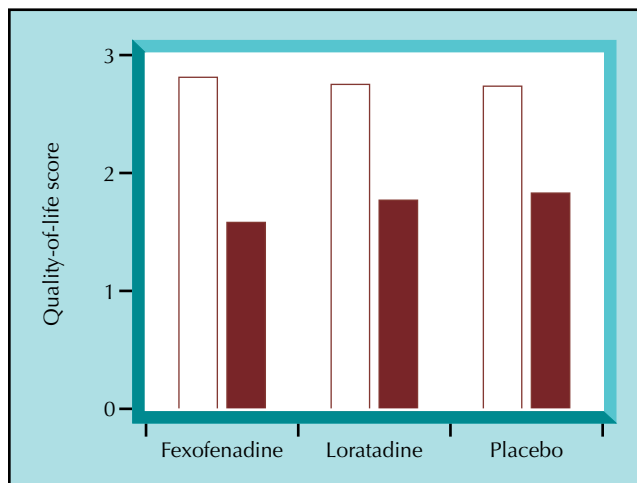


Figure 2. Mean changes in quality-of-life scores for patients with seasonal allergic rhinitis when treated with a single daily dose of fexofenadine (120 mg), loratadine (10 mg), or matched placebo tablet. The baseline scores are unfilled columns and the 14-day post-treatment scores are filled columns ($n = 639$), drawn from data in Van Cauwenberge et al. [8]. The changes from baseline were highly significant in all three treatment groups ($P < 0.0001$).

cognitive effects being important in humans. The true placebo effect of cough medicines and analgesics may be related to the generation of endogenous opioids [14]. The true placebo response of allergy treatments may be explained by psychoneuroimmunology, because there is a large and developing field of research in neurosciences and medicine that indicates the immune and endocrine systems are influenced by emotional states [15]. The basis of psychoneuroimmunology is that the mind and health are intertwined in a bidirectional manner [16•]. This rapidly developing field is accumulating evidence that the immune response can be modulated in many different ways by cognition and emotional state. Research in psychoneuroimmunology has focused on the negative effects of stress on the immune system [16•] and developed the thesis that acute stress may enhance the immune response whereas chronic stress down-regulates most measures of the immune response. It is likely that there will be much more interest in the positive effects of psychotherapy and the placebo effect in the future.

Positive and Negative Effects of Belief

The true placebo effect depends on a cognitive state in the patient and the belief that the treatment is beneficial. The degree of belief in the treatment will depend on many factors: healer-patient interaction; cultural beliefs about traditional treatments; environment in which the medicine is administered; properties of the medicine such as taste, color, and smell; advertising and claims made about the efficacy of the medicine; brand name of the medicine; and side effects associated with treatment that may reinforce the belief of efficacy. The placebo effect can be activated

merely by wishing oneself better or generating a feeling of remembered wellness [1].

The belief in the efficacy and action of the medicine may be influenced by factors such as the color of a tablet and the number of tablets. A group of medical students participated in a study on what they believed were two new medicines [17]. The students were divided into four groups and received either one or two red tablets, or one or two blue tablets. The students were not told the identity of the tablets but were asked to score sedative or stimulant effects. Those students taking blue tablets scored greater sedative effects whereas those taking red tablets scored greater stimulant effects. According to the students, the sedative or stimulant effects of two tablets were greater than those of one tablet. Unknown to the students, however, the medicines were inert placebo tablets without any sedative or stimulant pharmacology. This study demonstrates that, to the students, a blue color meant a sedative effect whereas a red color meant a stimulant effect. In general, red color tends to mean hot or danger in commonly used warning signs, whereas blue means cool or quiet, and these everyday concepts of what a color “means” may have influenced the students’ belief in the actions of the tablets.

The meaning of a belief in a treatment can also influence the outcome of an effect on the body. A harmful or negative “nocebo” effect is possible if the patient or subject believes that a procedure or treatment is harmful. The basis of the nocebo effect is that if the person believes they are going to become ill, then they will become ill. It is possible for patients in a clinical trial to experience adverse side effects of a placebo treatment, but these are placebo effects and not nocebo effects. What distinguishes the nocebo effect from the placebo effect is that the person has negative expectations and actually experiences a negative outcome. In this respect, both the placebo and nocebo effects depend on belief in a certain outcome. The most dramatic nocebo effects are those related to voodoo death. In some societies there is a belief that the voodoo practitioner can cause harm, and the effects of this belief can be fatal [18].

Less severe nocebo effects may be related to conditions such as hypochondria and psychogenic illness. Nocebo effects may occur as epidemics of mass hysteria when the belief that something harmful is going to happen rapidly affects a whole school or town. This form of mass hysteria nocebo effect has been reported to be triggered by factors such as the odor of a strange gas or an insect bite, and hundreds of persons may be affected simultaneously without any real cause being determined for the symptoms.

There are few scientific studies on the nocebo effect because of the ethical problems of inducing harmful effects. In one study on patients with asthma, the investigators reported that inhalation of saline triggered airway responses similar to those found with irritants and allergens, when the patients believed they were breathing these

noxious substances [19]. Relief from these symptoms was provided by inhalation of saline when the patients believed they were inhaling an active medicine to treat the airway symptoms. This experiment therefore demonstrates both nocebo and placebo effects in asthmatic patients.

Research on nocebo and placebo treatments is often limited by the degree that the investigators are able to induce a belief in a treatment. The fact that the investigators may need to deceive their patients in some way goes against the ethics of clinical research, and poses a dilemma to both investigators and the ethics committees that need to consider approval of this type of research.

Ethical Issues

In the past, physicians prescribed treatments to their patients that are now known to offer no specific immunological or pharmacological benefit, but they did this with a belief that the treatments were effective. The patients trusted and believed in the competence of their physician and believed that the treatments were beneficial. The treatments were no more than placebos, but they were administered without any intentional deception and provided benefit to the patients by means of a placebo effect. The modern physician is faced with a dilemma, because they know that placebo treatment may provide benefit but the deliberate deception of their patients is deemed unethical. One way around this problem is to recommend that the patient consult a practitioner of complementary medicine. In this case the practitioner of complementary therapy does believe in the treatment, and instills this belief in the patient, thereby enhancing the placebo effect of treatments such as aromatherapy. The use of complementary medicine has greatly increased over the last 10 to 20 years, and many physicians and hospitals offer treatments in complementary medicine alongside traditional medicine and surgery.

The use of placebos in clinical trials has been challenged by the World Medical Association (WMA). The WMA sets the international guidelines for clinical trials, and in the revised Declaration of Helsinki (Edinburgh, 2000) the WMA proposed that placebo treatments should not be allowed in clinical trials where there was an effective medicine against which the test medicine could be compared [20]. This recommendation by the WMA was criticized by those involved in clinical trials, and the WMA accepted an amendment to allow use of placebos at the Washington, DC, meeting in 2002 [20]. The ethical issue that the WMA tried to address concerns the use of a placebo control in clinical trials on new medicines. The WMA initially concluded that it was unethical to use a placebo control as a comparator with a new medicine when an effective existing medicine was available as a comparator. However, in a poorly designed or poorly executed clinical trial it may be possible to demonstrate that a new medicine is not significantly different in efficacy

from a currently available effective medicine. The lack of difference between the test medicines could be interpreted as meaning that the test medicines were equally effective, but this conclusion may be wrong if the clinical trial is not conducted to a high standard. The only way to validate the clinical trial is by showing that the existing effective medicine is more effective than a placebo control. If both the test medicine and the existing medicine are shown to be superior to a placebo control, then this validates the quality of the clinical trial. Therefore, for methodological reasons, the use of placebos in clinical trials is still necessary, even when there is an existing proven medicine for comparison with the new medicine.

Conclusions

The placebo is more than a control medicine in a clinical trial. The concept of a true placebo effect is evolving into a new way of treating patients, as our understanding of how the brain and emotion influence the immune system develops along with the new field of research in psychoneuroimmunology. The placebo effect is usually the greatest component of any treatment and there is a great challenge to modern medicine to harness the placebo effect for the benefit of patients.

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