

Placebo Effect in Clinical Trials Involving Patients with Allergic Rhinitis

A del Cuvillo¹, J Sastre², J Bartra³, J Mullol⁴, I Dávila⁵, J Montoro⁶,
M Ferrer⁷, I Jáuregui⁸, A Valero³

¹Astarté ENT Centre. Cádiz, Spain

²Department of Allergy, Jiménez Díaz Foundation, Madrid, Spain. Biomedical Research Centre Network for Respiratory Diseases (CIBERES)

³Allergy Unit. Department of Pneumology and Respiratory Allergy. Clinic Institute of Thorax (ICT). Clinical and Experimental Respiratory Immunoallergy (IDIBAPS). Clinic Hospital. Barcelona, Spain. Biomedical Research Centre of Respiratory Diseases (CIBERES)

⁴Rhinology Unit & Smell Clinic, ENT Department. Clinical and Experimental Respiratory Immunoallergy (IDIBAPS). Clinic Hospital. Barcelona, Spain. Biomedical Research Centre Network for Respiratory Diseases (CIBERES)

⁵Department of Immunoallergy, Salamanca University Healthcare Complex, Salamanca, Spain

⁶Allergy Section, Elda General Hospital, Alicante, Spain

⁷Department of Allergy. Clínica Universidad de Navarra. Medical School. Pamplona, Spain

⁸Department of Allergy, Basurto Hospital. Bilbao, Spain

■ Abstract

Interest in understanding the underlying mechanisms of the placebo effect has considerably grown during the last few decades. Studies made in this sense have led to a change in the conception of this peculiar phenomenon, and nowadays the placebo effect is viewed as a psychobiological event resulting from the interaction between individual patient factors and factors relating to the physician and the therapeutic environment. Investigation of the placebo effect in disease conditions such as pain or Parkinson's disease has improved our understanding of its underlying psychological and neurobiological mechanisms. Clinical studies directly designed to investigate the placebo effect have shown placebo to have a more beneficial effect upon diseases evaluated by means of physical or subjective parameters than by means of biochemical parameters. A strong placebo effect has been observed in allergic diseases, where the evaluating parameters tend to be physical or subjective. Biomedical research and the development of new drugs implies an important investment of human and economical resources for conducting clinical trials designed to evaluate the efficacy and safety of new medications. Knowledge of the mechanisms of the placebo effect and how the latter can influence the results of the different efficacy variables in these research studies appears essential in order to optimize the available resources in application to the development of new drugs.

Key words: Placebo effect. Clinical trial. Allergic rhinitis. Allergy. Allergic rhinoconjunctivitis.

■ Resumen

El interés por entender los mecanismos que subyacen al efecto placebo se ha incrementado mucho en las últimas décadas. Las investigaciones realizadas para comprender como actúa han llevado a un cambio en la concepción de este peculiar fenómeno y hoy se considera que se trata de un acontecimiento psicobiológico, resultante de la interacción entre factores individuales del paciente, del médico y del entorno terapéutico. La investigación del efecto placebo en condiciones patológicas como el dolor o la enfermedad de Parkinson han permitido conocer mejor los mecanismos psicológicos y neurobiológicos que lo explican. Los estudios clínicos dirigidos específicamente a investigar el efecto placebo han demostrado que los placebos tienen una acción más beneficiosa sobre las enfermedades evaluadas con parámetros físicos o subjetivos frente a las evaluadas con parámetros bioquímicos. Se ha comprobado una magnitud elevada del efecto placebo en las enfermedades alérgicas, en las que los parámetros de evaluación suelen ser físicos o subjetivos. La investigación biomédica y el desarrollo de nuevos fármacos supone la inversión de una gran cantidad de recursos humanos y económicos para llevar a cabo los ensayos clínicos que permiten evaluar la eficacia y seguridad de los nuevos fármacos. El conocimiento de los mecanismos del

efecto placebo y cómo este puede influir sobre los resultados de las diferentes variables de eficacia en estos estudios de investigación, parece esencial para optimizar los recursos disponibles en el desarrollo de nuevos fármacos.

Palabras clave: Efecto placebo. Ensayo clínico. Rinitis alérgica. Alergia. Rinoconjuntivitis alérgica.

Introduction

Although there is evidence of the use of the placebo effect in medical experiments dating back to the 18th century [1], no consensus-based definitions of the term placebo and its effects have been established to date. In general, it may be accepted that placebo in medicine is a patient intervention that has no effects upon the existing disease condition, though paradoxically the existence of an effect due to placebo is accepted.

Real interest in the placebo effect began with the generalized use in medical research of the randomized and controlled clinical trial design during the Second World War, resulting from the observation that the patients included in groups receiving placebo effectively improved of their disease condition, in some cases to a spectacular degree. This led to the publication of the famous article "The powerful placebo" [2], which generated growing interest in the study of this peculiar psychobiological effect. This interest persists to the present day. In effect, the number of publications addressing this subject has increased 5-fold in the last 20 years, and there are now many studies using rigorous methodology designed to clarify the mechanisms underlying the placebo effect, and not only in the clinical trial setting.

The results of these studies have made it possible to reconsider the placebo concept; rather than an intervention without effect, a more complex approach is now adopted, viewing placebo as a treatment simulation procedure set within a clinical context that produces a response in the patient [3]. This response is not of an exclusively psychosocial nature, and can reflect other aspects such as the natural course of the disease, the so-called regression to the mean phenomenon, symptom fluctuations, bias related to the way in which patients inform of their subjective symptoms, or the influence of other concurrent treatments.

The Spanish Language Dictionary of the Spanish Royal Academy (22nd edition) defines placebo as "a substance which, while lacking therapeutic action in itself, is able to induce a healing effect in the patient, if the latter is convinced that the substance truly has such an effect".

Placebo Effect Mechanisms

The studies carried out in the last decade support that the placebo effect is a genuine psychobiological event resulting from the interaction of individual patient factors, physician-related factors and others related to the therapeutic environment, including the nature of the intervention, the form of administration, and inherent characteristics in the physician-patient relationship (Figure) [3].

The mechanisms involved in placebo-type interventions are still subject to debate, but may be summarized as corresponding to two groups: psychological and neurobiological. This variety of mechanisms implies that there are multiple placebo effects, not just a single effect.

The psychological mechanisms include expectations, conditioning, learning, motivation, somatization, reward, the lessening of anxiety and significance. Of all these, the first two are the most extensively investigated:

- It has been shown that favouring patients prospects of improvement can enhance the result of a treatment intervention that is inactive from the conceptual viewpoint [4].

- It has also been shown that repeated association between a neutral stimulus (placebo) and a non-conditioned stimulus (medical treatment) can cause the neutral stimulus to induce response to the non-conditioned stimulus – the magnitude of this response being greater than that obtained when an expectations mechanism is present. This mechanism could mediate the changes induced by placebo in physiological processes such as hormone secretion or immune response [5].

The neurobiological mechanisms in turn have been investigated mainly in relation to the placebo action in situations of pain. It has been demonstrated that the analgesic effect of placebo can be partially or completely reverted by opioid antagonists or cholecystokinin, implying the existence of some endogenous opioid modulating mechanism in the placebo effect [3]. Other neurotransmitters and neuromodulators have also been found to mediate in the analgesic effect of placebo, according to the type of medication involved in the conditioning procedure [3]. Other neurobiological changes related to the placebo effect have been demonstrated in disorders such as Parkinson's disease, depression, or drug addiction, though the mechanism by which placebo leads to these results is still not fully clear [3].

Another interesting aspect related to the mechanisms of action of placebo is the observation, in several clinical trials, that different forms of administration of placebo intervention may result in different types and magnitudes of placebo effect [6], thus suggesting that the method of administration can modulate the therapeutic effect, independently of the intrinsic characteristics of the treatment intervention.

Considerations in the Study of the Placebo Effect

The study of the placebo effect has a number of implications:

- From the perspective of clinical practice, considering all that may be deduced from the therapeutic context of medical interventions, and also in view of the potential ethical implications of using placebo.

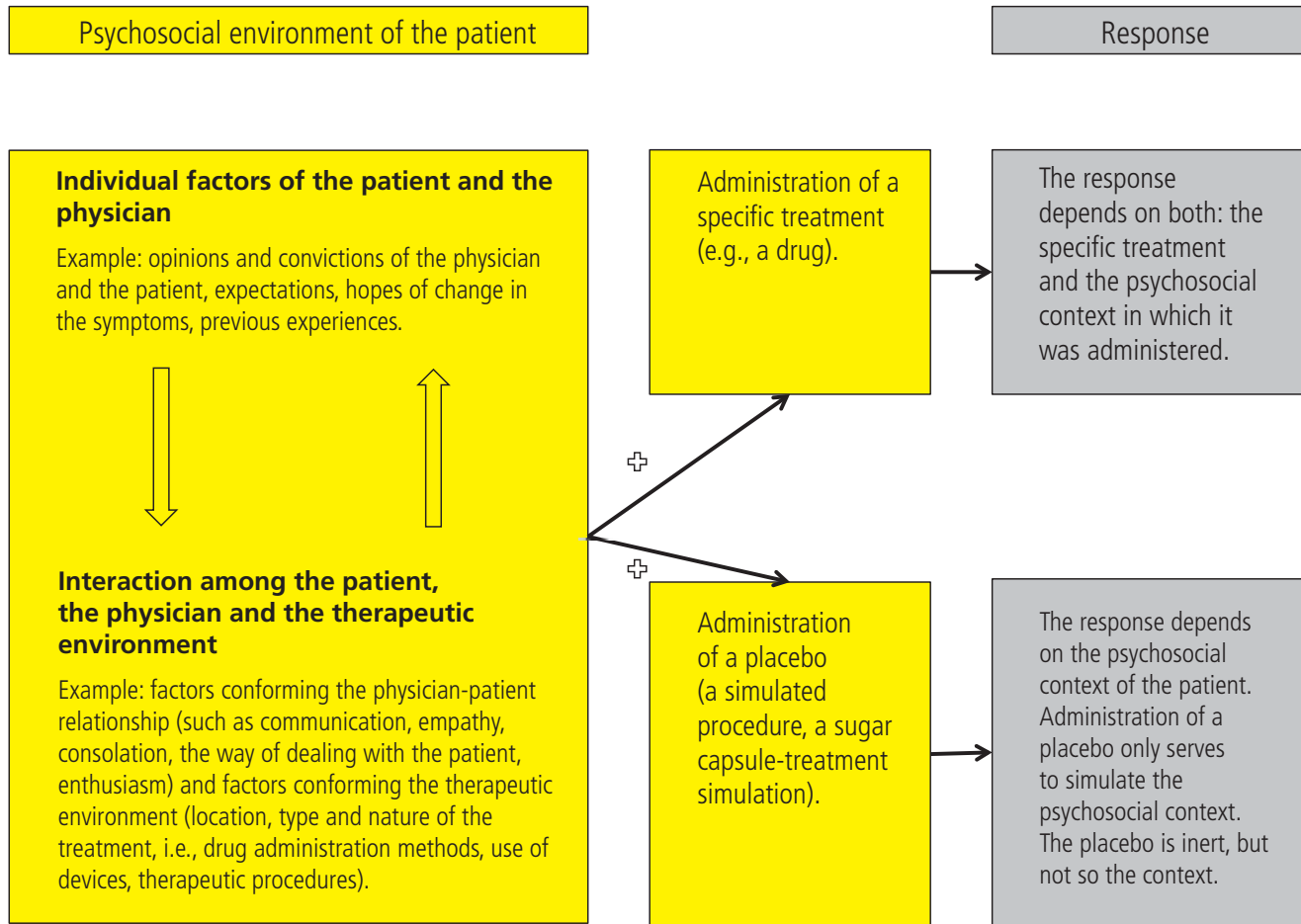


Figure. Psychosocial context of the patient.

- Related to medical research, improved understanding of the placebo effect might allow a more exact evaluation of the true efficacy of active treatment interventions, i.e., the effect upon the patient and the disease condition due to the intrinsic characteristics of the intervention – avoiding the interference with this treatment effect on those factors implicated in the therapeutic context which also contribute to the placebo effect.

Investigation of the placebo effect has been made based on laboratory studies in healthy subjects, randomized placebo-controlled clinical trials or, more recently, randomized clinical trials or studies with specific designs for assessing aspects related to the placebo effect – such as the “open/hidden” trials. Most randomized clinical trials are designed to evaluate the efficacy of the active treatment intervention, and do not include a control group of patients not receiving any intervention, to allow the evaluation of aspects such as the natural course of the disease, the mechanisms of regression to the mean, or aspects related to the therapeutic context, as already commented above.

The randomized clinical trials bound to evaluate the placebo effect have been especially designed to hide the nature of the placebo (adding or not adding information of the positive action of placebo, for example), or using different types of placebo.

The open/hidden design consists in comparing three ways of intervention: the active treatment is administered to one group of patients in the corresponding therapeutic context (routine clinical practice); another group receives placebo in a normal therapeutic context; and a third group will receive the active treatment, attempting to, in a hidden manner, override the therapeutic context. These studies make it possible to evaluate the intrinsic therapeutic effect of the active treatment, comparing the difference in effect between the open and the hidden group.

Studies have been made with this open/hidden design, in which the same treatment in the hidden group proved to be markedly less effective than in the open group in terms of reduction of different types of pain, anxiety symptoms or in application to Parkinson’s disease [7].

In the last two decades, some meta-analyses have been performed, including clinical trials with control groups lacking either active treatment or placebo [8]. These meta-analyses have concluded that therapeutic intervention with placebo generally exerts no important clinical effects, though in some scenarios placebo can improve the subjective patients symptoms (especially pain and nausea), though it is difficult to distinguish

this effect from a response bias. It is important to indicate that most of the clinical trials included in the meta-analysis aimed to evaluate the efficacy of the active treatment, not the placebo effect as such. It has been shown that the magnitude of the placebo effect is much greater in those studies that have been specifically designed to evaluate this aspect [9].

A recent study was carried out to conduct a review of clinical trials aimed to evaluate the placebo effect under different pathological conditions, distinguishing between those that included a control group without treatment and those with no such a group [10]. The main conclusion was that therapeutic interventions with placebo can improve physical processes more easily and effectively than biochemical processes. The authors found a significant improvement of diseases evaluated by means of physical parameters such as asthma, hypertension or chronic bronchitis, while no significant improvement response was recorded with placebo when the assay parameter was of a biochemical nature, as in rheumatoid arthritis, chronic hepatitis, chronic heart failure, hypercholesterolemia or coronary disease.

The Placebo Effect in Respiratory Allergic Diseases

In a meta-analysis specifically carried out to evaluate the placebo effect in clinical trials involving treatments for asthma, the patients that were administered placebo showed an improvement of 4.8% in forced expiratory volume in one second (FEV₁), and although the magnitude of the change was greater in the patients who received the active treatment, the difference failed to reach statistical significance. The study concluded that in an important group of long-term clinical trials conducted in patients with stable asthma, and involving a correct design and methodology, improvements of over 10% were observed in the parameters FEV₁ and peak expiratory flow (PEF) in the patients administered with placebo, and the placebo response was moreover highly variable among the different trials included in the meta-analysis [11].

Until now, an evaluation of the magnitude of the placebo effect in allergic rhinitis has not been carried out. Most clinical trials conducted to evaluate the therapeutic effect of the different treatments for allergic rhinitis use as a primary endpoint the difference in total symptoms score between the beginning and the end of the treatment period. The total symptom score is calculated as the mean of the scores of the different nasal and non-nasal symptoms, and as this is considered a subjective physical variable, therefore more likely to be improved by means of the placebo action than by biochemical variables, on the basis of the aforementioned scientific data [10].

A recently published study included a meta-analysis to evaluate the efficacy of the different treatments authorized in the United States for allergic rhinitis with very high magnitudes of placebo response being recorded: 15% improvement in the total symptoms score for seasonal allergic rhinitis and 24.8% improvement in the case of perennial allergic rhinitis [12]. When comparing these magnitudes with those obtained with the active treatments, antihistamines, antileukotrienes and cor-

ticosteroids were found to obtain a 1.56-, 1.13- and 2.71-fold greater improvement than placebo, respectively. Although the difference was statistically significant in favour of the active treatments, the magnitude of the differences seems small.

In a study aimed to evaluate the efficacy of antihistamines in improving the quality of life in patients with allergic rhinitis [13], placebo was seen to obtain a statistically significant and clinically relevant improvement in quality of life versus the baseline score at the beginning of the study. The groups of patients receiving active treatment also showed a statistically significant improvement in quality of life, though the differences versus placebo were not found to be clinically relevant.

Considerations Regarding the Placebo Effect in Clinical Trials Involving Patients with Allergic Rhinitis

The use of a placebo group in the design of clinical trials conducted to demonstrate the efficacy of medical interventions is presently considered necessary in order to avoid many of the biases commonly found in biomedical research. When the World Medical Association (WMA) proposed limiting placebo use in research only to studies involving interventions lacking a comparator group of demonstrated efficacy, pressure from the different investigating groups caused it to quickly issue an amendment to the Declaration of Helsinki accepting the use of placebo, provided such use does not pose an important risk for the subjects participating in the study. In this way it admitted that the comparator group with placebo allows a much better evaluation of the true efficacy and safety of any medical intervention.

However, it must be taken into account that the most recent researches indicate that the placebo effect can be highly variable, and even unpredictable – particularly when disease evaluation is based on physical parameters, or imply patient subjectivity – and that the magnitude of the placebo effect can be so important that a very high statistical power is required on the part of the clinical trial in order to detect statistically significant differences between the placebo group and the active intervention group.

Biomedical research for the development of drugs involves an incalculable investment of human, material and especially economical resources. As a result, in most cases the statistical power of the clinical trial for detecting differences between the medical intervention and placebo is limited by the costs, since it essentially depends on the study sample size.

On the other hand, it must be considered that if the clinical trial does not include a comparator group in which no intervention is made, it becomes impossible to determine the difference between the study intervention and the true life situation in clinical practice, since in the latter setting no placebo-type interventions are used (such interventions currently being limited to the experimental setting due to ethical considerations which are presently the subject of debate). For this reason the WMA, in its last revision of the Declaration of Helsinki, recommends that when investigating new medical treatment options, a comparator group should be included involving the most effective

treatment option for the disease under investigation, in order to assess the advantages and inconvenients of the new proposal.

In allergic rhinitis, clinical evaluation is fundamentally based on the patients perception of the symptoms. The usual outcome variables in clinical trials involving patients with allergic rhinitis are symptom scores obtained reflexively, determined from the mean score obtained (normally from 0-3) on asking the patient to rate the severity of the symptoms: nasal obstruction, mucous secretion, nasal itching and sneezing, and non-nasal symptoms such as tearing or lacrimation, eye itching and eye redness. Recently, allergic rhinitis specific questionnaires to score quality of life are being included as an outcome variable. In both cases these variables can be regarded as strongly influenced by patient subjectiveness, and therefore strongly susceptible to be influenced by the placebo effect.

In clinical trials designed to evaluate the efficacy of therapeutic vaccines with allergenic extracts in allergic rhinitis, the use of a rescue medication (allowed for ethical reasons) was found to induce a miscalculation in the assessing of the efficacy of the active intervention (immunotherapy). As a result, the recommendation now is to use combined indexes (with scores calculated on combining the total symptoms score with the score obtained on measuring the use of rescue medication) as primary efficacy endpoint in these clinical trials [14].

It seems necessary to find more efficient outcome variables to assess the efficacy of a new treatment for allergic rhinitis, perhaps combining the symptom scores with parameters that are less influenced by subjectiveness, and thus by the placebo effect, and which are relatively well correlated to the definition and severity of the disease – such as for example rhinomanometric measurements, nasal mucosal plasma flow, gland exocytosis, cytology, or measurements in the field of proteomics or genomics.

A recent review by Baraniuk [15] points out some of the key future elements in relation to this challenge, proposing syndromes such as chronic nasal pain or nasal autonomic dysfunction as new investigational models allowing a novel and more efficient approach for the development of new therapeutic interventions in rhinitis.

As a conclusion, it seems necessary to gain more in-depth knowledge of the placebo effect in order to improve the design of clinical trials in patients with allergic rhinitis, proposing new investigational models and describing new outcome variables allowing assessment of the intrinsic efficacy of the studied treatment options, independently of the placebo effect.

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Conflicts of interest

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■ **Alfonso del Cuwillo**

Avenida de la Ilustración 6, 1ª planta, local 1.
E-11011 Cádiz (Spain)
Tel & Fax: +34 956 286 640
E-mail: dr.cuwillo@comcadiz.es