Editorial

The placebo effect in asthma: Far more complex than simply "I shall please"

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Key words: *Asthma, placebo, leukotriene receptor, antagonist, clinical trials*

WHAT ARE THE EFFECTS OF PLACEBOS ON CLINICAL TRIALS?

The randomized, double-blind, placebo-controlled clinical trial is the gold standard by which efficacy, safety, and even mechanisms of action of treatments are evaluated and established. In the planning of clinical trials in asthma, it is anticipated that a placebo effect will occur and may often influence the interpretations of the outcomes or the perceived overall effectiveness of the treatment. Consequently, considerable effort is expended in the planning and design of a clinical trial. For example, entry criteria for recruited patients are often established to minimize the enrollment of subjects with characteristics that might promote a placebo effect or to avoid the selection of individuals who might be prone to a significant placebo effect. As demonstrated by the study of Robert Wise[1] and the American Lung Association Asthma Clinical Research Centers coinvestigators published in this issue of the *Journal*, placebo effects do indeed occur in asthma studies, but the effect of a placebo is not seen on all outcomes or under all conditions. From our perspective, the investigation by Wise et al[1] to assess, understand, and interpret more precisely the complexity of the placebo response will be helpful for *Journal* readers. Their observations should help asthma caregivers appreciate more comprehensively the placebo phenomenon in asthma clinical trials and the possible neuromechanisms involved in the participant's response to treatment.

HOW CAN RESPONSES TO PLACEBO BE INFLUENCED?

In general, placebos have been considered inert chemical substances. They are, however, an integral and necessary component to a proper double-blind, placebo-controlled, randomized clinical trial and a necessary component of these studies to determine most accurately the actual effect of a particular intervention. Placebos can be either tablets or inhaled inert materials whose inclusion is intended to "please the patient" (ie, from the Latin definition) and provide a necessary nontreatment arm by which the active intervention can be more accurately assessed.[2] However, experience with these chemically inert substances has shown that they have a demonstrable effect on a variety of outcomes in trials ranging in design from the assessment of pain management to the control of asthma symptoms. Because of these broad effects, investigators have begun to examine the response to placebos more comprehensively to understand their action more fully. Largely from studies of pain regulation, it is now appreciated that the response to a placebo is influenced by many patient-related factors including the conditioning and expectancy of that particular individual. It is also reasonable that these influences be applied to asthma, where patients have had experiences with various treatments for their disease and, consequently, may have developed a conditioned expectation. To influence the response to placebo further, or for that matter an active treatment, verbal suggestions or a more positive presentation of the test treatment also need to be considered in light of the patient's expectation toward the intervention or placebo. Finally, it is also known that conditioning and expectancy may have different effects on different symptoms or outcomes.[3]

WHAT DID WISE ET AL OBSERVE?

Based in part on this emerging background of information on placebos, Wise et al[1] designed a clinical trial in asthma to determine whether, and on what aspects of the measured asthma outcomes, the type of information given on a treatment—that is, enhanced or neutral—would influence the patient's response to a particular intervention. The study design was carefully crafted to address 2 important questions: whether enhanced expectation of benefit might account for a positive response to the placebo, and, equally important, whether a similar approach might also improve responses to the pharmacologic treatment.

To test their hypothesis, all of the enrolled participants were required to have uncontrolled asthma as defined by an elevated Asthma Control Questionnaire (ACQ) score, frequent use of short-acting β-agonists, or nighttime awakening from asthma. In their study design, the 2 principal interventions were the study drug (montelukast vs placebo) and treatment presentation (neutral vs enhanced of both montelukast and placebo). Key to an interpretation and appreciation of their results are the 4 comparative

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Supported by grants from the National Institutes of Health/National Heart, Lung, and Blood Institute (HL69116) and the National Institutes of Health/National Institute of Allergy and Infectious Diseases (N01-AI25496).

Disclosure of potential conflict of interest: W. Busse is a consultant or on the advisory board for Altair, GlaxoSmithKline, Merck, Wyeth, Pfizer, Centocor, Amgen, UCB, Johnson & Johnson, Novartis, AstraZeneca, Eisai, TEVA, CompleWare, KaloBios, Boehringer Ingelheim, and Sandoz, and has received research support from the National Institute of Allergy and Infectious Diseases, National Heart, Lung, and Blood Institute, Novartis, Centocor, GlaxoSmithKline, MedImmune, and Ception. R.F. Lemanske is a speaker or consultant for Merck, AstraZeneca, Map Pharmaceuticals, Gray Consulting, Medicus Group, Smith Research, Inc., Novartis, Quintiles/Innovax, RC Horowitz & Co., Inc., International Meetings and Science, and Scienomics, and has received research support from the National Heart, Lung, and Blood Institute and the National Institutes of Health.

Received for publication July 28, 2009; accepted for publication July 29, 2009.

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J Allergy Clin Immunol 2009;124:445-6.
0091-6749/$36.00
© 2009 American Academy of Allergy, Asthma & Immunology
doi:10.1016/j.jaci.2009.07.042

conditions studied: (1) placebo + neutral drug presentation, (2) placebo + enhanced expectancy drug presentation, (3) montelukast + neutral drug presentation, and (4) montelukast + enhanced expectancy drug presentation. This approach provided a 2×2 factorial design by which treatment effects could be measured and the effect of the presentation of information on the treatments could also be determined.

Tables II and IV of the Wise et al[1] article provide, in our estimation, the key findings of their study. First, montelukast caused a significant improvement in measures of pulmonary function compared with placebo; the enhanced message given with montelukast, however, had no effect on these physiological outcomes. With patient-reported outcomes, the investigators found the ACQ score improved when placebo was given with an enhanced message. Therefore the beneficial influence from the enhanced message was limited to the placebo treatment and to the patient-reported outcomes. No added benefit was found in association with an enhanced message to the active treatment, montelukast, or on measures of physiology, such as pulmonary functions.

Other studies in asthma amplify the results of Wise et al.[1] Kemeny et al[4] conducted a study to determine whether placebo treatment can suppress the airway response to methacholine in asthma. Similar to the study by Wise et al,[1] an assessment was made whether the physician-investigator introduction on the effect of the intervention—that is, communicating either a positive or neutral expectancy to the placebo or active treatment—would influence the response to 2 treatment arms: placebo or salmeterol. These investigators found that pretreatment with the placebo bronchodilator significantly reduced the bronchoconstriction response to methacholine. In contrast, enhancing the potential benefits in presenting the placebo had no effect on modifying the response to methacholine. Finally, and as expected, salmeterol had a greater suppressive effect on the airflow obstruction to methacholine than placebo, but, like the placebo experience, an enhanced presentation did not improve salmeterol's actions.

The studies by both Wise et al[1] and Kemeny et al[4] indicate that a placebo can affect certain parameters of asthma. Wise et al[1] add to our knowledge by showing that an enhanced message given with a study treatment may have limited effects to placebo and to asthma outcomes that were not physiologic.

HOW DO PLACEBOS INTERACT WITH THE NEUROCIRCUITRY TO AFFECT PATIENT RESPONSES?

The study of placebo effects has been evaluated more extensively in the response to pain. By using methods to regulate pain, investigators have begun to discover the potential neuromechanisms by which placebo effects may occur. To illustrate, Wager et al[5] used functional MRI to image the brain and evaluate whether central nervous system pathways, or circuitry, may be affected by placebo administration, and whether activation or regulation of these central nervous system pathways could be found in association with an alteration of the pain response. In the study by Wager et al,[5] 2 hypotheses were addressed and evaluated by functional MRI: (1) do placebos reduce the experience of pain, and (2) do placebos modulate the activity of the pain matrix by creating expectations for pain relief to inhibit activity in the pain-processing regions of the brain? In these elegant studies with brain imaging to assess activation of central nervous system regions, Wager and Nitschke[3] were able to show that

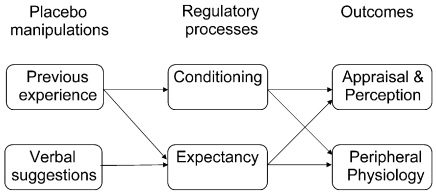

FIG 1. Diagram showing relationships between placebo treatment, internal regulatory processes, and outcomes. A challenge in placebo research is identifying the internal processes that are engaged by treatment and their brain substrates. Conditioning and expectancy may act on common or unique brain pathways, and the relationship between them may vary across disease processes and treatments. Another challenge is in identifying placebo effects on specific outcomes within the brain and periphery.[3] (Reprinted with permission)

administration of a placebo decreased responses in the brain regions that are pain-sensitive. In addition, and equally important, pain response areas of the brain were activated by expectation. This effect of the placebo on these brain regions was then found to be associated with a modulation of pain activity.

Wager and Nitschke[3] have proposed possible mechanisms to show how the placebo actions can be integrated in the brain's response to pain (Fig 1). Their concept proposes that verbal suggestions will affect the expectancy, but not necessarily conditioning processes, and these effects can then be translated to peripheral physiology. The findings of Wise et al[1] and Kemeny et al[4] add to our growing fund of knowledge in this area by demonstrating that there is also a variability by which nonphysiological outcomes are likely to be affected by placebo and the expectancy message given with the treatment.

SUMMARY

Wise et al[1] have added to our understanding and appreciation of the complexity underlying the response to placebos in asthma. When readers now evaluate data in light of a placebo response, it should become insightful for them to consider many variables, such as the effects measured, the disease being assessed, and the mode of presentation used in the trial—enhanced or neutral. Furthermore, studies evaluating placebo effects have helped to indicate the potential involvement of brain circuitry in these responses, as well as treatment determinants. Placebo responses are complex but an integral component of many clinical trials in asthma. To appreciate fully the impact of the placebo, aside from the "I shall please" action, it is now important to realize that a science underlies the placebo and the patient's response to it. The work of Wise et al[1] has added to this information in a most meaningful way and has made us more appreciative of the response to placebos.

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