Published in final edited form as:

J Allergy Clin Immunol. 2009 September ; 124(3): 445–446. doi:10.1016/j.jaci.2009.07.042.

The Placebo Effect in Asthma: Far more complex than simply “I shall please”

William W. Busse, M.D.¹ and Robert F. Lemanske Jr., M.D.²

¹Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI

²Department of Pediatrics, University of Wisconsin School of Medicine and Public Health, Madison, WI

What are the impacts of placebos on clinical trials?

The randomized double-blind, placebo-control 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 placed into 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 towards a significant “placebo effect.” As demonstrated by the study of Robert Wise⁽¹⁾ and the American Lung Association Asthma Clinical Research Centers co-investigators published in this issue of *The Journal of Allergy and Clinical Immunology*, 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 my perspective, the Wise et al’s⁽¹⁾ investigation to more precisely assess, understand, and interpret the complexity of “placebo response” will be helpful for *JACI* readers. Their observations should help asthma caregivers to more comprehensively appreciate 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?

Placebos have, in general, been considered as 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 most accurately determine the actual effect of a particular intervention. Placebos can be either tablets or inhaled inert materials whose inclusion is intended to “please the patient” (e.g. from the Latin definition) and provide a necessary “non-treatment” arm by which the active intervention can be more accurately assessed.⁽²⁾ However, experience with these chemical “inert” substances has shown that they have a demonstrable effect on a variety of outcomes

Corresponding author: William W. Busse, M.D., George R. and Elaine Love Professor, Chair, Department of Medicine, J5/219 CSC, MC 2454, 600 Highland Avenue, Madison, WI 53792, Phone: 608.263.6183, Fax: 608.262.6743, wwb@medicine.wisc.edu.

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 more fully understand their action. Largely from studies of pain regulation, it is now appreciated that the response to a placebo is influenced by many patient-related factors including 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 further influence the response to placebo, or for that matter an active treatment, verbal suggestions or a more positive presentation of the test treatment should also need to be considered in light of the patient's expectation towards 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, i.e., enhanced or neutral, would influence the patient's response to a particular intervention. The study design was carefully crafted to address two 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 pharmacological treatment.

To test their hypothesis, all of the enrolled participants were required to have uncontrolled asthma as defined by an elevated ACQ score, frequent use of short-acting beta agonists, or nighttime awakening from asthma. In their study design, the two 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 four comparative conditions studied: (1) placebo + neutral drug presentation; (2) placebo + enhanced expectancy drug presentation; (3) montelukast + neutral drug presentation; and (4) placebo + 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 2 and 4 of their publication provide, in my estimation, the key findings of their study. First, montelukast caused a significant improvement in measures of pulmonary function compared to placebo; the enhanced message given with montelukast, however, had no effect on these physiological outcomes. With patient reported outcomes (see Table 4), the investigators found the ACQ score improved when placebo was given with an enhanced message. In this well-designed study, the beneficial influence from the "enhanced" message was limited to placebo treatment and to 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 on the results of Wise and co-workers.⁽¹⁾ Kemeny, et al.⁽⁴⁾ conducted a study to determine whether placebo treatment can suppress the airway response

to methacholine in asthma. Similar to Wise et al.⁽¹⁾, an assessment was made of whether the physician-investigator introduction on the effect of the intervention, i.e. communicating either a positive or neutral expectancy to the placebo or active treatment, would influence the response to two treatment arms: placebo or salmeterol. These investigators found pre-treatment 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, 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.

Both studies, 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 was limited to placebo and, also, 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. 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 (f) MRI to image the brain and to 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⁾ two hypotheses were addressed and evaluated by fMRI: (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 CNS regions, Wager et al.⁽³⁾ were able to show that 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 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 and co-investigators⁽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, i.e., the effects measured, the disease being assessed, and mode of presentation used in the trial, i.e., enhanced or neutral. Furthermore, studies evaluating placebo effects have also 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 fully appreciate 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 to its response by a patient. The work of Wise and colleagues⁽¹⁾ has added to this information in a most meaningful way and has made us more appreciative of the response to placebos.

Acknowledgments

Supported by grants from the NIH-NHLBI HL69116 and NIH-NIAID N01-AI25496

References

1. Wise RA, Bartlett SJ, Brown ED, Castro M, Cohen R, Holbrook JT, et al. Randomized trial of the effect of drug presentation on asthma outcomes: The American Lung Association Asthma Clinical Research Centers. *J Allergy Clin Immunol*. In press.
2. Price DD, Finniss DG, Benedetti F. A comprehensive review of the placebo effect: recent advances and current thought. *Annu Rev Psychol*. 2008; 59:565–90. [PubMed: 17550344]
3. Wager TD, Nitschke JB. Placebo effects in the brain: linking mental and physiological processes. *Brain Behav Immun*. 2005; 19:281–2. [PubMed: 15908179]
4. Kemeny ME, Rosenwasser LJ, Panettieri RA, Rose RM, Berg-Smith SM, Kline JN. Placebo response in asthma: a robust and objective phenomenon. *J Allergy Clin Immunol*. 2007; 119:1375–81. [PubMed: 17451796]
5. Wager TD, Rilling JK, Smith EE, Sokolik A, Casey KL, Davidson RJ, et al. Placebo-induced changes in fMRI in the anticipation and experience of pain. *Science*. 2004; 303:1162–7. [PubMed: 14976306]

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⁾