Placebo response in asthma: A robust and objective phenomenon

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Background: Placebos are hypothesized to exert positive effects on medical conditions by enhancing patient expectancies. Recent reviews suggest that placebo benefits are restricted to subjective responses, like pain, but might be ineffective for objective physiologic outcomes. Nevertheless, mind-body links and placebo responsivity in asthma are widely believed to exist.
Objective: We carried out a randomized, double-blind investigation to (1) determine whether placebo can suppress airway hyperreactivity in asthmatic subjects, (2) quantify the placebo effect, (3) identify predictors of the placebo response, and (4) determine whether physician interventions modify the placebo response.
Methods: In a double-blind, crossover design investigation, 55 subjects with mild intermittent and persistent asthma with stable airway hyperreactivity were randomized to placebo or salmeterol before serial methacholine challenges. Subjects were additionally randomized to physician interactions that communicated either positive or neutral expectancies regarding drug effect.
Results: Placebo bronchodilator administration significantly reduced bronchial hyperreactivity compared with baseline (the calculated concentration of methacholine required to induce a 20% decrease in FEV_1 nearly doubled); 18% of subjects were placebo responders by using conservative definitions. Experimental manipulation of physician behavior altered perceptions of the physician but not the magnitude or frequency of the placebo response.
Conclusions: Objective placebo effects exist in asthma. These responses are of significant magnitude and likely to be meaningful clinically. The placebo response was not modulated by alterations in physician behavior in this study.
Clinical implications: The placebo response in patients with asthma is important in understanding the limitations of clinical research studies and in maximizing safe and effective therapies. This article confirms the existence of a strong placebo response in an objective and clinically relevant measure of disease activity. (J Allergy Clin Immunol 2007;119:1375-81.)

Key words: *Asthma, placebo, mind-body, psychology, bronchial hyperresponsiveness, central nervous system*

Recently, there has been a reawakening of interest in the placebo response. The term *placebo*, Latin for ''I shall please,'' was coined in the early 19 th century to describe a medicine ''adapted more to please than benefit the patient.''[1] Current ethical standards forbid the deceptive use of placebo to treat patients, but placebos are now often mandatory as controls in clinical studies of new therapeutics. In both cases, the placebos are assumed to have no significant effect on health. However, across a large number of clinical trials, benefit is often demonstrated in the placebo arm, raising the question of whether placebos can have psychologic, physiologic, and/or health effects.

A definitive health benefit from placebos cannot be inferred from clinical trials when the natural variation in the disease outcome is not measured because of the inability to differentiate between placebo effects and normal variability in disease status. A meta-analysis of placebo responses in clinical studies that did contain a natural history arm found that placebo administration induced beneficial changes in subjectively assessed outcomes, such as pain and depression, but not in objectively defined medical outcomes.[2] Although this report has been widely debated, it clearly questions the notion that placebos can affect peripheral physiologic processes or disease manifestations.

A primary aim of the current study was to determine whether there is a placebo response in objective measures of lung function in the context of asthma and, if so, to estimate the magnitude of that effect relative to natural variation in lung function and response to active drug. Asthma is a good disease model in which to study the placebo effect because disease-relevant objective end points can be assessed, such as air flow and bronchial hyperresponsiveness. Also, there is a long history of belief that psychologic factors play a role in the course of asthma, which is supported by recent research.[3-6] In the current study we compared the protective effect of the

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Abbreviations used
BMI: Body mass index
PC_{20}: Calculated concentration of methacholine required to induce a 20% decrease in FEV_1
PD_{20}: Dose level of methacholine during which a 20% decrease in FEV_1 was noted

long-acting bronchodilator salmeterol with placebo (the identical dry powder inhaler emptied of medication) when administered before a methacholine challenge.

A second aim was to determine the cognitive and affective mediators of the placebo effect. We hypothesized that treatment outcome expectancies—beliefs about a treatment's efficacy—would mediate placebo effects on airway hyperresponsiveness.[7-9] Expectancies regarding treatment outcome and disease course have predicted a variety of health outcomes, although most often in the setting of subjectively assessed measures.[10-15]

A third aim of the study was to determine whether the placebo response can be enhanced by induction of positive expectancies by a physician before placebo administration. Physician behavior was scripted to enhance (or not) positive treatment outcome expectancies and emotional care, the provision of support, empathy, reassurance, and warmth.[16] A review of studies that manipulated one or both of these dimensions of physician behavior demonstrates that positive health outcomes can result from these behavior patterns.[16]

METHODS

Participants

Subjects were recruited at the National Jewish Medical and Research Center and the University of Iowa. Eligible subjects were men and women, aged 18 to 55 years, with mild intermittent or persistent asthma[17] and a baseline FEV_1 of 80% of predicted value or greater. Major exclusion criteria included pregnancy or breast-feeding, serious systemic illness, recent respiratory tract infection, use of inhaled corticosteroids or other controller medications within 4 weeks, and smoking (>5 pack-year lifetime history). All subjects provided written informed consent before screening that did not reveal that the central purpose of the study was to explore the placebo response; this deception was revealed at a debriefing at the end of the protocol, when subjects were reconsented and given the opportunity to withdraw from the study. This study was reviewed and approved by the Institutional Review Boards of the University of Iowa; the University of California, San Francisco; the University of Missouri, Kansas City; and the University of Pennsylvania.

Procedures

Trial design. The study used a randomized, placebo-controlled trial design that included a crossover and required 6 visits (Fig 1). The first 3 visits (approximately 1 week apart) were used for screening and to establish the subjects' baseline characteristics, including the degree of airway hyperresponsiveness in the untreated state and after pretreatment with salmeterol (50 μg, Serevent Diskus, GSK, Research Triangle Park, NC). At visit 1, they were required to have a calculated concentration of methacholine required to induce a 20% decrease in FEV_1 (methacholine PC_{20}) of 4.0 mg/mL or less, with a second challenge (visit 2, a week later) positive within 1 dose level of the initial value. At visit 3, they needed to demonstrate significant protection (at least 1 dose level of improvement in PC_{20}) after inhalation of salmeterol (50 μg, Serevent Diskus, administered in a single-blind manner). The second phase of the study (visits 4 and 5) included a double-blind randomized intervention before methacholine challenge: administration of either placebo (Serevent Diskus from which the blister tape containing salmeterol was removed) or salmeterol, with a crossover to the alternate treatment arm. For these visits, the subjects were also randomized to receive *enhanced* or *efficient* interactions with a physician investigator (described below) before the administration of the active/sham inhaler: thus 4 groups were constituted by treatment order (placebo/salmeterol and salmeterol/placebo) and physician interaction (enhanced vs efficient). Finally, visit 6 consisted of a debriefing interview, at which time research subjects were informed that the central purpose of the study was to study placebo rather than treatment response and were provided the opportunity to withdraw their data from analysis with no penalty (not requested by any participant). Psychologic assessment included multiple questionnaires throughout the study (see below) that were administered with the goal of predicting placebo responsiveness. Other factors used in this analysis included sex, age, weight, and body mass index (BMI).

Pulmonary function measurement. Methacholine challenge testing was carried out according to standard procedures[18] to measure airway hyperresponsiveness, with serial doubling doses (diluent, 0.16, 0.31, 0.63, 1.25, 2.5, 5, 10, and 25 mg/mL) of methacholine aerosols with a calibrated dosimeter. The testing technician was blind to conditions. Each subject's screening methacholine PC_{20} (an average of the PC_{20} measured at visits 1 and 2) served as the baseline for comparison with subsequent challenges. The methacholine challenges during visits 4 and 5 were carried out 1 hour after the subject's use of the active/sham inhaler.

Physician encounters. On the basis of the literature, we proposed that a positive treatment outcome expectation communicated by the physician at the time of bronchodilator administration would increase positive expectancies regarding the treatment efficacy and thus enhance (or in the case of placebo induce) its physiologic effects. The *enhanced* physician encounter was designed to emphasize positive expectations, as well as the authority and supportiveness of the physician, whereas the *efficient* encounters minimized these factors, although they did not convey negative expectations. Enhanced and efficient physician investigators were selected by each site's principal investigator; all had expertise in asthma and possessed an interpersonal style matching either the enhanced or efficient style. Physicians who conducted the enhanced encounters were trained to transmit a positive expectation about the bronchodilator efficacy (for both of the crossover conditions) in reducing methacholine-induced symptoms by using specific scripted sentences (eg, ''You shouldn't have any symptoms''). Enhanced physician encounters also promoted authority (physicians wore a white coat and tie, were introduced as asthma experts, and were trained to speak with authority and conviction) in a supportive environment (encounters were longer, approximately 10 minutes, and included empathetic and respectful behavior, such as shaking hands with the subject). Physicians assigned to the efficient encounters were trained to convey an equivocal expectation about the bronchodilator efficacy (''It might work, and then again it might not'') and to minimize authority (no white coat or tie; introduction as a junior member of the team) and supportiveness (eg, encounters were about 2 minutes, and physicians displayed more efficient and brusque, although not negative, behaviors, such as inconsistent eye contact). The physician encounters took place just before administration of the salmeterol or placebo during visits 4 and 5. For the enhanced encounters, there was an additional brief interaction between the physician and patient immediately before the methacholine challenge. Training took place on site by an expert in