

## CORRESPONDENCE



## Placebo and Other Interventions in Asthma

**TO THE EDITOR:** Wechsler et al. (July 14 issue)<sup>1</sup> describe self-reported outcomes of albuterol treatment as compared with placebo in patients with mild-to-moderate asthma. One possible explanation for the lack of incremental benefit with respect to these outcomes may be related to the experimental design of the study. The benefit of the bronchodilator effect of albuterol could have not been appreciated by patients who were probably asymptomatic and had baseline mild airway obstruction, particularly because they were evaluated under resting conditions for 2 hours in a hospital setting. More information could have been obtained about subjective outcomes by allowing the patients to do some standardized tasks that simulate real-life conditions such as walking or climbing stairs and not just remaining seated in a hospital waiting room.

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No potential conflict of interest relevant to this letter was reported.

1. Wechsler ME, Kelley JM, Boyd IOE, et al. Active albuterol or placebo, sham acupuncture, or no intervention in asthma. *N Engl J Med* 2011;365:119-26.

**TO THE EDITOR:** Wechsler et al. underline the relevance of the placebo effect in patients with asthma, and they compare placebo with no treatment. Despite the strengths of the study design, we completely disagree with their conclusions, in which they extrapolate that “patient self-reports can be unreliable” and so “objective outcomes should be more heavily relied on for optimal asthma care.” These statements are not acceptable as a deduction because the authors did not study clinical outcomes other than patients’ symptoms at one time.

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**TO THE EDITOR:** Regarding Moerman’s editorial<sup>1</sup> concerning the study of interventions for asthma reported on by Wechsler et al.: first, Moerman categorizes inflammatory bowel disease as a “subjective and functional condition” like migraine or back pain. The concept of inflammatory bowel disease being a functional disorder has been abandoned.<sup>2</sup> Second, he concludes, “a patient-centered approach requires that patient-preferred outcomes trump the judgment of the physician.” This statement is problematic because the decision to rely on patient-centered items, physician-determined biologic markers, or a combination of the two for measurement of outcomes in a given dis-

ease should be guided, in part, by the appraisal of whether the persistence of untreated biologic abnormalities will result in organ damage or not. The stronger the effect of the altered biologic markers on the disease course, the more critical their assessment becomes. For example, arterial hypertension may be asymptomatic, but failing to treat it can have serious consequences. As such, the efficacy of therapeutic interventions should be judged on the basis of a continuum of patient-oriented outcomes and biologic measures, the balance between which is highly disease-specific.<sup>3,4</sup>

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**THE AUTHORS REPLY:** Rolla and Bucca postulate that our finding of a lack of incremental benefit of albuterol over placebo for subjective outcomes in patients with asthma was due in part to the fact that these persons were tested at rest. Although it is possible that the degree of physiological deficit in some of these patients may not have been clinically significant enough for them all to have symptoms at rest, not all patients with asthma who have deficits in lung function appreciate the degree to which their asthma contributes to symptoms of airflow limitation until they are given bronchodilators, with resultant improvement in lung function and symptoms.<sup>1-4</sup>

In our study, active bronchodilator resulted in a substantial improvement in lung function as compared with no treatment control (20.1% vs.

7.1% improvement in the forced expiratory volume in 1 second), and patients were able to perceive this difference (50% vs. 21% improvement in symptoms). The fact that these patients reported improvements and that these improvements differed among patients who received no treatment and the other treatments suggests that these patients had a degree of symptoms at rest; otherwise, they could not have detected improvement, and a differential improvement, at that. Had we tested the subjects under stress, we suspect that the differences we observed would have been magnified, since there would have been even more room for improvement.

Although we value and recognize the importance of patient self-reports in the treatment of the individual patient, we disagree with the comments by Bibalo et al. and maintain that patient self-reports can be unreliable and that patients have a considerable response to placebo. This finding has been observed by us and by many others<sup>5</sup> and is the reason we believe that subjective outcomes need to be put in the context of concurrent objective findings in the management of asthma.

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Since publication of their article, the authors report no further potential conflict of interest.

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**THE EDITORIALIST REPLIES:** Straumann et al. make several assertions. Many bowel disorders have varying physical signs, but many of them cause only symptoms that are often extremely debilitating.

None of them seem to be curable, but most symptoms fluctuate over time, and some may be manageable with treatments that are associated with varying amounts of distress. Clearly, regular and supportive doctor–patient discussions about what is possible in such conditions, as well as what is desirable, are probably in order in most of these illnesses.

Hypertension, of course, is entirely different in that it causes no symptoms at all and can be diagnosed only by screening followed by treatments, many of which have side effects that

limit their clinical usefulness. Hence, reliable treatment is problematic (as attested by 6508 citations identified with the PubMed query “hypertension compliance”) but preferable to prevent complication. The solution to this dilemma is, again, conversations between the patient and caregiver.

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Since publication of his article, the author reports no further potential conflict of interest.

## Vemurafenib in Melanoma with BRAF V600E Mutation

**TO THE EDITOR:** In the study by Chapman et al. (June 30 issue),<sup>1</sup> vemurafenib clearly improved rates of overall and progression-free survival among patients with untreated melanoma with the BRAF V600E mutation. Since half of cutaneous melanomas carry this activating mutation, the administration of vemurafenib to patients with mutation-bearing melanomas has the potential to change the grim prognosis associated with this disease. We have two questions. First, was there any correlation between drug response and the ratio of mutant to wild-type alleles (BRAF amplification)? Second, we wonder whether any intrinsic or acquired resistance to vemurafenib, or both, could result from the existence or emergence of drug-resistant mutations in the genes related to the alternative mitogen-activated protein kinase (MAPK) signaling pathway.<sup>2</sup> Such secondary mutations might explain the high frequency of cutaneous squamous-cell carcinoma and keratoacanthoma observed in the vemurafenib group.

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No potential conflict of interest relevant to this letter was reported.

1. Chapman PB, Hauschild A, Robert C, et al. Improved survival with vemurafenib in melanoma with BRAF V600E mutation. *N Engl J Med* 2011;364:2507-16.

2. Smalley KS, Sondak VK. Melanoma — an unlikely poster child for personalized cancer therapy. *N Engl J Med* 2010;363:876-8.

**TO THE EDITOR:** Vemurafenib is an inhibitor of mutated BRAF. The phase 3 trial of this agent for the treatment of metastatic melanoma showed impressive results.<sup>1</sup>

In our center, five patients with metastatic melanoma with the V600E mutation who received vemurafenib and six patients who received dacarbazine underwent systematic total body-surface monitoring of skin with a dermoscope. Six atypical lesions were removed in four patients in the vemurafenib group; these patients were otherwise having a response to treatment between week 4 and week 12. The lesions were small. Two local dermatopathologists and one additional expert diagnosed five early primary melanomas (such as the one shown in Fig. 1) and one dysplastic nevus. All of the lesions were wild-type for BRAF.

The effect of V600E BRAF inhibitors on BRAF wild-type melanocytic lesions is a crucial unresolved question.<sup>2</sup> Paradoxical activation of the RAF-MEK-ERK pathway by CRAF activation has been suggested by *in vitro* studies.<sup>3</sup> Unlike vemurafenib-induced squamous-cell carcinomas, early changes in melanocytic lesions are difficult to identify and require examination with the use of dermoscopy.

Observation of early BRAF wild-type primary melanomas in vemurafenib-treated patients, who otherwise had a clinically significant response, suggests a different behavior of melanoma cells according to their BRAF status and highlights the importance of repeated skin examination, including dermoscopy, in these patients.<sup>4</sup>