

CORRESPONDENCE



Reducing Asthma Treatment

TO THE EDITOR: The study by the American Lung Association Asthma Clinical Research Centers (May 17 issue)¹ showed that for patients with mild persistent asthma who were receiving twice-daily fluticasone, switching to treatment with once-daily fluticasone plus salmeterol was as effective as continuing treatment with twice-daily fluticasone. Asthma control often worsens over time because compliance with a twice-daily medication regimen decreases, which is an impetus for once-daily treatment. Since all participants used inhalers twice daily in this study, the findings do not allow one to determine whether once-daily treatment improves compliance and leads to better control. To determine whether once-daily treatment with fluticasone and salmeterol leads to better compliance and improved asthma control, we also need to undertake randomized studies that are unblinded and in which participants are monitored less closely, even if this approach is not as objective as that of a double-blind, placebo-controlled trial.

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Dr. Black reports receiving payment from GlaxoSmithKline for undertaking contract research. No other potential conflict of interest relevant to this letter was reported.

1. The American Lung Association Asthma Clinical Research Centers. Randomized comparison of strategies for reducing treatment in mild persistent asthma. *N Engl J Med* 2007;356:2027-39.

TO THE EDITOR: In the study by the American Lung Association Asthma Clinical Research Centers, the patients had asthma that was well controlled with twice-daily inhaled fluticasone. During the run-in period, patients were treated with fluticasone twice daily; at the onset of randomized treatment, the dose of inhaled corticosteroids was sharply decreased in two of the three groups. This approach did not take into account the clinical deterioration that can occur after cessation or reduction of inhaled corticosteroids in patients with asthma, as reported in previous investigations,^{1,2} which could have led to the remarkably higher cumulative percentage of patients with treatment failure during the first 4 weeks in the montelukast group. In future studies, there should be a dose-tapering interval between the run-in period and the double-blind treatment period.

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1. Hahtela T, Jarvinen M, Kava T, et al. Effects of reducing or discontinuing inhaled budesonide in patients with mild asthma. *N Engl J Med* 1994;331:700-5.

2. Hawkins G, McMahon AD, Twaddle S, Wood SF, Ford I, Thomson NC. Stepping down inhaled corticosteroids in asthma: randomized controlled trial. *BMJ* 2003;326:1115-20.

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TO THE EDITOR: The study by the American Lung Association Asthma Clinical Research Centers did not include an important treatment group. Although the fluticasone dose was reduced in the group for which treatment with salmeterol was

added, the addition of salmeterol cannot be considered part of a step-down approach. Special attention should be paid to the package warning — mandated by the Food and Drug Administration on the basis of study findings^{1,2} — that long-acting β_2 -agonists should be used only in patients whose asthma is inadequately controlled with low-dose or medium-dose inhaled corticosteroids.³ To evaluate a true step-down approach, the study should have included a treatment group that received a low dose of a once-daily inhaled corticosteroid.

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1. Nelson HS, Weiss ST, Bleecker ER, Yancey SW, Dorinsky PM. The Salmeterol Multicenter Asthma Research Trial: a comparison of usual pharmacotherapy for asthma or usual pharmacotherapy plus salmeterol. *Chest* 2006;129:15-26. [Erratum, *Chest* 2006;129:1393.]
2. Castle W, Fuller R, Hall J, Palmer J. Serevent nationwide surveillance study: comparison of salmeterol with salbutamol in asthmatic patients who require regular bronchodilator treatment. *BMJ* 1993;306:1034-7.
3. Food and Drug Administration. Serevent Diskus, Advair Diskus, and Foradil information (long acting beta agonists). Bethesda, MD: Department of Health and Human Services, 2006. (Accessed July 12, 2007, at <http://www.fda.gov/cder/drug/infopage/LABA/default.htm>.)

THE AUTHORS REPLY: Black correctly points out that our trial, like most randomized, double-dummy trials, examined the efficacy of three approaches to the treatment of mild, persistent asthma. We decided that blinding was more important for making a fair comparison of these treatments than was incorporating into the design the “added value” that once-daily treatment might confer in the fluticasone–salmeterol group. Our study population was diverse, however, with an age range from 6 to 76 years and nonwhite patients accounting for more than 30% of the participants, which enhances the generalizability of our results.

Chen suggests that our protocol should have

included an intermediate step-down in the twice-daily dose of fluticasone (100 μg) before the initiation of either once-daily treatment with fluticasone–salmeterol or montelukast, citing Haahtela et al.¹ and Hawkins et al.² Both of those studies involved patients with asthma of greater severity (defined on the basis of the forced expiratory volume in 1 second), and much higher doses of inhaled corticosteroids (1200 μg of budesonide per day and a mean of 1430 μg of beclomethasone per day, respectively) before the therapy was stepped down. Those stepped-down doses were more similar to the dose of inhaled corticosteroids at which our patients documented good asthma control than to our stepped-down doses. Therefore, we suggest that a step-down had already occurred in our trial. A step-down approach like the one suggested by Chen is probably not necessary in a closely monitored study.

Zitt and Rachelefsky raise two important issues: whether changing therapy from twice-daily inhaled corticosteroids to once-daily inhaled corticosteroids at one half the dose, with the addition of a long-acting beta-agonist, is really a “step down,” and whether our approach is a departure from current guidelines that recommend use of long-acting beta-agonists only in patients whose asthma is not adequately controlled by an inhaled corticosteroid alone. Whether a change from twice-daily fluticasone to once-daily fluticasone–salmeterol represents a step across rather than a step down is a semantic issue we do not wish to debate; the once-daily therapy is certainly simpler and involves half the dose of inhaled corticosteroids used in the twice-daily regimen. Our goal was to evaluate alternatives to twice-daily fluticasone. Once-daily montelukast was an obvious choice, and combination treatment with fluticasone and salmeterol once daily was a reasonable choice, given the results of the Salmeterol Multicenter Asthma Research Trial (SMART).³

We agree that our approach of using once-daily fluticasone–salmeterol is at odds with current recommendations. It is based on the firm scientific rationale that in persons with mild asthma, the bronchodilation produced by once-daily fluticasone–salmeterol lasts for at least 24 hours⁴ and involves an intervention that minimizes the need for the regular use of long-acting beta-agonists and should result in increased adherence. Furthermore, mounting evidence suggests that a reduced dose of inhaled corticosteroids may maintain con-

trol in patients with mild asthma.⁵ A goal of clinical investigation should be to provide new information and a firm scientific rationale from which to devise the next set of guidelines.

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2. Hawkins G, McMahon AD, Twaddle S, Wood SF, Ford I, Thomson NC. Stepping down inhaled corticosteroids in asthma: randomised controlled trial. *BMJ* 2003;326:1115-20.
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4. Masoli M, Weatherall M, Ayling J, Williams M, Beasley R. The 24 h duration of bronchodilator action of the salmeterol/fluticasone combination inhaler. *Respir Med* 2005;99:545-52.
5. Boushey HA, Sorkness CA, King TS, et al. Daily versus as-needed corticosteroids for mild persistent asthma. *N Engl J Med* 2005;352:1519-28.

Beclomethasone and Albuterol in Mild Asthma

TO THE EDITOR: In the study of rescue use of beclomethasone and albuterol in a single inhaler for mild asthma reported by Papi et al. (May 17 issue),¹ the morning peak expiratory flow rate (based on peak-flow diaries) was the primary end point, although there is enough reason to doubt its clinical relevance, its validity, and its physiological meaning in a disease that predominantly affects smaller airways. The peak expiratory flow rate reflects mainly central-airway mechanics² and is insensitive for the monitoring of peripheral-airway patency. Only because no Bonferroni correction was used, the morning peak expiratory flow rate — but not the evening peak expiratory flow rate or variability in peak expiratory flow rate — was marginally significantly different ($P=0.04$) between the as-needed combination group and the as-needed albuterol group, whereas the secondary end points of forced expiratory volume in 1 second and forced vital capacity (percent of the predicted value) proved to be much more sensitive in detecting a treatment effect. A similar situation was reported previously,³ and the study by Papi et al. once again illustrates that measures of peak expiratory flow rate are insensitive and therefore, in my opinion, do not reflect the disease adequately.

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2. Pedersen OF, Brackel HJL, Bogaard JM, Kerrebijn KF. Wave-speed-determined flow limitation at peak flow in normal and asthmatic subjects. *J Appl Physiol* 1997;83:1721-32.

3. Boushey HA, Sorkness CA, King TS, et al. Daily versus as-needed corticosteroids for mild persistent asthma. *N Engl J Med* 2005;352:1519-28.

TO THE EDITOR: The conclusions by Papi and colleagues with respect to the effectiveness and medication-sparing capacity of inhaled beclomethasone–albuterol as intermittent therapy for mild persistent asthma are based on their study of adults. The application of this method to children requires proof of principle. Lung growth, which affects treatment outcomes over time in children, could obviously not be accounted for in their study.

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THE AUTHORS REPLY: Merkus is concerned that the use of the morning peak expiratory flow rate, based on peak-flow diaries, may be misleading because it is insensitive and may not reflect small-airway abnormalities. Measurement of the peak expiratory flow rate is still recommended in international guidelines¹ for monitoring asthma. It is incorrect to state that the peak expiratory flow rate did not differ significantly between the groups in our study, since the morning peak expiratory flow rate was indeed sensitive enough to detect significant differences, in direct comparisons of the experimental treatment (as-needed use of combination albuterol–beclomethasone and regular use of beclomethasone) and the control treatment (as-needed