

## COMPARISON OF REGULARLY SCHEDULED WITH AS-NEEDED USE OF ALBUTEROL IN MILD ASTHMA

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**ABSTRACT**

**Background** Inhaled  $\beta$ -agonists are the most commonly used treatment for asthma, but data suggest that regularly scheduled use of these agents may have a deleterious effect on the control of asthma. We compared the effects of regularly scheduled use of inhaled albuterol with those of albuterol used only as needed in patients with mild chronic, stable asthma.

**Methods** In a multicenter, double-blind study, we randomly assigned 255 patients with mild asthma to inhale albuterol either on a regular schedule (126 patients) or only as needed (129 patients). The patients were followed for 16 weeks.

**Results** The primary outcome indicator, peak expiratory air flow measured in the morning, did not change significantly during the treatment period in the scheduled (416 liters per minute after the run-in period and 414 liters per minute after the treatment period) or the as-needed (424 liters per minute at both times) treatment groups ( $P=0.71$ ). There were no significant differences between the two groups in peak flow variability, forced expiratory volume in one second, the number of puffs of supplemental albuterol needed, asthma symptoms, asthma quality-of-life score, or airway responsiveness to methacholine. The statistically significant differences between the groups in evening peak flow and in the short-term bronchodilator response to inhaled albuterol were small and judged to be clinically unimportant.

**Conclusions** In patients with mild asthma, neither deleterious nor beneficial effects derived from the regular use of inhaled albuterol beyond those derived from use of the drug as needed. Inhaled albuterol should be prescribed for patients with mild asthma on an as-needed basis. (N Engl J Med 1996; 335:841-7.)

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**A**STHMA affects 5 to 7 percent of the population of North America and Europe; about 60 to 70 percent of patients with asthma have mild disease and are treated with inhaled  $\beta$ -agonists.<sup>1-4</sup> Before 1990, a number of standard reference works recommended the use of inhaled  $\beta$ -agonist medications on a regular basis<sup>5-8</sup> as a treatment for mild asthma. The recommendation, based on evidence that this approach

resulted in better control of asthma than the use of  $\beta$ -agonists on an as-needed basis,<sup>9-12</sup> has been reinforced by subsequent studies.<sup>13,14</sup> In 1990 and in a follow-up paper in 1993, Sears and coworkers<sup>15,16</sup> reported that regular use of  $\beta$ -agonists was associated with diminished asthma control and suggested that the use of  $\beta$ -agonists could account for increasing worldwide asthma morbidity. Subsequent reports have also reinforced these observations.<sup>17-19</sup> However, none of these studies, either in favor of or against the regularly scheduled use of  $\beta$ -agonists, have involved sufficiently large cohorts of patients with clinically uniform disease for a long enough period to be used in drafting recommendations for treatment. Indeed, the debate about the safety and efficacy of  $\beta$ -agonists as a class continues.<sup>20-32</sup>

Since mild asthma is the most prevalent form of asthma and the type for which inhaled  $\beta$ -agonists are most likely to be the sole therapy,<sup>3,4</sup> the Asthma Clinical Research Network of the National Heart, Lung, and Blood Institute undertook a study to test the following hypothesis: In patients with mild asthma whose only asthma treatment is inhaled  $\beta$ -agonists, the addition of scheduled treatment with inhaled  $\beta$ -agonists to treatment on an as-needed basis will result in no effect on the control of asthma. In this report we summarize the results of a 26-week randomized, multicenter, double-blind, placebo-controlled trial in patients with mild asthma. The trial compared the control of asthma in a group of patients treated with regularly scheduled albuterol with that in a group of patients treated with albuterol only as needed.

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\*Other participating investigators are listed in the Appendix.

## METHODS

## Patient Recruitment

Patients with mild asthma, as defined by the criteria shown in Table 1, were recruited from existing study populations and by advertising. Eligible patients entered a six-week single-blind run-in period, during which they used a placebo inhaler on a regular basis (two inhalations four times a day) and took supplemental puffs of open-label albuterol as needed. During the run-in period, patients were evaluated three times at two-week intervals, at which time asthma control was assessed by the review of a number of criteria.

## Patient Selection

Patients were randomly assigned to a treatment group if over the six-week period their asthma was clinically stable and they demonstrated their ability to comply with the study procedures, as indicated by the regular use of the placebo inhaler (monitored by a Chronolog recording device) and their ability to record their peak flow (twice daily, using a Mini-Wright peak-flow meter [Clement Clarke, Columbus, Ohio]) and asthma symptoms (once daily) in a diary. The treatments assigned consisted of either inhaled albuterol on a regular basis (two inhalations four times a day) plus albuterol as needed or inhaled placebo on a regular basis (two inhalations four times a day) plus albuterol as needed. Albuterol and placebo inhalers were generously supplied by Schering-Plough (Memphis, Tenn.). Patients were instructed to have their regularly scheduled inhalations in the morning after recording their morning peak flow, at midday, in the late afternoon, and on retiring to sleep after recording their evening peak flow. They were instructed to allow at least four hours between their regularly scheduled inhalation in the late afternoon and the recording of their evening peak flow.

## Patient Treatment

Over the ensuing 16 weeks, while patients received blinded treatment, the control of asthma was monitored daily, through peak flow rates and symptoms recorded by patients, as well as during clinic visits, which were scheduled every two to three weeks.

TABLE 1. CHARACTERISTICS USED TO DEFINE MILD ASTHMA.\*

CHARACTERISTIC	ALLOWABLE RANGE
FEV <sub>1</sub> †	≥70% of predicted value
Age	12 to 55 yr
PC <sub>20</sub>	≤16 mg/ml
Use of β-agonists	6 to 56 puffs of albuterol/wk; patients using less than 6 puffs of albuterol/wk at visit 1 had to have a PC <sub>20</sub> of ≤8 mg/ml
Use of other asthma medications	None, no corticosteroids for 6 wk
Other serious medical conditions, including pregnancy	Not allowed
Smoking	None in past year, maximal history of 5 pack-years permitted

\*FEV<sub>1</sub> denotes forced expiratory volume in one second, and PC<sub>20</sub> the concentration of methacholine required to decrease the FEV<sub>1</sub> by 20 percent.

†The FEV<sub>1</sub> was measured after at least eight hours without bronchodilator medications.

At the completion of the randomized-treatment period, all the patients were switched to single-blind treatment with inhaled placebo for a four-week withdrawal period; during this time patients continued to use open-label albuterol as needed.

Seven outcome indicators were monitored: peak flow, the symptom record, quality of life, the change in the forced expiratory volume in one second (FEV<sub>1</sub>) in response to an inhaled bronchodilator, the concentration of methacholine required to decrease the FEV<sub>1</sub> by 20 percent (PC<sub>20</sub>), asthma exacerbations, and treatment failure. Peak flow, the primary outcome indicator, was measured twice daily by patients using a Mini-Wright peak-flow meter; the best of three efforts was recorded. Patients recorded their asthma symptoms and the number of puffs of supplemental albuterol used daily. Asthma symptoms were recorded on a 4-point scale, with 0 representing no symptoms and 3 representing severe symptoms. Asthma-specific quality-of-life scores were recorded during clinic visits, with an instrument validated by other investigators.<sup>33</sup> To determine the spirometric response to an inhaled bronchodilator, the difference in the FEV<sub>1</sub> before and 15 minutes after two inhalations of albuterol was measured (and reported as percent improvement) during clinic visits when responsiveness to methacholine was not tested. Patients refrained from taking their study medications for at least eight hours before all clinic visits. To measure PC<sub>20</sub> for methacholine, methacholine aerosols were generated with a nebulizer (model 646, DeVilbiss Health Care, Somerset, Pa.) and a calibrated dosimeter (S&M Instruments, Doylestown, Pa.). The PC<sub>20</sub> for methacholine was determined by standard procedures.<sup>34</sup> Asthma exacerbations were monitored during each clinic visit; patients were asked about their asthma control, and all asthma exacerbations were recorded. An asthma exacerbation was defined as an increase in symptoms of cough, chest tightness, or wheezing in association with one or more of the following: an increase over the base-line use of supplemental β-agonist treatments of 8 or more puffs per 24 hours for a period of 48 hours, the use of 16 or more puffs of a supplemental β-agonist per 24 hours for a period of 48 hours, or a fall in peak flow of 35 percent or more from the best three-day average (morning and evening) during the run-in period. Treatment was considered to have failed if patients who had asthma exacerbations and were treated with increased doses of β-agonists did not respond adequately — that is, if they continued to meet the criteria for exacerbation. Such patients were treated with a short course of prednisone, as determined by their physicians; their data continued to be collected, and they remained in the trial (in accordance with the intention-to-treat method).

## Standardization and Quality-Assurance Techniques

All clinical laboratory tests — that is, measurements of lung function, skin testing for allergies, methacholine challenges, and quality-of-life assessments — were performed at each center with the use of equipment and procedures that were standardized for the entire network. Workers participating in the network were tested to ensure proficiency and uniformity in all network-related skills and had to pass certification examinations before the data they gathered could be used in the network. All results of spirometric testing (Collins Eagle 2 spirometer, Quincy, Mass.), including that for the methacholine challenge, were confirmed by a single network member. Peak-flow meters were tested against spirometers during each clinic visit and were replaced if they failed to meet previously established performance standards. A distributed data-entry system allowed each clinical center to submit its data over the Internet directly to the Data Coordinating Center. The Data Coordinating Center entered the data a second time to verify it.

## Compliance

Each patient was given a digital wristwatch with multiple alarms to improve treatment compliance. In addition, Chronolog recording devices were used with the randomly assigned metered-dose inhalers to provide an electronic record of the date and time of inhaler use.

### Statistical Analysis

Morning peak flow was chosen as the primary outcome variable for the calculation of sample size. A minimum of 200 patients made it possible to detect a difference of 25 liters per minute between groups with 80 percent statistical power. A goal of recruiting 250 randomized patients was established on the assumption that the dropout rate would be less than 20 percent. This sample size also provided 80 percent statistical power to detect a difference of 0.19 liter in FEV<sub>1</sub> and 0.70 doubling dilution in the PC<sub>20</sub> values for methacholine.

Response variables — that is, peak-flow values, medication use, and asthma symptoms — from the patients' diary cards were averaged each week. Because of the longitudinal nature of most of the response variables, a mixed-effects linear model was applied<sup>35,36</sup>; this approach allowed all data obtained to be used, not just the data obtained at a single visit. For each response variable, a segmented linear model was fitted with an intercept and with slopes for the last 4 weeks of the run-in period, the first 5 weeks of the treatment period, the remaining 11 weeks of the treatment period, and the withdrawal period. The "break point" after five weeks of randomized treatment was chosen on the basis of rates of asthma exacerbation reported by Sears et al.<sup>15</sup> For each outcome measure, values were calculated from the models for the end of the run-in period, for the end of the double-blind-treatment period, and for the end of the withdrawal period. This statistical model was determined before the start of the study, and therefore other models were not considered during data analysis. The groups were compared with respect to rates of treatment failure with the use of Fisher's exact test. To ensure patient safety, an interim analysis was conducted after approximately 40 percent of the randomized patients had completed the trial or withdrawn consent; as a result of this analysis, the P value considered to indicate statistical significance was reduced from 0.05 to 0.03 for the final analyses.<sup>37,38</sup>

## RESULTS

### Enrollment and Retention

Of the subjects recruited, 255 were eligible for enrollment at the end of the six-week run-in period and were randomly assigned to receive double-blind treatment (Table 2). There were no significant differences between the treatment groups with respect to any of the indexes monitored. During the period of randomized treatment and withdrawal, 25 subjects dropped out of the trial — 10 in the scheduled-treatment group and 15 in the treatment-as-needed group. Two hundred thirty patients completed the entire trial.

### Compliance

Compliance with the use of inhaled medication, either active or placebo, on a regular basis was greater than 80 percent, as indicated by Chronolog treatment records and an analysis of diary cards. Of the 3172 scheduled visits to patients' clinical centers, 26 were missed, for a rate of compliance of over 99 percent.

### Asthma Exacerbations

Asthma was exacerbated 24 times (11 times in the scheduled-treatment group and 13 times in the treatment-as-needed group) during the active treatment period and 4 times during the withdrawal pe-

**TABLE 2. CHARACTERISTICS OF PATIENTS IN THE TWO TREATMENT GROUPS.**

CHARACTERISTIC*	ALBUTEROL TREATMENT†	
	REGULARLY SCHEDULED (N=126)	AS-NEEDED ONLY (N=129)
Male sex — no. (%)	57 (45.2)	55 (42.6)
Minority racial or ethnic group — no. (%)‡	41 (32.5)	43 (33.3)
Atopy — no. (%)	122 (96.8)	127 (98.4)
Age — yr	28.6±9.0	29.3±9.2
Age <18 yr — no. (%)	16 (12.7)	10 (7.8)
Morning peak flow — liters/min§	418.3±100.5	421.6±99.8
Evening peak flow — liters/min§	437.6±101.5	440.7±99.1
Peak-flow variability — %§¶	3.9±5.7	3.7±6.9
Symptom score§	0.46±0.40	0.38±0.34
No. of supplemental puffs of β-agonist per day§	1.5±2.0	1.7±2.2
FEV <sub>1</sub> — liters (% of predicted value)**	3.1±0.74 (89.0±12.7)	3.15±0.68 (91.4±13.9)
Quality-of-life score**††	2.28±0.82	2.44±0.82
PC <sub>20</sub> — mg/ml**‡‡	0.64±1.82	0.64±1.82
FEV <sub>1</sub> response to albuterol inhalation — % change from base line§§	10.5±8.3	10.8±9.2

\*FEV<sub>1</sub> denotes forced expiratory volume in one second, and PC<sub>20</sub> the concentration of methacholine required to decrease the FEV<sub>1</sub> by 20 percent.

†Plus-minus values are means ±SD unless otherwise indicated.

‡Fifty-nine percent of the minority patients in the scheduled group were black, and 65 percent in the as-needed group were black.

§Values represent averages for the last four weeks of the run-in period.

¶Peak-flow variability was calculated as [(evening peak flow – morning peak flow) ÷ evening peak flow] × 100.

||Asthma symptoms were graded by the patient each day, from 0 for no symptoms to 3 for incapacitating symptoms.

\*\*This characteristic was measured from week 6 of the run-in period.

††Asthma-specific quality-of-life questionnaires were completed by the patients during clinical-center visits. A score of 1.0 indicates that asthma had no effect on the overall quality of life; a score of 2.0, that the patient's life was "a little limited" by asthma; a score of 3.0, that there was "some limitation"; and a score of 7.0, that there was "total limitation."

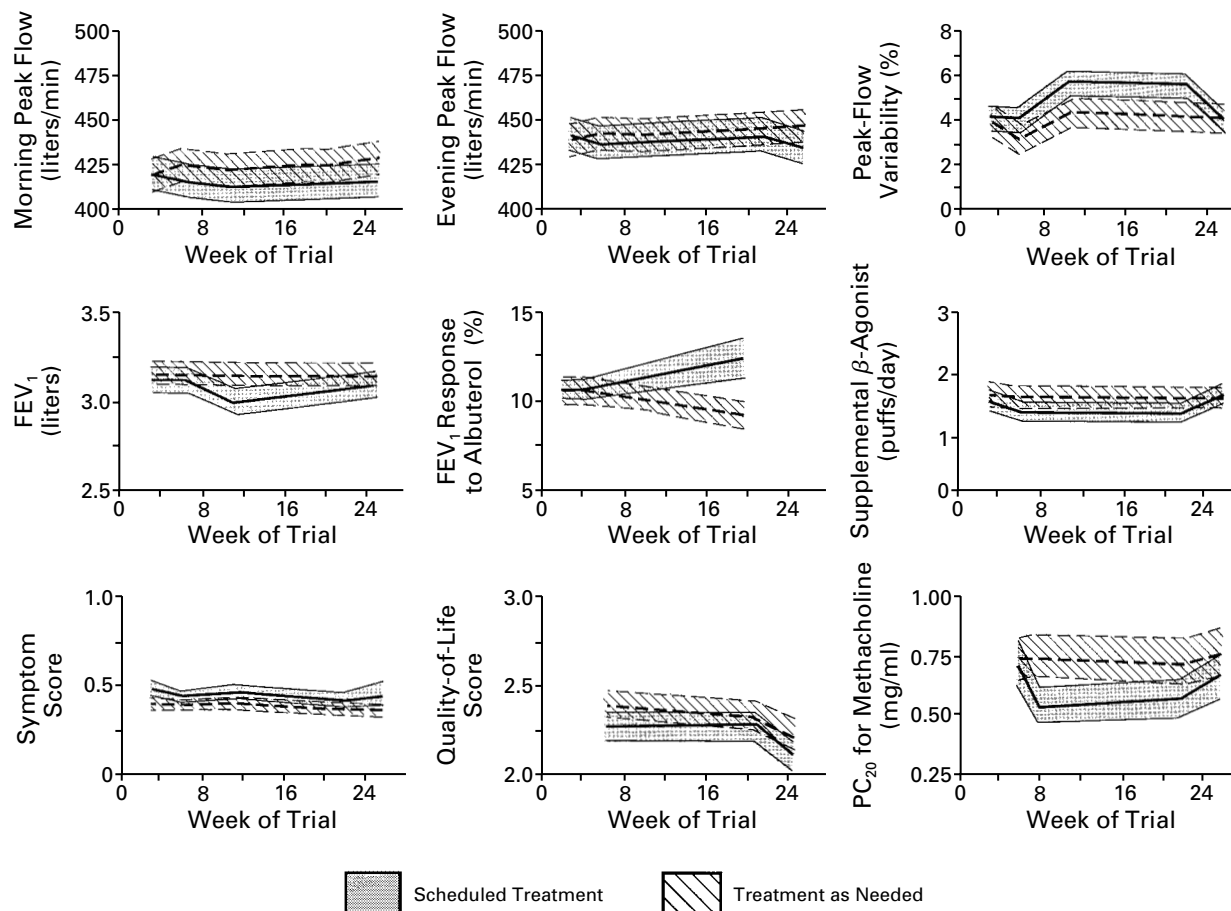
‡‡Values are medians and interquartile ranges.

§§Data are the averages from weeks 2 and 4 of the run-in period.

riod (twice in each treatment group). The 28 exacerbations occurred in 12 patients in the scheduled-treatment group and 11 patients in the treatment-as-needed group.

### Treatment Failures

Treatment was considered to have failed in 11 patients during the 16-week period of randomized treatment (5 in the scheduled-treatment group and 6 in the treatment-as-needed group) and in 2 during the withdrawal period (both in the scheduled-treatment group). There were three visits to the emergency room for asthma (two in the scheduled-treatment group and one in the treatment-as-needed group). No patients were hospitalized for asthma



**Figure 1.** Model Values for the Outcome Indicators Monitored throughout the Trial.

The thick solid and broken lines represent the mean data from the piecewise linear model. The thin lines indicate standard errors for the data shown. The statistical significance of the differences within and between groups is indicated in Table 3. FEV<sub>1</sub> denotes forced expiratory volume in one second, and PC<sub>20</sub> the concentration of methacholine required to decrease the FEV<sub>1</sub> by 20 percent. Peak-flow variability was calculated as  $(\text{evening peak flow} - \text{morning peak flow}) \div \text{evening peak flow} \times 100$ .

during the trial, and none died. There were no significant differences in any of the event rates between the two treatment groups.

#### Efficacy Outcomes

Lung function (indicated by morning peak flow, evening peak flow, peak-flow variability, FEV<sub>1</sub>,  $\beta$ -agonist responsiveness, and PC<sub>20</sub>) and asthma symptoms (determined by the number of uses of the supplemental  $\beta$ -agonist metered-dose inhalers, diary scores, and quality-of-life scores) as derived from the regression analysis performed for each patient group are shown in Figure 1 and Table 3. Graphic displays of values predicted by the model as compared with sample means showed excellent goodness of fit by the statistical model (data not shown). There were no significant differences in morning peak flow between the two treatment groups (Table 3). Even though the average use of albuterol was 9.3 puffs per

day in the scheduled-use group and 1.6 puffs per day in the treatment-as-needed group, the extra use of medication did not lead to differences in peak-flow variability, FEV<sub>1</sub>, supplemental albuterol use, asthma symptoms, quality of life, or PC<sub>20</sub>.

Two significant differences were found between the groups. One was in the change in evening peak flow from the end of the treatment period to the end of the withdrawal period: mean evening peak flow fell 7.7 liters per minute in the scheduled-treatment group but increased 1.3 liters per minute in the treatment-as-needed group. The other significant difference was in the change in bronchodilator responsiveness between the run-in period and the treatment period (Table 3). The FEV<sub>1</sub> response to treatment with albuterol increased from a 10.7 percent improvement to a 12.5 percent improvement in the scheduled-treatment group and decreased from a 10.7 percent improvement to a 9.2 percent im-

**TABLE 3.** MODEL ESTIMATES (USING INTENTION-TO-TREAT DATA) FOR THE END OF THE RUN-IN PERIOD (WEEK 6), THE END OF THE ACTIVE-TREATMENT PERIOD (WEEK 22), AND THE END OF THE WITHDRAWAL PERIOD (WEEK 26).\*

OUTCOME†	AFTER RUN-IN PERIOD		AFTER TREATMENT PERIOD		AFTER WITHDRAWAL PERIOD	
	SCHEDULED	AS NEEDED	SCHEDULED	AS NEEDED	SCHEDULED	AS NEEDED
Peak flow (liters/min)						
Morning	415.9	424.1	414.4	424.5	414.8	427.3
Evening	436.3	441.1	441.3	445.2	433.6	446.5
					P=0.005‡	
					P=0.021§	
Peak-flow variability (%)¶	4.1	3.2	5.7	4.3	4.0	4.2
			P<0.001		P<0.001‡	
FEV <sub>1</sub> (liters)	3.09	3.13	3.04	3.12	3.06	3.12
Albuterol response (%)**	10.7	10.7	12.5	9.2		
			P=0.005††			
Extra albuterol (puffs/day)	1.4	1.6	1.3	1.6	1.6	1.6
					P=0.013‡	
Symptom score‡‡	0.4	0.4	0.4	0.4	0.4	0.4
Quality-of-life score‡‡	2.3	2.4	2.3	2.3	2.1	2.2
					P=0.003‡	
					P=0.006§§	P=0.008§§§
PC <sub>20</sub> (mg/ml)	0.73	0.73	0.56	0.72	0.66	0.76
			P=0.013			

\*Values differ from those in Table 2 because Table 2 contains the mean data rather than estimates from the model.

†FEV<sub>1</sub> denotes forced expiratory volume in one second, and PC<sub>20</sub> the concentration of methacholine required to decrease the FEV<sub>1</sub> by 20 percent.

‡P value is for the within-group comparison of the response at the end of the treatment period with that at the end of the withdrawal period.

§P value is for the comparison between groups of the change in response from the end of the treatment period to the end of the withdrawal period.

¶Peak-flow variability was calculated as [(evening peak flow – morning peak flow) ÷ evening peak flow] × 100.<sup>39</sup>

||P value is for the within-group comparison of the response at the end of the treatment period with that at the end of the run-in period.

\*\*Bronchodilator response was last measured during the run-in period at week 4 and during the active-treatment period at week 20.

††P value is for the comparison between groups of the change in response from the end of the run-in period to the end of treatment period.

‡‡See the footnotes to Table 2 for an explanation of the scoring system.

§§P value is for the within-group comparison of the response at the end of the run-in period with that at the end of the withdrawal period.

provement in the treatment-as-needed group. A number of small but statistically significant changes within the groups were noted among the various treatment periods, as shown in Table 3. Results of the analysis in which data collected after the subjects in whom treatment was considered to have failed were excluded were essentially the same as those derived with the use of the intention-to-treat method.

### DISCUSSION

Over the past five years, health professionals have been concerned about potential deleterious effects of inhaled β-agonists on asthma control.<sup>20-32</sup> In part because of concern about potential adverse effects of regular β-agonist use, most current guidelines for the management of asthma recommend their use on

an as-needed basis only,<sup>3,4,40</sup> even though there is no sound clinical evidence on which to base this recommendation. Our study provides reassurance about the use of inhaled albuterol by clearly demonstrating, in patients with mild asthma, that its regular use is not associated with a deleterious effect on asthma control. At the same time, however, in this group of patients with mild asthma we were unable to demonstrate any additional beneficial effect of regularly scheduled treatment with inhaled albuterol beyond that achieved with albuterol used on an as-needed basis only.

We observed no change attributable to treatment in our primary outcome variable, morning peak flow. The only effect during randomized treatment that was attributable to the different treatment reg-

imens was the change in bronchodilator responsiveness. The FEV<sub>1</sub> response to treatment with albuterol was less than 12 percent in both treatment groups before the initiation of randomized therapy, probably because the patients had mild asthma. The small increase in bronchodilator responses observed in the scheduled-treatment group was somewhat surprising, since many have speculated that the regularly scheduled use of inhaled  $\beta$ -agonists may produce tolerance to their effects. Although we have no specific explanation for these findings, our data provide clinically meaningful reassurance that tolerance to the acute effect of inhaled albuterol does not occur with its regularly scheduled use.

The only other change attributable to the difference in treatment regimens occurred in evening peak flow between the end of treatment and the end of withdrawal. Evening peak flow rose slightly, but not significantly, during randomized treatment in the scheduled-use group and then fell significantly after the end of randomized treatment. We attribute this effect to the residual action of inhaled albuterol. Even though patients taking their scheduled albuterol were instructed to withhold it for four hours before measuring evening peak flow, albuterol is known to have a residual bronchodilator effect up to six hours after administration.<sup>13</sup> This observation also provides a basis for our finding that variability in peak flow increased with treatment and then decreased during withdrawal in the scheduled-treatment group.

An important aspect of our trial design was the incorporation of a "withdrawal" period, when all patients were treated with inhaled albuterol only as needed. This aspect of the study design allowed us to ascertain whether the scheduled use of inhaled albuterol masked underlying changes in lung function or asthma symptoms. We compared asthma control during the run-in and withdrawal periods to determine whether lung function deteriorated during scheduled treatment with albuterol. We found no statistically or clinically significant changes in any of the outcome indicators monitored; thus, there were no masked deleterious effects of scheduled albuterol use.

Although there were no other effects attributable to differences in treatment between the groups, it is of interest to examine one of the statistically significant changes that occurred in one of the treatment groups. In the two weeks after the start of treatment with regularly scheduled inhaled albuterol, we observed a small increase (one half of a doubling dilution) in airway responsiveness. This increase in airway reactivity did not progress as the scheduled treatment continued, disappeared as soon as the scheduled treatment was stopped, and was not associated with a change in any other index of asthma control. Thus, we were able to confirm what has been noted by oth-

ers — that the scheduled use of inhaled  $\beta$ -agonists slightly increases airway responsiveness to methacholine.<sup>16</sup> However, our data extend these findings in an important way by demonstrating that this change in airway responsiveness is not associated with any other alteration in asthma control in patients with mild asthma.

Our study differs in a number of ways from previously published studies addressing the same general question. Unlike the study by Sears and colleagues,<sup>15,16</sup> in which over 75 percent of the patients were using inhaled corticosteroids, our study was limited to patients with mild asthma whose mean lung function was near normal — that is, whose FEV<sub>1</sub> values were approximately 90 percent of the predicted value — and whose only asthma treatment was inhaled  $\beta$ -agonists. As a consequence of this difference in asthma severity, our patients had far fewer asthma exacerbations: fewer than 1 in 10 of our patients had a significant asthma exacerbation, as compared with 3.1 exacerbations per patient in the study by Sears et al. Since our data are relevant only to patients with mild asthma, it may not be appropriate to extrapolate our findings to patients with more severe asthma.

Over the past five years, there has been substantial debate about inhaled  $\beta$ -agonists as a class of asthma treatment.<sup>20-32</sup> In this study, despite a more than fivefold difference in the amount of  $\beta$ -agonist administered (9.3 puffs vs. 1.6 puffs per day), there was no clinically significant difference in asthma control between the treatment groups, indicating that patients with mild asthma should receive inhaled albuterol on an as-needed basis only; this approach also reduces the cost of medication. On the other hand, if, in an individual case, a patient with mild asthma and his or her physician perceive that scheduled treatment is beneficial, our results indicate that this practice will not be detrimental in this population.

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## APPENDIX

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