

# Efficacy and safety of loratadine plus pseudoephedrine in patients with seasonal allergic rhinitis and mild asthma

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**Background:** Antihistamines have been shown to have a variety of therapeutic effects in asthma. Although nasal obstruction may play an important role in modulating lower airway function, no prior trial has used a decongestant in combination with an antihistamine in patients with allergic rhinitis and concomitant asthma.

**Objective:** We sought to determine the efficacy and safety of loratadine (5 mg) plus pseudoephedrine (120 mg) (L/P) twice daily in patients with seasonal allergic rhinitis and mild asthma.

**Methods:** We conducted a randomized, double-blind, placebo-controlled trial of L/P in 193 subjects during the fall allergy season. Nasal and chest symptoms, albuterol use, and peak expiratory flow rates were recorded daily for 6 weeks. Spirometry was measured at baseline and after 1, 2, 4, and 6 weeks of therapy, and health-related quality of life was rated at the beginning and end of the study.

**Results:** Total rhinitis and asthma symptom severity scores were significantly reduced in patients receiving active therapy compared with those receiving placebo throughout the 6-week study. Peak expiratory flow rates improved significantly in patients treated with L/P during weeks 2 through 6 (peak effect [mean  $\pm$  SEM]: L/P, 26.23  $\pm$  4.64 L/min vs placebo, 8.52  $\pm$  3.53 L/min,  $p = 0.002$ ) as did FEV<sub>1</sub> (peak effect [mean  $\pm$  SEM]: L/P, 170  $\pm$  53 ml vs placebo, 20  $\pm$  40 ml,  $p = 0.01$ ) at all clinic visits. In addition, select measures of

asthma-specific quality of life improved significantly relative to placebo.

**Conclusions:** L/P significantly improved nasal and asthma symptoms, pulmonary function, and quality of life in patients with seasonal allergic rhinitis and concomitant mild asthma. (*J Allergy Clin Immunol* 1997;100:781-8.)

**Key words:** Loratadine, pseudoephedrine, rhinitis, asthma, peak expiratory flow rate, spirometry, albuterol, quality of life, nasal obstruction

The incidence of respiratory allergy in the United States has increased gradually over the past several years, and current estimates suggest that allergic rhinitis and bronchial asthma affect approximately 20% and 5% of the population, respectively.<sup>1,2</sup> Rhinitis and asthma frequently coexist, and large-scale population surveys indicate that up to 38% of patients with rhinitis have asthma, and up to 78% of patients with asthma have chronic nasal symptoms.<sup>3,4</sup> A growing body of research has also suggested that nasal allergy may play a role in modulating lower airway function.<sup>5-8</sup> In support of this concept, several clinical trials have demonstrated that topical treatment of allergic rhinitis with intranasal corticosteroids resulted in improvements in asthma symptoms, peak expiratory flow rates (PEFRs), and nonspecific bronchial hyperresponsiveness.<sup>9-12</sup>

Histamine has been shown to be an important mediator of allergic reactions in both the upper and lower airways.<sup>13,14</sup> Although oral antihistamines significantly reduce the symptoms of allergic rhinitis,<sup>15</sup> clinical studies of these agents in patients with asthma have yielded inconsistent results.<sup>16-24</sup> Furthermore, several studies that demonstrated benefits to lower airway symptoms and function used antihistamine doses that were higher than those approved for clinical use, making their relevance questionable.<sup>16-20,23</sup>

Loratadine is a highly potent and specific H<sub>1</sub>-histamine antagonist, which has proven to be efficacious in the treatment of seasonal allergic rhinitis.<sup>15</sup> Recent studies have demonstrated that loratadine plus pseudoephedrine (L/P) significantly reduces nasal congestion

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*Abbreviations used*

L/P: Loratadine plus pseudoephedrine  
PEFR: Peak expiratory flow rate

and relieves symptoms of rhinitis more effectively than either loratadine or pseudoephedrine alone.<sup>25</sup> Because nasal obstruction has been shown to be a potentially important factor contributing to lower airway dysfunction,<sup>7,8</sup> an antihistamine-decongestant combination might be expected to more effectively improve the clinical parameters of asthma than an antihistamine alone. This study was therefore conducted to assess the efficacy of L/P in the treatment of patients with seasonal allergic rhinitis and concomitant mild asthma.

**METHODS****Subjects**

Patients between 12 and 70 years of age with a history of seasonal allergic rhinitis and asthma occurring during the fall season for 2 or more years were screened for participation in the study. At the time of entry into the trial, subjects were required to have the following: active symptoms of allergic rhinitis (total nasal symptom score  $\geq 6$  with congestion score  $\geq 2$  during the 24 hours before the screening visit [see Efficacy assessments]); asthma symptoms occurring two or more times per week, but not daily; a positive skin prick or intradermal skin test response to a local weed allergen known to pollinate during the fall season; and FEV<sub>1</sub> of 70% or greater of predicted value. The criteria for exclusion were as follows: systemic disease or lung disease other than asthma; pregnancy; use of nasal, inhaled, or systemic corticosteroids or nasal or inhaled cromolyn within 2 weeks of study initiation; or escalating doses of immunotherapy during the study. The study protocol and informed consent were approved by an institutional review board at each site, and written informed consent was obtained from all patients or from the parent or legal guardian if the patient was younger than age 18 years.

**Study design**

The study was conducted as a randomized, double-blind, placebo-controlled, parallel-group trial performed at 12 investigative sites during the fall season of 1995. Patients underwent an initial screening visit consisting of history, physical examination, physician assessment of rhinitis and asthma symptoms, allergy skin tests, and spirometry. After they qualified for the study, patients entered a 1-week baseline evaluation period during which they recorded asthma and rhinitis symptoms and PEFR twice daily, total daily albuterol use, and number of nighttime awakenings caused by asthma. Patients returned to the study site (baseline visit) at which time they underwent spirometry and completed a health-related quality-of-life questionnaire. They were randomized to receive either a sustained-release formulation of loratadine (5 mg) plus pseudoephedrine (120 mg) (Claritin-D; Schering-Plough Corp., Kenilworth, N.J.) or placebo, taken twice daily on a regular basis, and were given an albuterol metered-dose inhaler (Proventil; Schering-Plough Corp.) with the recommendation to take two puffs every 4 to 6 hours (or more often during exacerbations) as needed for asthma symptoms. No rescue therapy for rhinitis symptoms and no other medications for asthma were allowed during the trial.

**TABLE I.** Demographic characteristics and baseline values for the efficacy population

	L/P (n = 92)	Placebo (n = 92)
Age (yr)	29.0 (9.5)	30.0 (11.1)
Sex [male patients (%)]	38.0 (41.0)	38.0 (41.0)
Total nasal symptom severity		
AM	7.7 (2.4)	7.0 (2.0)*
PM	7.3 (2.4)	6.7 (2.1)
Total asthma symptom severity		
AM	5.5 (2.6)	5.4 (2.4)
PM	5.5 (2.6)	5.4 (2.3)
Albuterol use (puffs/day)	2.5 (2.3)	2.5 (2.2)
PEFR (L/min)		
AM	295.1 (89.5)	382.4 (102.6)
PM	400.7 (93.2)	393.1 (103.8)
FEV <sub>1</sub> (L)	3.27 (0.7)	3.17 (0.8)
FEV <sub>1</sub> (percent predicted)	90.7 (13.0)	89.0 (11.4)

Data expressed as mean ( $\pm$  SD).

\*p = 0.04.

Patients returned to the clinic 1, 2, 4, and 6 weeks after starting study medication for review of diaries, adverse events, and medication compliance and spirometry was performed. At the final visit (week 6), patients completed final quality-of-life questionnaires and rated the overall response of their rhinitis and asthma symptoms.

**Procedures**

**Efficacy assessments.** Rhinitis and asthma symptom severity were rated by the patient as absent (0), mild (1), moderate (2), or severe (3). Rhinitis symptoms consisted of congestion, sneezing, pruritis, and rhinorrhea; asthma symptoms included wheezing, chest tightness, dyspnea, and cough. Ratings were performed twice daily, during the morning and evening (before taking study medication), and were based on patients' symptoms since their last diary entry. Total rhinitis and asthma symptom severity scores were calculated as the sum of the individual scores (maximum = 12). The overall responses of rhinitis and asthma symptoms to treatment were rated by the patient using an improvement score of complete relief (1), marked relief (2), moderate relief (3), slight relief (4), or treatment failure (5).

**Pulmonary function testing.** PEFRs were measured by patients with a Mini-Wright meter (MiniWright, Columbus, Ohio) in the morning and evening. PEFR measurements were performed in triplicate, with only the best effort recorded. Spirometry included measurements of FEV<sub>1</sub>; forced vital capacity; and forced expiratory flow, mid-expiratory phase, performed in triplicate before use of albuterol at the same time of day at each study visit.

**Quality-of-life questionnaire.** We used a health-related quality-of-life questionnaire (SF-36) that assesses eight separate dimensions of health, including physical functioning, limitation in usual role activities caused by physical problems (role-physical), bodily pain, general health perceptions, vitality (energy and fatigue), social functioning, limitation in usual role activities caused by emotional problems (role-emotional), and general mental health (psychologic distress and well-being).<sup>26</sup> We also used two asthma-specific modules: the first assesses breathlessness, mood, social concerns, and total symptoms<sup>27</sup>; and the second assesses psychosocial impact and physical symptoms

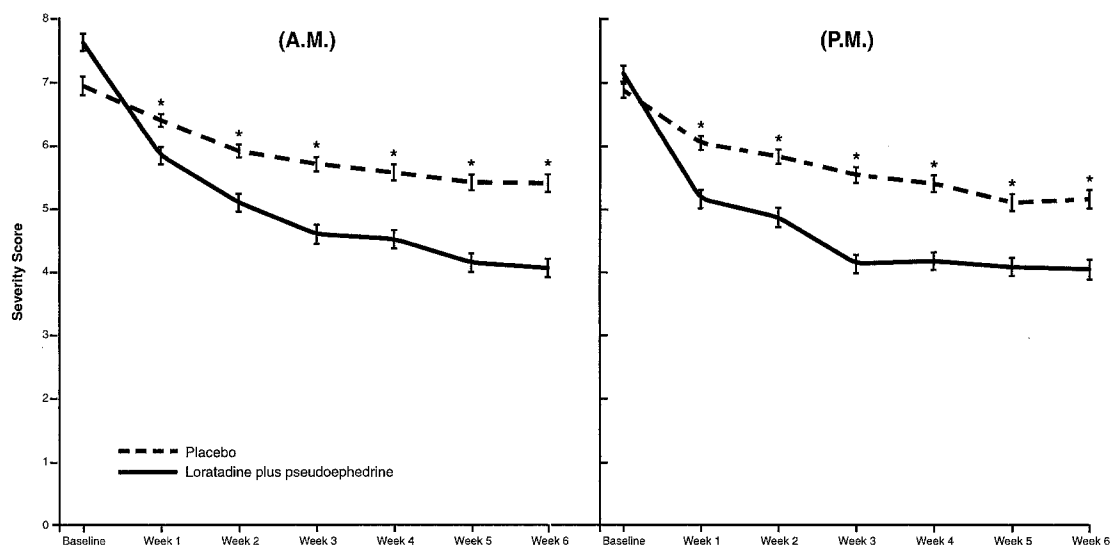


FIG. 1. Total nasal symptom severity scores (mean  $\pm$  SEM) in morning (A.M.) and evening (P.M.). \* $p < 0.05$ .

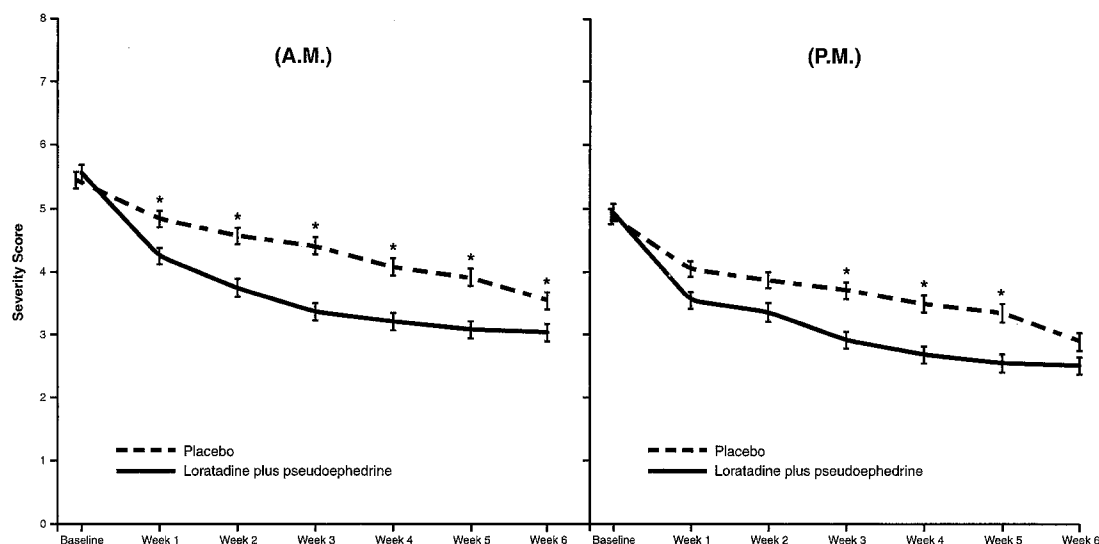


FIG. 2. Total asthma symptom severity scores (mean  $\pm$  SEM) in morning (A.M.) and evening (P.M.). \* $p < 0.05$ .

caused by asthma.<sup>28</sup> All three of these questionnaires have been validated in previous studies.

### Statistical analysis

Data generated from the daily diaries, including rhinitis and asthma symptoms and morning and evening peak flow rates, were averaged on a weekly basis. Changes in peak flow rates, symptoms, spirometric indices (FEV<sub>1</sub>; forced vital capacity; and forced expiratory flow, mid-expiratory phase), and quality-of-life parameters were assessed between treatment groups by comparing the baseline week with each subsequent week of the study by using analysis of variance. Nighttime awakening caused by asthma and overall responses of rhinitis and asthma to treatment were analyzed by means of the Cochran-Mantel-Haenszel test. Efficacy and safety analyses were performed in

patients who received at least 7 days and one dose of medication, respectively. All tests of hypotheses were two-tailed and performed at the 0.05 significance level.

## RESULTS

### Patients

Ninety-seven patients were randomized to receive L/P, and 96 were randomized to receive placebo according to computer-generated random numbers. Of the patients who started active treatment, 12 discontinued early: five because of possible adverse reactions, three because of noncompliance with the protocol, two because of treatment failure, and one for reasons unrelated to the study. One was lost to follow-up. Nine patients in

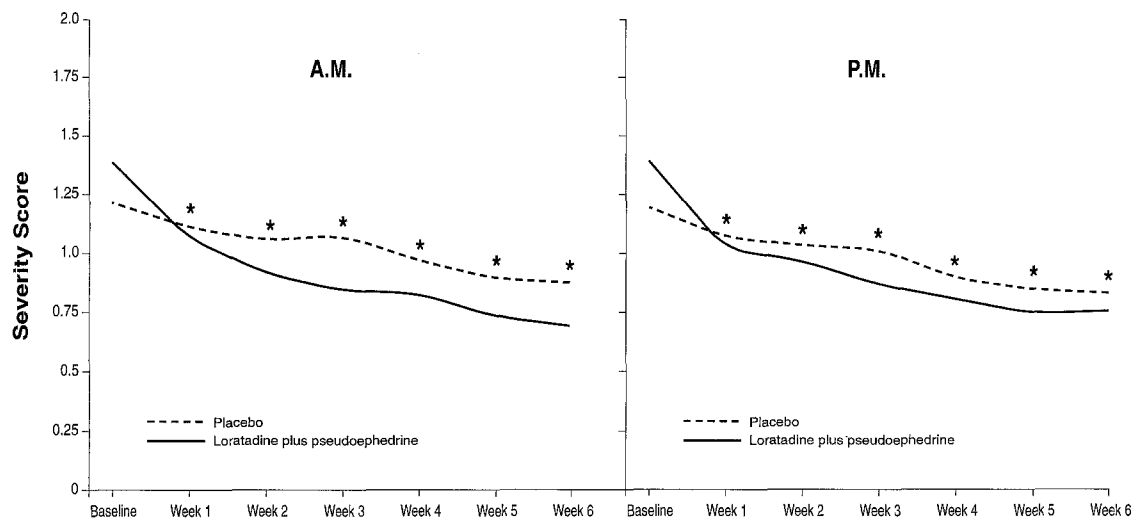


FIG. 3. Mean cough scores in morning (A.M.) and evening (P.M.). \* $p < 0.05$ .

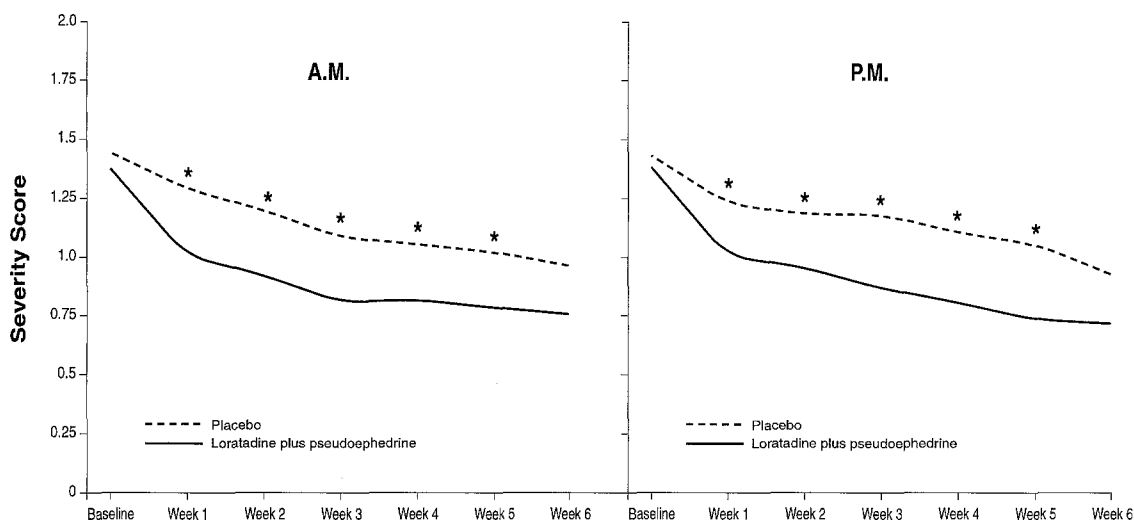


FIG. 4. Mean dyspnea scores in morning (A.M.) and evening (P.M.). \* $p < 0.05$ .

the placebo group discontinued early: three because of possible adverse reactions, one because of noncompliance, four because of treatment failure, and one for reasons unrelated to the study. A total of 92 patients in each treatment group met the criteria for inclusion in the efficacy analyses.

Demographic characteristics and baseline values of the efficacy population are shown in Table I. With the exception of total nasal symptoms, the remainder of patient characteristics and baseline values were comparable in the two groups.

#### Rhinitis symptoms

Total rhinitis symptoms including congestion, sneezing, pruritis, and rhinorrhea, responded within the first week and remained significantly improved in patients treated with L/P compared with those given placebo.

The total rhinitis symptom severity scores are shown in Fig. 1.

#### Asthma symptoms and albuterol use

Total asthma symptom severity scores measured in the morning were significantly improved over placebo throughout all 6 weeks of the study, whereas the evening symptom severity scores were significantly reduced during weeks 3 through 5 (Fig. 2). Cough and dyspnea responded most significantly to active therapy. Cough was significantly reduced during the morning and evening during all 6 weeks (Fig. 3), and dyspnea was significantly reduced during both the morning and evening during weeks 1 through 5 (Fig. 4). Morning wheezing and chest tightness improved significantly during weeks 1 through 5 and 2 through 5, respectively, but evening assessments of the symptoms

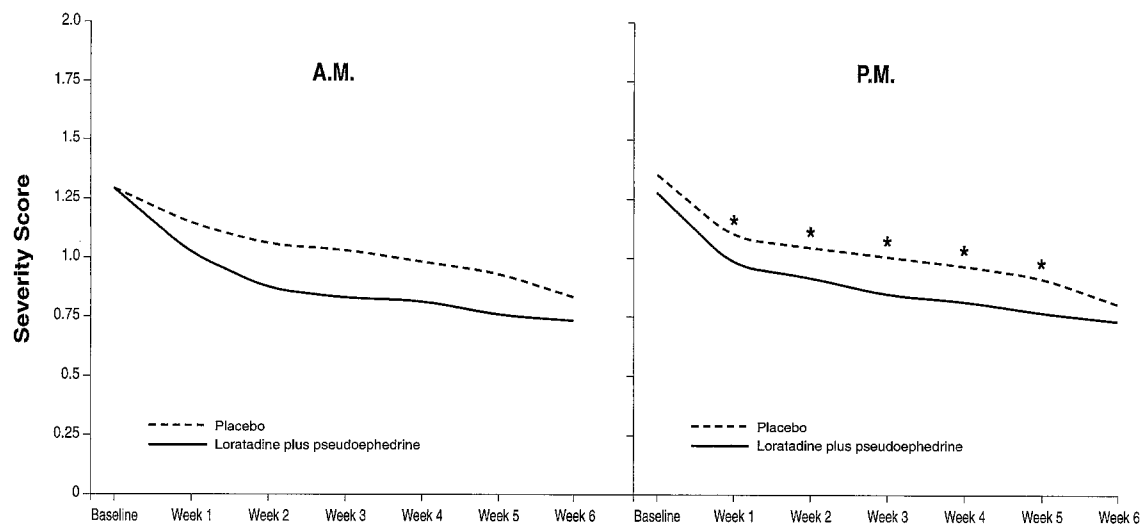


FIG. 5. Mean wheezing scores in morning (A.M.) and evening (P.M.). \* $p < 0.05$ .

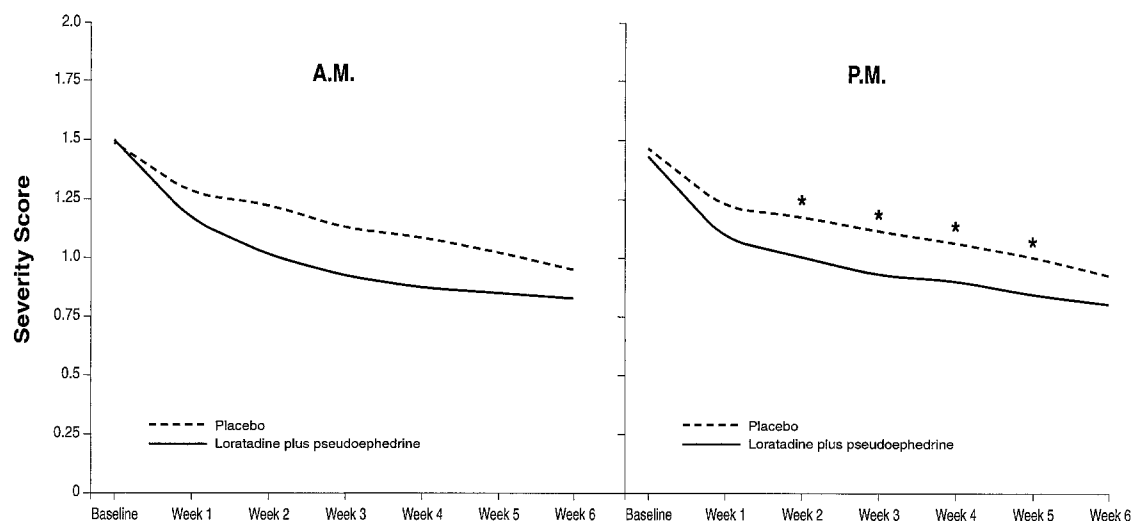


FIG. 6. Mean chest tightness scores in morning (A.M.) and evening (P.M.). \* $p < 0.05$ .

were not significantly improved with active treatment (Figs. 5 and 6).

Significantly fewer patients experienced more than one nighttime awakening caused by asthma per week in the group receiving L/P during weeks 3 and 5, and this number was at borderline significance at week 6 ( $p = 0.056$ ).

Albuterol was used sparingly throughout the study by both treatment groups (L/P group, 1.76 to 2.03 puffs per day; placebo group, 1.81 to 2.18 puffs per day). Although there was a trend toward less use in the active treatment group, this difference was not statistically significant.

#### Pulmonary function testing

Mean improvements in peak flow rates were two- to threefold higher in patients receiving L/P compared with those receiving placebo (Fig. 7). Both morning and

evening PEFs were significantly higher in the active drug group during weeks 2 through 6, with the peak effect occurring at week 6. FEV<sub>1</sub> also increased significantly relative to placebo at all four clinic visits (weeks 1, 2, 4, and 6), with the peak improvement occurring during week 4 (Fig. 8).

#### Overall response to treatment

At the end of the study, 49% of patients receiving active therapy rated their rhinitis symptoms as either completely or markedly improved compared with 24% of patients in the placebo group ( $p = 0.001$ ). Asthma symptoms responded similarly well to active therapy, with 43% of patients in the L/P group rating their symptoms as completely or markedly improved compared with 23% of patients receiving placebo ( $p = 0.01$ ).

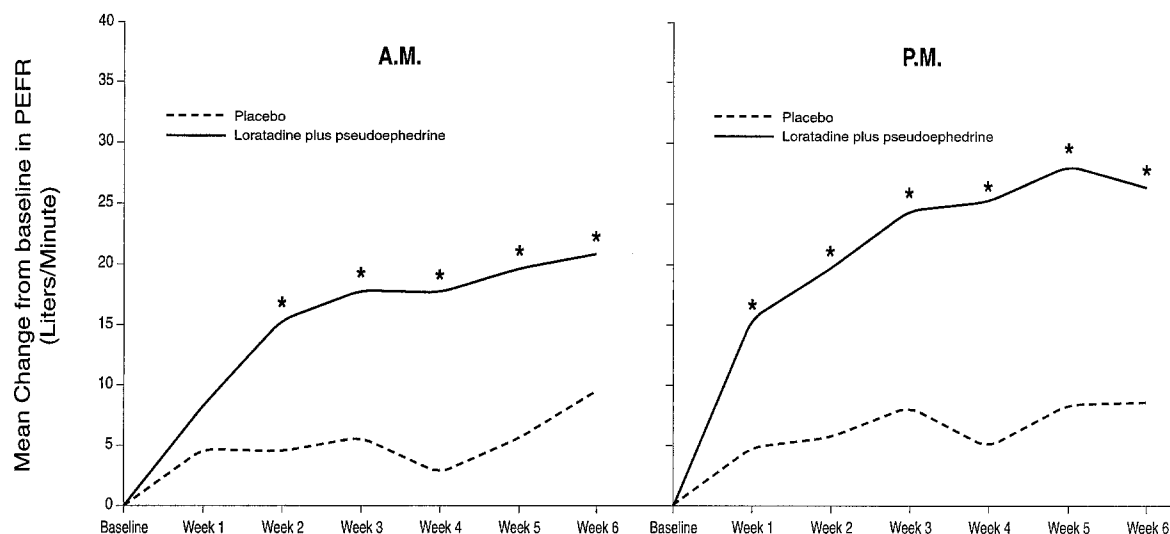


FIG. 7. PEFRs in morning (A.M.) and evening (P.M.), expressed as mean changes from baseline. \* $p < 0.05$ .

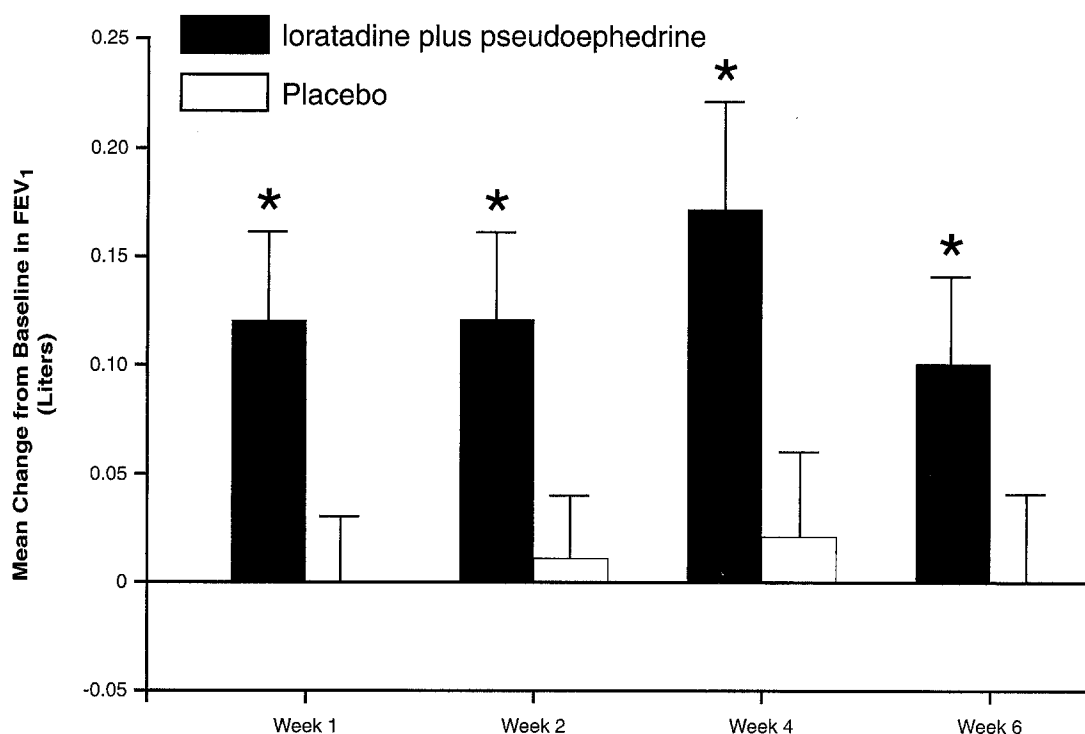


FIG. 8. FEV<sub>1</sub> (mean  $\pm$  SEM) measured at clinic visits, expressed as changes from baseline. \* $p < 0.05$ .

### Health-related quality-of-life assessment

At the end of the study, patients receiving L/P demonstrated improvement in seven of the eight domains (with the exception of role-physical) compared with those receiving placebo, but these changes were not statistically significant (data not shown). The asthma-specific modules demonstrated that patients receiving L/P had lower scores for all scales, and statistically significant improvements

were observed for psychosocial impact and physical symptom scores related to asthma (Fig. 9).

### Adverse events

One hundred twenty of 193 patients enrolled in the study reported adverse events, including 56 (57.7%) patients receiving active therapy and 64 (66.7%) receiving placebo ( $p = 0.236$ ). Adverse events were similar in

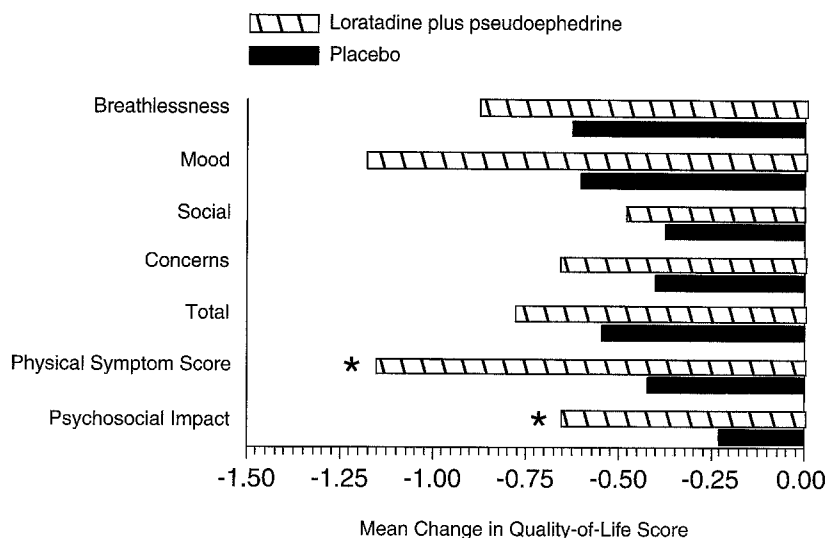


FIG. 9. Asthma-specific quality-of-life measurements, expressed as mean changes from baseline. \* $p < 0.05$ .

the two groups with the exception of insomnia, which occurred in 10.3% of patients taking L/P compared with 1% of patients taking placebo ( $p = 0.010$ ). The most common adverse events are shown in Table II.

## DISCUSSION

This study is the first to evaluate the efficacy of an antihistamine-decongestant combination medication in patients with seasonal nasal allergy and concomitant mild asthma, and it has demonstrated that L/P significantly improves both rhinitis and asthma symptoms and pulmonary function. In addition, this is the first trial, to our knowledge, to demonstrate improvements in asthma-specific quality of life with therapy for allergic rhinitis.

Home monitoring of PEFs provides a daily objective measure of lung function and may therefore be the most important parameter assessed in our study. Improvements in mean morning and evening PEFs in patients taking L/P were 20.87 and 26.23 L/min, respectively, as compared with 9.34 and 8.52 L/min in patients receiving placebo. Because daily albuterol use remained the same in the two treatment groups, these changes in airway caliber are attributable to the effect of antihistamine-decongestant therapy. Prior clinical trials of antihistamines in patients with asthma demonstrated improvements in PEFs only when administered in very high doses.<sup>17, 18</sup> Even more striking, the improvements in PEFs observed in our study are similar to those seen with inhaled anti-asthma medications, including nedocromil (difference of 16.5 L/min<sup>29</sup>) and cromolyn sodium (difference of 28 L/min<sup>30</sup>).

The mechanisms by which L/P improved asthma symptoms and lung function in our study may relate to effects of this medication on both pulmonary and nasal physiology. Antihistamines have been shown to have multiple direct effects on the lower airways, including bronchodilation and blockade of bronchial challenge

TABLE II. Adverse events for the safety population

	L/P (n = 97)	Placebo (n = 96)
Headache	31 (32)	31 (32.3)
Pharyngitis	3 (3.1)	9 (9.4)
URI	5 (5.2)	5 (5.2)
Insomnia	10 (10.3)	1 (1.0)*

Data are expressed as number (%) of patients.

URI, Upper respiratory tract infection.

\* $p = 0.01$ .

with allergen and histamine.<sup>31</sup> Doses of pseudoephedrine equivalent to those used in our study, however, have not been shown to have bronchodilatory effects.<sup>32</sup> Changes in asthma observed in this study may equally relate to concomitant improvements in nasal disease. Recent studies have explored the role of rhinitis in provoking asthma and suggest that allergic rhinitis may have important direct and indirect effects on pulmonary function. Nasal provocation with histamine and allergen in patients with rhinitis and asthma has been shown to cause reductions in lower airway caliber and increases in nonspecific bronchial responsiveness, respectively.<sup>5, 6</sup> Indirect effects of rhinitis on asthma have been demonstrated by studies that correlated nasal obstruction with increases in bronchospasm elicited by exercise, inhalation of cold air, and possibly exposure to pollen.<sup>7, 8, 33</sup> Therefore in this study treatment with an antihistamine-decongestant medication may have resulted in secondary improvements in asthma symptoms and pulmonary function by blocking the effects of histamine on the nasal mucosa and reducing nasal obstruction.

Although our study demonstrates that L/P significantly improved lower airway symptoms and function, it also provides further evidence that second-generation antihistamine-decongestants are safe to use in patients

who have allergic rhinitis and concomitant asthma. The approved labeling for antihistamines has, until recently, included a warning that these drugs should be used with caution in patients with asthma because of possible aggravation of bronchospasm. Although it has been recommended that the above warning be deleted from antihistamine labeling, many physicians have been reluctant to prescribe this class of medications for patients with allergic rhinitis and concomitant asthma.<sup>34</sup> This study and other recently performed large-scale trials suggest that antihistamines are safe for use by patients with asthma.<sup>22</sup>

A growing body of literature suggests that the upper airway may play a significant role in modulating lower airway function in patients with allergic rhinitis and concomitant mild asthma. L/P, used on a regular basis, effectively reduced the symptoms of seasonal allergic rhinitis and also significantly improved subjective and objective measures of mild bronchial asthma. Future efficacy trials are required to determine whether therapy for rhinitis can reduce the need for anti-asthma medications in patients with moderate to severe asthma, and whether treatment of allergic rhinitis can have a significant impact on health care costs related to lower airways disease.

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