A Large-Scale, Office-Based Study Evaluates The Use Of A New Class Of Nonsedating Antihistamines

A Report From CEN

***Abstract*: The two newest agents in the class of nonsedating antihistamines were studied in a wide variety of family practice patients. In a Phase IV, prospective, alternating sequence, open-label design, patients having allergic rhinitis (AR) were assigned to receive either astemizole (n = 659) or terfenadine (n = 639). The resultant treatment groups, typical of family practices, were comparable for demographics, signs and symptoms of allergic rhinitis, and clinical profile. The groups differed in that astemizole patients had a longer history of AR and a higher frequency of family history of AR. Patients who were treated for 3 to 8 weeks were grouped for analyses. The frequency and severity of the signs and symptoms of AR and patient complaints decreased markedly in both groups. Self-reported improvement in quality of life based on nine measures was the same for each group. No differences were seen between treatments when positive-rated outcomes were combined in the final overall assessment by physicians and patients. In rating the success of therapy, physicians' ratings of "excellent" and patients' ratings of "felt much better" were reported more frequently ($P < 0.05$) for astemizole, while physicians' ratings of "good" and patients' ratings of "better" were reported more frequently ($P < 0.05$) for terfenadine. (J Am Board Fam Pract 1990; 3:241-52.)**

An estimated 20 percent of the United States population is affected by allergic rhinitis,[1] and more than 30 million people take antihistamines during the course of a year.[2] While the signs and symptoms of allergic rhinitis are not life-threatening, the social and economic consequences are staggering. Overall, more than $500 million is expended each year on the direct health care costs associated with nasal allergy.[1,3]

Despite their widespread use, the first generation or classical H_1-receptor antagonists, i.e., chlorpheniramine or diphenhydramine, are known to cause a variety of adverse reactions, including depression and excitation of the central nervous system (CNS), anticholinergic effects (e.g., dry mouth, constipation, urinary retention, blurred vision), and gastrointestinal disturbances (e.g., decreased appetite, nausea, vomiting).[4-8] However, it is the CNS depressant effects of these drugs — sedative effects in particular — that have proved their greatest liability.

The high rate of sedation side effects associated with the use of the classical antihistamines creates a real-world problem for many patients who find it difficult to remain alert during the workday. The fact that many antihistamines are used as over-the-counter sleep aids attests to this. Moreover, because of sedation, many patients do not comply with recommended dosage regimens and thus fail to obtain full benefits of therapy. The problem is compounded because allergic rhinitis is a seasonal (up to 6 months each year) or perennial condition and therefore requires long-term or even chronic drug therapy. Side effects that may be tolerable for a brief time frequently become unacceptable during longer treatment. Ideally, the goals of optimal drug therapy for long-term management of allergic rhinitis should include adequate symptom control without troublesome side effects.

In the search for novel compounds with improved therapeutic properties, a new generation of antihistamines has been developed whose chemical structure is unrelated to the classical antihistamines.[4,5,9,10] Both terfenadine (Seldane™), introduced in 1985, and astemizole (Hismanal™) in 1989, are lipophobic and therefore do not cross the blood-brain barrier as readily as did their predecessors.[10-12] In fact, these new agents are the most specific H_1-receptor antagonists

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available today.[12] Because of their unique structural attributes, the efficacy of these drugs is comparable with the first-generation antihistamines, while their sedative effects are indistinguishable from placebo.[2,4,6,13-16]

The widespread use of terfenadine and astemizole to treat allergic rhinitis makes further study of their relative efficacies and safety profiles clinically interesting both to allergists and family physicians. Compliance, quality of life, and patient perception of therapy are important in evaluating a new drug's overall clinical usefulness.

This report describes the results of a large-scale study conducted by 141 family physicians in the Clinical Experience Network™ (CEN). CEN™ is comprised of more than 1000 board-certified family physicians under the direction of 5 past presidents of the American Academy of Family Physicians or American Board of Family Practice, a pharmacotherapeutics specialist, and a consultant in the field of allergy. Physicians are selected because of their academic and professional credentials and their interest in office-based clinical research. While most clinical research is conducted in large academic institutions or medical centers, often using atypical populations, CEN™ provides a base for family physicians to conduct clinical investigations in standard medical practices.

The research conducted by the Network is considered Phase IV, defined as studies performed after marketing approval, occurring under conditions of usual clinical use of the drug, with or without a control group.[17] Because of their large size, Phase IV studies can overcome the limitations of the premarketing evaluation process by expanding knowledge about a drug's adverse event frequency, drug interactions, drug use and cost-benefits, and comparative or long-term efficacy in patients normally excluded from investigational trials.

This study was designed to compare and evaluate the clinical profiles of terfenadine and astemizole in a large, diverse patient population. It is one in a series of studies conducted by the CEN™ and is the largest of its type on allergic rhinitis.

Methods and Study Design

Patient Selection

Ordinary family practice patients having seasonal allergic rhinitis were enrolled in the study. To qualify for inclusion, patients were required to be ≥ 12 years of age and to exhibit ≥ 2 of the following signs and symptoms: rhinorrhea, nasal block, lacrimation, ocular redness, ocular-nasal pruritus, sneezing, coughing, and wheezing. Patients could be newly diagnosed or known but requiring a change in therapy because of inadequate efficacy, adverse reactions, or serious noncompliance with previous therapies. All eligible patients signed an informed consent form.

We excluded nursing mothers, patients who were pregnant or who were judged by their physicians not to be practicing adequate birth control per package-labeling guidelines, and patients with demonstrated hypersensitivity to the study drugs or other antihistamines. All injectable corticosteroids were discontinued at least 30 days before study entry, and no antihistamine-containing medications, oral or inhaled corticosteroids, or topical-inhaled cromolyn sodium were allowed after entry. During the study, patients were counseled not to use over-the-counter decongestants, and all medications taken for related or unrelated conditions were recorded by the investigator.

The participating physicians were informed about potential problems associated with the use of the two study drugs — in particular, the anticholinergic effects of terfenadine that may present a risk in patients having lower airway disease (e.g., asthma). Also, patients receiving astemizole take an above-average amount of allergen to induce a wheal and flare response on skin testing.

Study Drugs

Each patient was assigned to receive one of the two antihistamines: astemizole 10 mg once daily (QD) (taken on an empty stomach) or terfenadine 60 mg twice daily (BID). Dosage adjustments were not encouraged.

Study Design

The study was designed as a Phase IV, prospective, open-label, parallel study of astemizole and terfenadine in seasonal allergic rhinitis. Patients were enrolled at 141 centers across the United States from April 1, 1989, until September 30, 1989. Each center enrolled an average of 10 patients (range = 1–58; 3 centers enrolled more than 20 patients), who were assigned treatment groups according to an alternating sequence design.

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The study was designed to be conducted within the daily routine of the participating family physician's practice and did not require any change in the usual approach to treatment of seasonal allergic rhinitis, except that patients were instructed to avoid using concomitant antihistamine-containing preparations.

At study entry (baseline), medical and antihistamine medication histories were obtained from each patient. Signs and symptoms of allergic rhinitis, other patient complaints, and the severity of each were noted. Concomitant medications currently being taken by the patient also were recorded. A physical examination was performed noting any abnormalities relevant to allergic rhinitis or therapy, as well as results and dates of any hypersensitivity tests.

Following 2 weeks of treatment with the study drug, patients were seen by their physician or interviewed by telephone to determine whether there were any untoward reactions to therapy. After 3 to 8 weeks, each participating physician recorded the following: compliance with the prescribed regimen, signs and symptoms of allergic rhinitis, patient complaints, quality of life, and overall effect of therapy on the patient's symptoms. Changes in concomitant medications and relevant abnormalities were noted. Patients filled out an evaluation form at this time.

Data Collection and Management

Standardized data collection forms were completed by the participating family physicians, and the data were compiled by an independent firm, HLS Clinical Systems, Little Falls, NJ, for review, coding, data entry and analysis, and manuscript preparation.

Analytical Methods

Eligibility for analyses was determined by the duration of therapy. Twelve hundred ninety-eight patients had at least one follow-up visit and complete records. When therapy lasted 3 to 8 weeks (1099 patients), efficacy, compliance, quality of life, and patient and physician overall evaluations were analyzed. When therapy was less than 21 days (130 patients) or more than 56 days (69 patients), these variables were not analyzed. All patients with at least one follow-up visit (1385 patients), regardless of duration of therapy, were included in the safety analysis.

Safety

Physicians recorded general complaints, suspected adverse effects, and reasons for discontinuation that were believed to be therapy related. Complaints at entry and at other visits were ranked 0 = none, 1 = mild, 2 = moderate, and 3 = severe. Mean scores for each complaint were calculated. Differences between entry (baseline) and final visit were calculated by subtracting the mean scores. Suspected adverse reactions were tabulated for each drug.

Efficacy

Physicians rated the severity (0 to 3) of each presenting sign or symptom of allergic rhinitis at entry and at the final visit. Differences between entry and final visits were calculated by subtracting the mean scores. The sum of the severity scores for each symptom were calculated as the total symptom score and compared for differences between entry and final visits.

Quality of Life

At the final visit, patients reported their quality of life, comparing it with what it was before they began taking the prescribed medication. Nine variables were rated using a 5-point scale (1 = much better, 2 = better, 3 = same, 4 = worse, 5 = much worse). Mean scores for each variable were calculated and used to determine differences, if any, between treatment groups.

Overall Response

Both patients and physicians were asked to rate their overall satisfaction with the outcome. Physicians responded to the question – "Please rate the overall effect of the study medication on the patient's symptoms." Patients were asked – "How do you feel since you began taking the prescribed allergy medication?" Answers were rated on a 5-point scale, and mean scores were compared.

Statistical Analysis

Standard statistical procedures were employed using the SAS™ package for analysis of variance, Wilcoxon Rank Sum Tests, chi-square tests, and Fisher's exact test.

Subgroup Analysis

Within each treatment group are large subgroups defined by gender, race, history of allergic rhini-

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Table 1. Distribution of Patients.

	Total (n)	Astemizole (n)	Terfenadine (n)
At least one follow-up	1385	703	682
Complete records	1298	659	639
Treated ≥ 21 days	1168	588	580
Treated ≥ 21 but ≤ 56 days	1099	556	543

tis, smoking, and age. It is unlikely that each subgroup contributes equally to the total outcomes. Thus, the data base was analyzed to determine which subgroups differed from the averaged results of all groups, i.e., those groups that had the most influence on the outcomes. The proprietary computer program, Genesis II, was used for the subgroup analyses.

Results

Assignment of Patients

One hundred forty-one family practitioners in 48 states enrolled 1485 patients in the study, of whom 1385 had at least one follow-up visit and were included in the safety analysis. Of these, 1099 patients met the criteria of 3 to 8 weeks' treatment for inclusion in the efficacy analysis (Table 1).

Reasons for discontinuation from the study are listed in Table 2. Most patients in both treatment groups completed the study. Among those who discontinued treatment, the reason given most often was inadequate control of the symptoms of allergic rhinitis, reported by 7 percent in the astemizole group and 5.2 percent in the terfenadine group. Patient complaints thought to be drug related were reported by 5.0 percent in the astemizole group and 3.3 percent in the terfenadine group.

Table 2. Discontinuations from Study by Treatment Group.

	Astemizole (n = 659)		Terfenadine (n = 639)	
Reason	≤ 20 Days n (%)	All Patients n (%)	≤ 20 Days n (%)	All Patients n (%)
Inadequate control of allergy symptoms	30 (4.6)	46 (7.0)	25 (3.9)	33 (5.2)
Adverse events	24 (3.6)	33 (5.0)	18 (2.8)	21 (3.3)
Lost to follow-up	15 (2.3)	28 (4.2)	15 (2.4)	30 (4.7)
Other	2 (0.3)	3 (0.5)	1 (0.2)	1 (0.2)
Total	71 (10.8)	110 (16.8)	59 (9.2)	85 (13.5)

Demographic Variables

As shown in Table 3, the study population was typical of the average family practice by gender, age, and racial distribution.[18,19]

Clinical Variables at Entry

History of Allergic Rhinitis

Table 4 shows that the two treatment groups were homogeneous for history of allergic rhinitis, percent not controlled, frequency of colds and sinus problems, previous use of antihistamines, and negative effect of work environment. However, the astemizole group had a greater ($P < 0.05$) frequency of family history of allergic rhinitis (67 percent versus 60 percent), a longer duration of the condition (12.0 yrs versus 10.5 yrs), and more had used terfenadine in the recent past (15.6 percent versus 2.2 percent), which was due probably to the longer market availability of terfenadine and potential exposure to the drug.

Table 3. Selected Demographic Variables of Patients at Entry by Treatment Group.

	Astemizole (n = 556)	Terfenadine (n = 543)
Variable	n (%)	n (%)
Gender		
Men	216 (38.9)	200 (36.5)
Women	340 (61.1)	343 (63.5)
Mean age (years)	38.2	38.3
Race		
White	519 (93.4)	492 (90.6)
Black	23 (4.1)	32 (5.9)
Other	14 (2.5)	19 (3.5)
Tobacco users	77 (13.9)	81 (14.9)

Signs and Symptoms of Allergic Rhinitis

The percentages of patients having specific signs and symptoms, the mean severity scores for each sign and symptom, and the total severity scores at entry did not differ between treatment groups. The most prominent complaints in both treatment groups were rhinorrhea, nasal block, and sneezing.

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Patient Complaints

Frequency and severity of most complaints in the two treatment groups at entry were comparable; however, patients in the terfenadine group reported complaints of depression, drowsiness, and gastrointestinal distress more frequently and had a higher mean complaint score than patients in the astemizole group (Table 5).

Clinical Variables at Follow-Up

Compliance

In both groups, the percentage of patients reporting some lapse in taking prescribed medication was small (astemizole, 8 percent; terfenadine, 9 percent). Approximately 91 percent were more than 80 percent compliant, and dosage adjustments occurred in only 4 percent of all patients.

Other Drugs

Use of other drugs during the study period was similar in the two treatment groups. Only 8 patients reported using another antihistamine or decongestant (3 in the astemizole group and 5 in the terfenadine group).

Control of Signs and Symptoms

In both treatment groups, patients treated 21 to 56 days experienced marked improvement in their signs and symptoms of allergic rhinitis (Table 6). Total symptom scores also decreased markedly; from 10.6 to 2.7 ($P < 0.01$) for astemizole and from 10.8 to 3.4 ($P < 0.01$) for terfenadine.

Patient Complaints

By the final evaluation, the various complaints that patients reported at baseline had decreased significantly, both in frequency and severity (Table 7). There were no statistically significant differences between treatments. The largest changes seen in both groups were in fatigue and headache. Most changes were comparable in the group-to-group comparisons. However, for three complaints – depression, drowsiness, and gastrointestinal disturbances – there were differences in the magnitude of the changes when the groups were compared. Because the mean severity scores for these three symptoms were significantly different at entry (but not at follow-up) in the two treatment groups (see Table 5), a comparison of the change in mean severity scores could not be made.

Table 4. History of Allergic Rhinitis.

Variable	Astemizole (n = 556)	Terfenadine (n = 543)
History of AR	80.0%	76.8%
Mean yrs since first sign of AR	12.0 yr*	10.5 yr
Previous antihistamine use	80.2%	76.9%
Prior use of terfenadine	15.6%*	2.2%
AR not presently controlled	90.3%	90.5%
Frequent colds/sinus problems	66.0%	67.0%
Family history of AR	67.0%*	60.0%
Work environment contributes to allergy	17.8%	16.6%

*Statistically significant difference, $P < 0.05$.

One complaint – appetite increase – was more common at the final evaluation. In both treatment groups, there was a slight increase in frequency and the mean severity score for this complaint.

In addition to the common complaints reported, physicians recorded a wide variety of "other" complaints in 27 patients (4 percent) in each treatment group. No single complaint was reported by more than 0.5 percent of the patients in either treatment group.

Table 5. Patient Complaints at Entry by Treatment Group.

	Astemizole (n = 556)		Terfenadine (n = 543)	
Complaint	%	Mean Severity Score*	%	Mean Severity Score*
Anorexia	15	0.21	17	0.25
Increased appetite	9	0.13	8	0.11
Depression	17	0.25	23†	0.33
Dizziness	30	0.41	29	0.40
Drowsiness	44	0.71	48†	0.79
Dry mouth	46	0.76	47	0.78
Fatigue	63	1.07	62	1.08
GI distress	18	0.25	19†	0.30
Headache	55	0.98	56	1.00
Insomnia	31	0.53	34	0.66
Irritability	37	0.59	38	0.62
Tremor	7	0.11	9	0.13
Other	4	–	4	–
Total mean complaint score		6.00		6.35

*Mean severity score: 3 = severe, 2 = moderate, 1 = mild, 0 = none.
†Statistically significant difference, $P < 0.05$.

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Table 6. Physicians' Ratings of Effect of Therapy on Signs and Symptoms of Allergic Rhinitis.

	Astemizole (n = 556)				Terfenadine (n = 543)			
	Entry		Final		Entry		Final	
Sign-Symptom	Percent Patients	Mean Severity Score*	Percent Patients	Mean Severity Score*	Percent Patients	Mean Severity Score*	Percent Patients	Mean Severity Score*
Rhinorrhea	89	1.8	34	0.9†	92	1.8	42	0.5†
Nasal block	91	2.0	41	0.6†	92	1.9	45	0.6†
Lacrimation	73	1.3	20	0.3†	76	1.4	23	0.3†
Ocular redness	67	1.1	15	0.2†	66	1.2	20	0.3†
Pruritus	63	1.2	22	0.3†	61	1.2	24	0.3†
Sneezing	89	1.8	33	0.4†	88	1.8	39	0.5†
Coughing	59	1.0	21	0.3†	60	1.0	23	0.3†
Wheezing	29	0.5	10	0.1†	31	0.5	12	0.2†
Total		10.6		2.7†		10.8		3.4†

*Mean severity score: 3 = severe, 2 = moderate, 1 = mild, 0 = none.
†Statistically significant improvement from entry, $P < 0.01$.

Adverse Reactions

Adverse events were cited as the reasons for discontinuation in 54 cases (Tables 2 and 8). Central nervous system effects were most often the cause of discontinuation in both treatment groups. Gastrointestinal complaints leading to discontinuation were reported by 1.4 percent of astemizole patients and 0.6 percent of terfenadine patients.

Quality of Life

Patient ratings at follow-up of the effect of antihistamine therapy on the quality of life showed that, on average, patients in both treatment groups felt improved. For the nine quality-of-life variables (routine activities, sleeping habits, tension, driving ability, mental alertness, energy level, work or school attendance, general well-

Table 7. Patient Complaints at Entry and Follow-up by Treatment Group.

	Astemizole (n = 682)*			Terfenadine (n = 630)*		
Complaint	Percent Entry	Percent Follow-up	Change Mean Severity Score†	Percent Entry	Percent Follow-Up	Change Mean Severity Score†
Improved						
Anorexia	15	5	0.15	17	6	0.19
Depression‡	17	9	0.13	23	8	0.23
Dizziness	30	8	0.32	29	10	0.29
Drowsiness‡	44	13	0.54	48	13	0.64
Dry mouth	46	23	0.41	47	21	0.44
Fatigue	63	25	0.74	62	24	0.75
GI distress‡	18	9	0.13	19	7	0.21
Headache	55	19	0.70	56	21	0.75
Insomnia	31	9	0.39	34	11	0.41
Irritability	37	14	0.40	38	14	0.46
Tremor	7	4	0.06	9	4	0.10
Other	4	3	—	4	3	—
Worsened						
Increased appetite	9	14	0.05	8	9	0.03

*Includes any patient whose data was recorded, even if longer than 56 days.
†Mean severity score: 0 = none, 1 = mild, 2 = moderate, 3 = severe.
‡Statistically significant difference between treatments at baseline, but not follow-up; thus, change in mean severity scores not compared statistically.

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Table 8. Adverse Events Leading to Discontinuation of Therapy by Treatment Group.

Category	Astemizole (n = 659)	Terfenadine (n = 639)
CNS		
Drowsiness, fatigue	9	7
Hallucinations, depression	0	3
Anxiety	5	1
Insomnia	2	1
Headache	7	2
Visual disturbances	1	0
GI		
GI disturbances	9	4
Dry mouth	3	0
Decreased appetite	1	0
Increased appetite	0	1
Other	4*	4†
Total	41 (1.24/patient)	23 (1.1/patient)

*Rash, shortness of breath.
†Palpitations, thrombophlebitis, myoclonic seizures.

being, and emotional stability), there were no significant differences between the responses for the astemizole or terfenadine groups.

Overall Assessment

An equal number of physicians reported an "excellent," "good," or "fair" rating of overall satisfaction with astemizole and terfenadine (90 percent and 91 percent, respectively) (Table 9). Patients also reported that they felt "much better" or "better" since beginning astemizole (83 percent) and terfenadine (85 percent).

However, astemizole was rated highest by 38 percent of physicians ("excellent") and 40 percent of patients ("much better") compared with 30 percent of physicians and 34 percent of patients giving terfenadine the highest rating. These between-treatment differences were statistically significant ($P < 0.05$).

Terfenadine was rated "good" by 48 percent of physicians and "better" by 52 percent of patients compared with 40 percent of physicians and 44 percent of patients giving astemizole these ratings. These between-treatment differences were statistically significant ($P < 0.05$).

Subgroup Analysis

With a large, heterogeneous population, it is always possible that while the global results are the same, different subgroups could have contributed differently to the results. Thus, the demographic variables, signs and symptoms of allergic rhinitis, and the overall responses were tested statistically, both singly and in combination, to determine whether there were any subgroups that impacted on the outcome of therapy.

Subgroup analyses are useful in identifying specific patient populations in which significant differences between treatments emerge. What implications such differences may have clinically and how the data are used to determine treatment decisions are open to interpretation. Because patient response to therapy varies widely, these analyses identify specific subgroups who may benefit maximally from specific treatment regimens. These subgroups should then become the focus in future studies designed to assess clinically significant differences between treatments.

We found that differences at entry between the treatment groups (family history, years since first sign of allergy, previous use of antihistamines in general and terfenadine in particular) did not in-

Table 9. Overall Assessments by Physicians and Patients by Treatment Group.

Physicians' Ratings			Patients' Ratings		
	Astemizole (n = 556)	Terfenadine (n = 541)		Astemizole (n = 541)	Terfenadine (n = 529)
Excellent	38.1%*	29.8%	Much better	39.7%*	33.5%
Good	39.9%	48.4%*	Better	43.6%	51.8%*
Fair	12.4%	12.6%	Same as before	14.2%	12.1%
Poor	8.6%	7.8%	Worse	2.2%	2.5%
Worse	0.9%	1.5%	Much worse	0.2%	0.2%

*Statistically significant difference, $P < 0.05$.

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Table 10. Physicians' Assessment of Overall Satisfaction with Therapy by Treatment Subgroups.

	Astemizole Rating* (n)	Terfenadine Rating* (n)	Intergroup Difference
All subjects	1.94 (556)	2.03 (541)	NS†
Workplace not a problem	1.96 (457)	2.07 (451)	NS†
Entry symptom score >8	1.94 (292)	2.09 (284)	$P = 0.02$
Entry symptom score ≤8	2.00 (165)	1.91 (167)	NS†

*Excellent = 1, Good = 2, Fair = 3, Poor = 4, Worse = 5.
†NS = difference NOT significant.

fluence the outcomes. However, one factor—a work environment that contributes to the patient's respiratory problems or other symptoms—had a powerful influence on the outcome. As part of the medical history, physicians asked patients if their work environment contributed to any respiratory or other problems. The workplace contributed to allergy symptoms in 17 percent of the study population. Subgroup analysis in these patients showed that those receiving astemizole reported more adverse experiences than those receiving terfenadine (33 percent versus 18 percent, $P < 0.03$). However, these astemizole patients gave a better overall assessment of treatment than the terfenadine patients (1.63 versus 1.86, $P = 0.05$).

Data from the remaining 83 percent of the patients in whom the workplace was not a contributing factor also were subjected to subgroup analysis. This group was analyzed by the second most important factor affecting outcome—degree of severity of presenting signs and symptoms. At study entry, 63 percent of the patients had a total symptom score > 8 (Table 10). Mean results of the physicians' overall assessment indicated that among patients having a total symptom score > 8 at entry, the rating of overall satisfaction with the outcome of therapy was significantly ($P = 0.02$) better in the astemizole group than in the terfenadine group (Table 10). For patients with a total symptom score ≤ 8, there was no significant difference between the two treatment groups.

When both physicians' and patients' overall assessments were analyzed for the highest rating ("excellent" by physicians, "much better" by patients), again, we found that among those with a total symptom score > 8 at entry, the percentage of patients with this rating was significantly ($P < 0.01$) higher in the astemizole group (40 percent) than in the terfenadine group (31 percent). For the physicians' rating, the difference between treatments was even greater; 37 percent of astemizole-treated patients versus 26 percent of terfenadine-treated patients received "excellent" ratings. Statistically, this difference was significant ($P < 0.004$). As in the previous analysis, among patients with total symptom scores ≤ 8 at entry, there was no difference between the treatment groups.

Patients' overall ratings of how they felt since starting each treatment were plotted against the patients' entry total symptom scores (Figure 1). While there was no correlation between entry total symptom score and patient satisfaction on terfenadine, there was a strong, positive correlation ($r = 0.90$, $P = 0.05$) on astemizole. The higher the patients' total symptom score at entry, the greater their satisfaction with astemizole.

Discussion

Comparative Trials

Several studies comparing the clinical efficacy and safety of terfenadine with astemizole suggest that astemizole may be more effective in the treatment of seasonal allergic rhinitis, possibly because of its greater potency.[5,20-22] In an early 8-week, double-blind, randomized study in 90 patients with seasonal allergic rhinitis, astemizole was significantly more effective than terfenadine

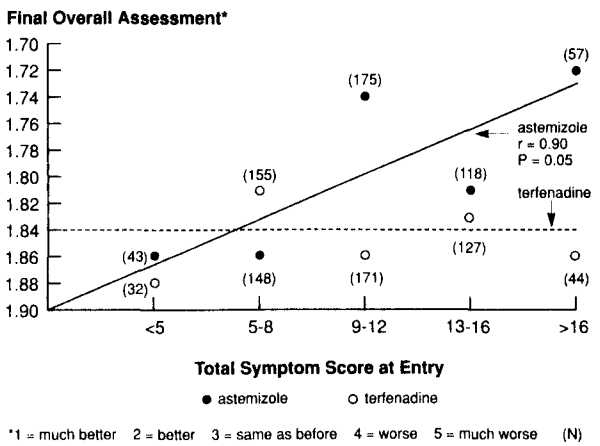

Figure 1. Relation between patients' entry total symptom score and final overall assessment of treatment.

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or placebo in alleviating rhinorrhea, sneezing, and itching eyes.[20] In a single-blind, randomized study comparing the two drugs, the patient's self-reported severity of symptoms scores was significantly lower with astemizole than with terfenadine. The group consisted of 85 patients with seasonal allergic rhinitis who were enrolled after they had become symptomatic.[21]

Another double-blind, randomized 7-week trial in 60 patients with ragweed pollen-induced rhinoconjunctivitis has provided additional evidence.[22] Therapy with both terfenadine and astemizole was initiated 1 week before the start of the ragweed pollen season and was continued for 1 week following the end of the season. Supplementary steroidal nasal spray and eye drops were permitted in the event of symptom breakthrough. The results of this trial indicated that astemizole was significantly more effective than terfenadine in controlling rhinorrhea, and astemizole-treated patients relied less on supplemental nasal spray. Both compounds, however, provided similar relief of the other signs and symptoms of rhinoconjunctivitis.

Significant Findings

In the treatment groups reported here, which are representative of family practice, both astemizole and terfenadine were well tolerated and effective in controlling symptoms of allergic rhinitis; 90 percent of the patients stayed on therapy for at least 3 weeks and had good relief of symptoms.

Marked improvement in the severity of signs and symptoms of allergic rhinitis, a decrease in both the severity and frequency of patient complaints (with the exception of appetite increase), and improvement in quality of life were reported in both treatment groups.

A major difference between treatments was that overall satisfaction with the outcome of therapy was rated highest by more physicians and patients for astemizole than terfenadine ($P < 0.05$).

When subgroup analyses were performed to eliminate confounding factors influencing the outcome of treatment, further differences between astemizole and terfenadine emerged. When data were analyzed for the 83 percent of study patients in whom the work environment was *not* a factor, a second factor – degree of severity of presenting signs and symptoms – was found to influence the outcome. Among patients with total symptom scores > 8 at study entry, overall satisfaction with the outcome of therapy was significantly ($P < 0.05$) greater for those treated with astemizole than with terfenadine. Additionally, in this group of patients with a high entry symptom score, astemizole was rated "excellent" or "much better" on the overall assessment by a significantly higher percentage of both physicians ($P < 0.01$) and patients ($P < 0.004$).

This more favorable rating of astemizole is consistent with the findings of Boland,[23] who, in a double-blind study, found that at 2 weeks and 4 weeks, both clinicians and patients rated astemizole higher than terfenadine for overall response. Our results show that patients with higher total symptom scores at entry report the most favorable results, which is consistent also with Boland's results. In three other comparative trials, astemizole was reported to exhibit superior efficacy.[20-22] Equal efficacy was reported in one.[24] In our study, however, a clear superiority of astemizole by symptom scores was not seen, and findings from the subgroup analyses suggest a possible explanation.

Previous comparative studies were carefully timed to begin either immediately before[20,22] or during[21,23,24] the allergy season in a specific geographic area, while the present study was conducted over a broader period of time in a widespread geographic area. In the more precisely timed studies,[20-22] astemizole's superior efficacy was more readily demonstrated when pollen counts were highest. In the present study, patients were treated at various points in the pollen cycle, and it is likely that for many, the study period did not coincide with the period of peak pollen counts. This averaging effect across time would have reduced between-treatment differences. The differences between treatment groups are clear when the groups of patients with the more severe symptom scores at study entry are analyzed separately.

Finally, with regard to the increase in appetite in both treatment groups, this fact has been reported in previous comparative trials.[20,21] Such appetite increases in patients receiving antihistamines have not been associated with significant weight gain,[22] however, and they are possibly the result of improved gustatory sensations brought about by relief of symptoms of allergic rhi-

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nitis rather than an undesirable effect of the medication.

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Editorial Comment

The regulation of the marketing of drugs in the United States is the responsibility of the U.S. Food and Drug Administration (FDA). The FDA establishes the standards by which new drugs can be introduced into the marketplace. Premarketing studies are usually done on small populations under carefully controlled experimental conditions. The object of these studies is to provide evidence of the drugs' safety and efficacy. However, because these studies are tightly controlled and limited to small populations, usually with limited variables, the conclusions reached are difficult to generalize to larger, undifferentiated populations seen in practice.

There is a general feeling that additional epidemiologic information about safety and efficacy would be desirable—but could only be done effectively after the drugs are marketed. Thus, there has been increased interest in postmarketing surveillance of drugs. However, the FDA is not authorized by statute to require such studies. It has requested postmarketing surveillance in selected instances. What is evident is that, irrespective of the requirements for premarketing study, only after marketing can the full potential (both therapeutic and adverse) of a drug be determined under the actual conditions of clinical use.[1]

This report from the Clinical Experience Network is the result of an attempt to evaluate representative drugs of a new class of nonsedating antihistamines. It represents a methodology designed to meet the requirements of postmarketing surveillance (Phase IV study). There have been several methodologies proposed to evaluate drugs after they have been marketed. No single method has yet been found to be "perfect." Previous studies have been carried out on such drugs as L-dopa, enflurane, dantrolene, prazosin, and cyclobenzaprine.

The study reported here requires the use of observational rather than traditional experimental methods. The application of epidemiologic techniques to the problem has been termed drug epidemiology. The primary purpose of the study is to describe the use of the drug in question in the real world of physician-patient interaction and to identify the results of the use of the drug. These techniques are not likely to establish causal relations but, rather, to make observations about the safety and efficacy of drugs as they are used in realistic clinical settings. If there are unexpected results, then experiments can be developed under controlled circumstances to try to establish causal relations.

Observational studies of the nature reported here must be evaluated in terms of their intent. It is necessary to involve a large number of patients in various locations in order to identify rare or unusual occurrences. It would seem that the CEN is organized in such a way as to provide a reasonably practical system for conducting this type of study. We believe that this study is valuable not only for the specific results obtained, but also as a prototype for the conduct of Phase IV studies of commonly used drugs.

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