

Clinical aspects of allergic disease

A double-blind, placebo-controlled evaluation of sublingual immunotherapy with standardized cat extract

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Background: In light of the controversial status of sublingual immunotherapy in patients with allergic rhinitis, we undertook a double-blind study of this form of treatment.

Methods: Forty-one subjects with cat allergy presenting as rhinoconjunctivitis underwent 105 days of sublingual immunotherapy, with 20 subjects receiving a standardized cat extract (total dose approximately 4,500,000 allergy units) and 21 a matching placebo. Effectiveness of treatment was assessed by changes in symptoms and nasal-blockage index during 90 minutes of exposure in an apartment containing cat dander, which was performed before and after the course of treatment. Changes in cat-specific IgG and IgE levels and skin-test reactions were also monitored.

Results: Although there were fewer symptoms and less nasal obstruction on cat dander exposure at the end of the study the changes were not significantly different in those receiving active or placebo treatment. Specific IgG and IgE levels and prick skin test results did not change significantly during the course of the study.

Conclusions: We conclude that sublingual immunotherapy with high-dose standardized cat extract was no more effective than placebo in reducing symptoms or affecting immunologic measures of cat sensitivity. (*J ALLERGY CLIN IMMUNOL* 1993;92:229-36.)

Key words: Sublingual, immunotherapy, cat allergy

Treatment of allergic respiratory disorders by the sublingual administration of allergen extract, although long practiced by some physicians,¹ has been considered controversial by others.² As of 1982 when Grieco² reviewed the subject of controversial practices in allergy, no controlled studies of sublingual desensitization had been reported.

Subsequently three double-blind studies in which sublingual immunotherapy was used have been reported that claim efficacy in reducing the symptoms of allergic rhinitis.³⁻⁵ Two used house-

Abbreviations used

AU: Allergy units

Fel d I: *Felis domesticus* allergen I

dust mite extract,^{3, 4} and the other study used a mixed grass-maize extract.⁵ The first was a brief trial of low-dose house-dust mite extract that had somewhat equivocal results.³ The other two used high doses of dust-mite⁴ or grass⁵ extract each in a substantial number of subjects for periods greater than 1 year. Both reported favorable clinical responses, and in the mite study there were, in addition, changes in a number of objective parameters. It should be noted, however, that in all three studies, although the extract was administered sublingually, subjects subsequently swallowed any remaining extract, making it impossible in these studies to distinguish the results of sublingual and oral immunotherapy.

Because of these encouraging reports and in light of the continuing controversy surrounding this form of therapy, we undertook a double-blind placebo-controlled trial to examine the efficacy of

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sublingual immunotherapy. We used cat extract, which has been shown in several double-blind studies to be effective when administered by standard injection therapy.^{6, 7} We had subjects expectorate the residual extract to limit absorption, as much as possible, to the sublingual route. As a means of assessing efficacy, we monitored the subjects' response to 90 minutes of exposure to an apartment contaminated with cat dander, inasmuch as this model adequately demonstrated reduction in symptoms with standard cat immunotherapy.⁶

METHODS

Subjects

Forty subjects aged 18 to 74 years were enrolled in this study. Subjects were required to have symptoms of allergic rhinoconjunctivitis with or without asthma after exposure to cats and a positive result to a prick skin test to cat extract (100,000 allergy units [AU] per milliliter resulting in a wheal of at least 5 mm in diameter greater than of negative control). Subjects were excluded from the study if they were chronically exposed to cat; had asthma that required daily medication or had had emergency room visits or hospitalization within the previous 6 months; currently used astemizole, corticosteroids, or sodium cromolyn; had other significant medical illnesses; had received immunotherapy with cat allergen within the past 2 years; or had had an upper respiratory infection during the 2 weeks preceding entry into the study. Women were required to use reliable methods of birth control. All subjects were required to withhold antihistamines for 72 hours before clinic visits.

The protocol under which this study was conducted was approved by the Institutional Review Board of the National Jewish Center for Immunology and Respiratory Medicine. All subjects signed informed consent statements before participation in the study.

Study design

Subjects who met entry criteria underwent exposure to cat dander in an apartment for 90 minutes. Those subjects whose symptom scores increased by 3 or more above baseline levels during cat apartment exposure were randomized to receive either active cat extract or placebo. The duration of sublingual immunotherapy was 105 days and included a 15-day build-up phase followed by 90 days of maintenance therapy. Cat apartment exposure was repeated on conclusion of the study on day 105. Blood for determination of levels of specific IgE and IgG to cat was drawn and titrated prick skin tests to standardized cat extract and histamine were performed at baseline and after days 15 and 105.

Cat exposure apartment

This apartment housed four cats, which were confined to the bedroom during the exposure sessions. To reduce the possibility that changes in symptom scores

were caused by variations in airborne *Felis domesticus* allergen I (*Fel d* I) levels, doors and windows of the apartment remained closed for 48 hours before each exposure and no house-cleaning activities were performed on the day of exposure. At the end of each week during which exposures had been conducted, air sampling was performed from midnight to 8 AM with the use of a Sentinel Air Sampler (Quan-Tec-Air, Inc., Minneapolis, Minn.). The air sampler processed a volume of 3 L of air per second. The particulate material was collected on a polytetrafluoroethylene filter with a 0.3-mm pore size. The collected material was eluted from the filter and cat allergen content was assayed by an ELISA inhibition assay standardized to allergen units of standardized cat allergen extract.

Cat apartment exposure

Subject exposures in the apartment were conducted at baseline and after 105 days of sublingual therapy. Subjects were not allowed to undergo challenge if their FEV₁ was 70% of predicted or less. Before each cat apartment challenge, subjects were required to discontinue medications as follows: terfenadine 72 hours, pseudoephedrine 12 hours, oxymetazoline nasal spray 12 hours, and albuterol 4 hours. Before subjects entered the apartment they recorded ocular, nasal, and lower-respiratory symptoms (itchy eyes, watery eyes, itchy nose, runny nose, nasal obstruction, sneezing, itchy throat, chest tightness, shortness of breath, and wheezing were all scored on a scale of 0 [none] to 3 [severe]) and performed oral and nasal peak flow tests to obtain a "blockage index."⁸

The subjects remained in the apartment for 90 minutes unless intolerable symptoms developed or the oral peak expiratory flow rate fell by 15%. At 15-minute intervals subjects recorded symptoms and performed peak expiratory flow measurements. Subjects in whom lower-respiratory symptoms developed or who had a 15% drop in oral peak expiratory flows during cat apartment exposure were promptly treated with an albuterol metered-dose inhaler and were observed until symptoms resolved and peak flows normalized.

Prick skin tests

Titration prick skin tests were performed on the back with the use of a template with sites separated by 5 cm. Five serial, fivefold dilutions of 100,000 AU/ml standardized acetone-precipitated cat hair and epithelium extract (Hollister-Stier, Spokane, Wash.) and of histamine phosphate (10 mg histamine base per milliliter) were tested. Results were recorded at 15 and 10 minutes, respectively, by tracing the wheal with ink and transferring the outlines with transparent tape to a permanent record. Subjects also were prick skin-tested with the highest concentration available of Rocky Mountain juniper, common cottonwood, American elm, and Siberian elm. Wheals 3 mm or more greater than those for saline control pricks were considered positive for the pollen skin tests.

Cat-specific IgG and IgE

Test specimens, standards, and controls were placed in micro-assay wells coated with standardized cat hair and dander extract (ALK, Milford, Conn.). Specific antibody was detected by addition of affinity purified goat antihuman IgG (heavy and light chains) conjugated to horseradish peroxidase. Chromogenic substance was added and the color read on a spectrophotometer. The concentration of cat-specific IgG was calculated by comparison of results with those from a standard serum test run at the same time (100 arbitrary units/ml). Cat-specific IgE was determined by ELISA with standard methods (Pharmacia Diagnostics, Piscataway, N.J.) and expressed in Phadebas RAST units per milliliter.

Assay for airborne cat allergen

Filters were eluted with Coca's solution. An aliquot was incubated with a reference cat allergic serum and placed in micro-assay wells coated with standardized cat hair and dander extract (ALK). After incubation with enzyme-labeled anti-IgE and washing, IgE level was determined with the use of standard reagents (Pharmacia Diagnostics). The concentration of cat allergen in the filter samples was determined by comparison of results with an inhibition curve derived from serial dilutions of the same standardized cat extract and expressed as allergy units per sample.

Nasal blockage index

Subjects performed six oral and six nasal peak expiratory flow measurements each time for calculation of a blockage index.⁸ To obtain the nasal expiratory flow, the Mini-Wright peak flowmeter (Armstrong Medical Industries, Inc., Lincolnshire, Ill.) was fitted to an Artec mask (Artec, Indianapolis, Ind.). The blockage index was calculated by oral peak flow minus nasal peak flow, and the result divided by the oral peak flow and multiplied by 100 to yield a percentage.

Sublingual therapy

Subjects were randomized to receive either active or placebo sublingual therapy. Subjects randomized to the active group received reconstituted lyophilized standardized acetone-precipitated cat hair and epithelium extract 100,000 AU/ml in 50% glycerin (containing between 10 and 20 *Fel d I* units/ml, Hollister-Stier). Those randomized to the placebo group received histamine phosphate (1 mg/ml histamine base in 50% glycerin with caramelized sugar for color). Both solutions were given to the patients in dropper bottles containing 60 ml of sterile product.

Sublingual immunotherapy schedule

Drops were taken once daily sublingually in the morning before breakfast. They were held under the tongue for at least 1 minute; then the remaining liquid was expectorated without swallowing. To allow for maximal absorption, subjects were instructed not to eat,

drink, or rinse out their mouths with any liquids for 15 minutes. Subjects received increasing daily doses during the build-up period (day 1, 1 drop; day 2, 3; day 3, 5; day 4, 7; day 5, 10); the dosage then increased daily by 1 drop per day to 20 drops per day by day 15. Maintenance therapy after the build-up phase consisted of 20 drops taken sublingually before breakfast Monday, Wednesday, and Friday mornings for 90 days (total dose approximately 4,500,000 AU of extract in subjects who had no adverse events). Subjects randomized to both the active and placebo groups followed this schedule. Subjects were instructed to modify the schedule in the event of adverse reactions to the drops.

All subjects were provided with an epinephrine inhaler (Medihaler-Epi), which they were to use in the event that any of the following symptoms occurred after the study medication was taken: (1) for itchiness or tightness of the throat, shortness of breath, or wheezing they were to take 5 inhalations; (2) for generalized pruritus, hives, or swelling 20 puffs were to be taken under a regimen of 5 inhalations initially, then 5 more inhalations every 5 minutes for a total of four doses. If any of these symptoms occurred, further dosing with the study medication was suspended until the investigators were notified.

Statistical analysis

Symptoms were calculated as the total increase over baseline values during the 90 minutes in the cat apartment (total score for all six 15-minute assessments minus six times the baseline score). The blockage index was computed by subtracting the cumulative sum total of the six nasal peak flow values from the six oral peak flow values, dividing the resultant number by the cumulative sum total of the six oral peak flows, and multiplying by 100 to yield a percentage. In subjects unable to remain in the challenge apartment for the full 90 minutes, the last recorded value was carried forward.

Comparisons between active and placebo-treated groups for median symptoms and nasal patency (expressed as blockage index) were made by Wilcoxon's rank sum test at baseline. Changes in mean values from baseline to day 105 were calculated and tested for significance separately in active and placebo groups by paired Student's *t* test. Median changes between values at baseline and day 105 for each parameter were compared for active versus placebo treatment by Wilcoxon's rank sum test. Nonparametric tests were used to compare the two treatment groups because of unequal variances.

Because specific IgG and IgE had log-normal distributions the natural logs of the variables were analyzed. Repeat measures analysis of variance was used. Skin test data were analyzed by a random coefficient model.

RESULTS

Subjects

Forty-one of the 44 subjects originally enrolled completed the study. Three subjects terminated

TABLE I. Symptom scores and nasal blockage index*

	Day 0	Day 105	Day 0-105	p Value
Symptom scores				
Active treatment				
Median	28.00	10.50	-15.00	< 0.001
Mean	29.10	12.15	-16.95	
SEM	4.02	1.94	3.32	
Placebo				
Median	30.00	15.00	-15.00	< 0.01
Mean	35.53	18.67	-16.76	
SEM	5.68	2.96	5.19	
Nasal blockage index (%)				
Active treatment				
Median	3.50	1.00	-3.00	< 0.001
Mean	6.60	0.95	-5.65	
SEM	3.56	1.75	3.54	
Placebo				
Median	3.00	5.00	-4.00	NS
Mean	6.33	5.00	-1.33	
SEM	4.96	3.09	6.86	

The increase over baseline in symptoms and nasal blockage index that occurred during 90 minutes of exposure in an apartment contaminated with cat dander. Indicated are the levels at baseline (day 0) and at the end of the study (day 105), as well as the difference and the level of significance for the change in the means. There were no significant differences between active and placebo-treated groups in the median levels of either variable at baseline, nor in the differences between baseline and day 105. NS, Not significant.

participation in the study because of scheduling conflict, headache symptoms, and an unrelated allergen exposure (one each). Of the 41 subjects who completed the study, 20 received standardized cat extract and 21 received placebo. Subjects who received active therapy included 7 men (ages 20 to 74) and 13 women (ages 18 to 46). In the placebo group there were 6 men (ages 25 to 48) and 15 women (ages 19 to 40). Each of the treatment arms included 3 subjects who reported a history of asthma.

Thirty subjects (13 receiving active and 17 receiving placebo treatment) had one or more positive results to prick skin tests for trees, which may have been pollinating during the time the final exposure to the cat apartment occurred. None, however, were having clinical seasonal allergic rhinitis.

Doses attained

All subjects were able to attain the maximum total dose of sublingual cat extract (approximately 4,500,000 AU or between 450 and 900 *Fel d* I units).

Symptom scores

The symptoms during baseline exposure in the cat apartment did not differ significantly for the

two treatment groups (Table I). There were significantly fewer symptoms in both groups on re-exposure on day 105; however, the changes in symptoms between baseline exposures and day 105 did not differ significantly between the two groups (Fig. 1).

Nasal blockage index

At baseline the increases in nasal blockage index during the 90 minutes of cat apartment exposure were not significantly different in the two groups (Table I). The increase in nasal blockage index was significantly less in the group receiving active treatment on day 105 when compared to that at baseline, whereas the difference between the results of the two exposures in the placebo group was not significant. Comparison of the changes in nasal blockage index between baseline and day 105 in the two groups revealed no significant difference.

Cat-specific IgG and IgE

Baseline levels of cat-specific IgG did not differ significantly between the two treatment groups, nor was there any significant change with time or treatment (Table II). Cat-specific IgE levels did differ significantly at baseline, with higher levels in the active treatment group ($p = 0.04$). When

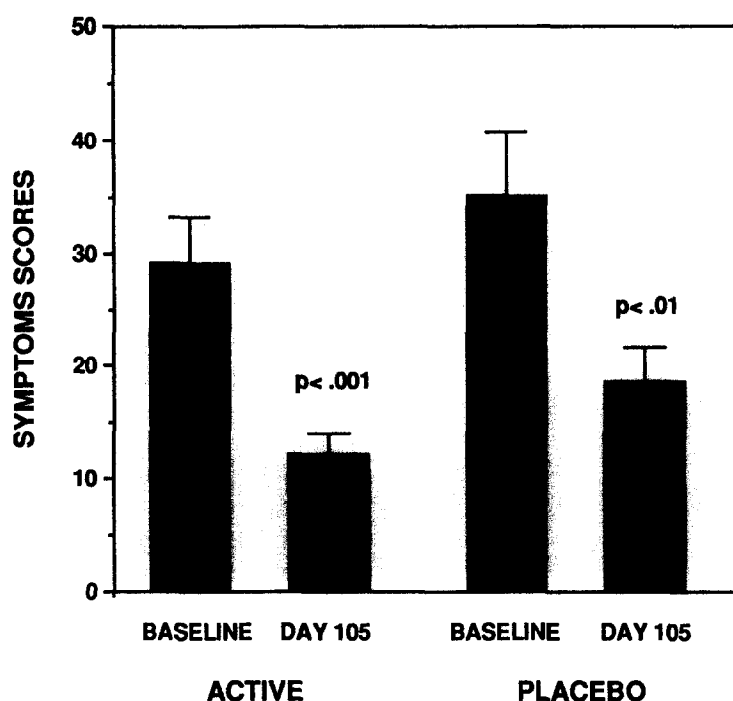


FIG. 1. Symptom scores. Indicated are increases in symptom scores experienced during 90 minutes of exposure in cat apartment. Both groups experienced significantly fewer symptoms during second exposure on day 105; however, changes in two groups did not differ significantly.

TABLE II. Levels of cat-specific IgG and IgE

	Day 0	Day 15	Day 105
LN IgG (mean values in arbitrary units)			
Active treatment	2.70 ± 0.13	2.83 ± 0.14	2.81 ± 0.16
Placebo	2.57 ± 0.13	2.64 ± 0.10	2.58 ± 0.11
LN IgE (mean values in PRU)			
Active treatment	0.86 ± 0.36	1.02 ± 0.39	1.00 ± 0.35
Placebo	-0.12 ± 0.27	-0.05 ± 0.32	0.05 ± 0.32

Values measured at baseline (day 0), after reaching maintenance (day 15), and at the end of the study (day 105). Values are given in natural logs (LN). There are no differences at baseline and no treatment effects for IgG. The IgE levels do differ significantly at baseline ($p = 0.04$), however there is no effect of treatment on IgE levels.

the baseline differences were subtracted from those for days 15 and 105, there were no differences as a result of treatment.

Titrated prick skin test reactivity

The titrated prick skin tests to cat extract and histamine were separately analyzed by the random coefficient model. There were no significant treatment effects seen on any of the skin tests ($p > 0.05$).

Adverse events

Overall the incidence of adverse reactions during the course of sublingual immunotherapy was

similar in both groups (Table III). None of the study subjects had serious adverse events; however, pharyngeal pruritus was noted by eight subjects receiving cat extract and four subjects receiving the placebo, which contained 1 mg/ml histamine base.

Apartment levels of cat allergen

Apartment levels of cat allergen were measured for eight nighttime hours at the end of each week that exposures were conducted. During the eight baseline weeks (Nov. 27, 1989, to Jan. 26, 1990) the cat allergen level was above the level of detection (30 AU per 8 hours) in only one of eight

TABLE III. Adverse events

System	Active treatment	Placebo
Dermatologic (total)	0	1
Urticaria	0	1
HEENT (total)	12	8
Pruritus rhinoconjunctival	0	1
Rhinorrhea/nasal obstruction	3	2
Pharyngeal pruritus	8	4
HEENT other	1	1
Gastrointestinal (total)	3	0
Indigestion	1	0
Gastrointestinal other	2	0
Respiratory (total)	2	6
Asthma symptoms	1	5
Cough	1	1
CNS (total)	5	3
Headache	4	2
CNS other	1	1
Musculoskeletal	1	1
Upper-respiratory infection	2	3
Total adverse events	25	22

The incidence of adverse events was not significantly different between the two groups.

HEENT, Head, eyes, ears, nose, throat; CNS, central nervous system.

samples. During the 8 weeks of the final challenges (March 3 to May 14, 1990) cat allergen levels were above the threshold for detection in seven of eight weeks, with a mean level of 69.5 ± 43.7 AU per 8 hours.

Effectiveness of blinding

To assess the effectiveness of blinding during the study, each participant was asked at the conclusion of the study to express an opinion as to which treatment they received. Thirty-seven of the subjects reported that they did not know, one patient who had received active therapy believed he or she had been receiving placebo, two subjects randomized to placebo thought they had received active therapy, and one subject who received active therapy correctly identified the agent he had received.

DISCUSSION

In light of the controversial status of sublingual immunotherapy in patients with allergic rhinitis, we undertook a double-blind study of this form of treatment with standardized cat extract. To assess effectiveness we used the response to exposure to an apartment containing cat dander, measuring change from baseline levels in symptom scores

and nasal obstruction (measured by blockage index). We also assessed changes in immunologic parameters, consisting of cat-specific IgG and IgE and titrated prick skin test reactivity to cat extract. None of the changes in these parameters were significantly different when active therapy (cumulative dose of cat extract approximately 4,500,000 AU) was compared with placebo. There was a significant reduction in both groups in symptoms and in the active treatment group in nasal obstruction when the final challenge results were compared with baseline figures. This occurred despite a probable increase in cat allergen levels in the apartment and possible exposure to tree pollen to which some of the subjects were skin-test reactive. The reason for the improvement in both parameters is unclear, but may be related to the known strong placebo effect seen in most immunotherapy studies.

In administering the extract we instructed subjects to hold it beneath their tongue for 1 minute, then expectorate the excess, and not to eat or drink for 15 minutes. This was done to maximize possible absorption from the oral cavity while allowing the results of sublingual absorption to be clearly distinguished from those of absorption of the extract farther along the gastrointestinal tract, which might have occurred had swallowing of the residual extract been permitted. The authors have conducted a separate study of the effectiveness of oral (swallowed) cat extract in a similar group of subjects, which will be reported separately.

In general, sublingual immunotherapy was well tolerated, with all subjects achieving the projected maximal dose. There were no systemic reactions caused by cat allergen extract, however, eight subjects who received active treatment did report pharyngeal pruritus compared with only four who received the histamine-containing placebo.

As a rough measure of cat dander exposure in the apartment, airborne levels of *Fel d 1* were measured from midnight to 8 AM at the end of each week that exposures took place. Sampling was not performed during the actual exposures, inasmuch as the high-volume sampling necessary to detect airborne levels of *Fel d 1* could have acted as an air cleaner and reduced the amount of dander to which the subjects were exposed. The *Fel d 1* levels measured at the end of each exposure week showed moderate week-to-week variation, which was probably a reflection of the small amount of dander in the air compared with the large reservoir in the carpets and furnishings and the major impact of human activity on airborne

dander levels. Cat allergen levels were higher during the final challenges than they had been during the baseline studies. Swanson et al.⁹ reported that the ventilation rate can influence the airborne levels of cat allergen. Thus the increased concentration in the cat allergen levels in the apartment may be explained by buildup during the winter when there was limited introduction of fresh air into the apartment.

One assessment of the response to exposure to the cat dander apartment was change in the nasal blockage index calculated as the difference between peak expiratory flow through the nose and through the mouth expressed as a percent. Although this is a somewhat crude assessment of nasal obstruction, comparative studies in the same subjects have revealed, for resting readings in normal subjects, a correlation of 0.88 between the blockage index and measurement of nasal airway resistance by posterior rhinometry.⁸ Furthermore, serial measurements in normal subjects revealed that the coefficient of variation of the blockage index was only 0.18, whereas it was 0.32 for posterior rhinometric measurements of nasal airway resistance.⁸

The results of our study do not confirm the efficacy of sublingual immunotherapy, which has recently been reported. A controlled study of sublingual grass-maize immunotherapy was conducted in South Africa by Van Niekerk and De Wet.⁵ This study was conducted in 40 young adults who had grass-induced allergic rhinitis. The study lasted for 2 years and began well before the onset of the "summer" hay fever season the first year. During the first year of the study those patients receiving active therapy had significantly fewer symptoms of allergic rhinitis in the summer months than those in the placebo group. The second year of the study was unblinded. All participants were given active therapy, and both groups had markedly lower total mean monthly symptom scores than the patients receiving placebo had had the previous summer. The aqueous extract was well tolerated and no significant side effects were reported. The dose of allergen used for the study was the same as that used for conventional injection therapy.

Tari et al.⁴ studied 58 patients allergic to both *Dermatophagoides pteronyssinus* and *Dermatophagoides farinae* who received 18 months of sublingual therapy with placebo or dust-mite extract. Treated patients had significant reductions in nasal symptom scores, sensitivity on nasal and bronchial challenge with mite extract, bronchial hyper-

responsiveness to methacholine (in those subjects with asthma), and skin reactivity to mite extract, as well as significant changes in mite-specific IgG and CD8+ lymphocytes. There were no significant changes in these parameters in the subjects who received placebo.

Scadding and Brostoff³ reported the results of 2 weeks of very low-dose sublingual therapy with house-dust mite extract in a double-blind crossover study in 18 subjects. They reported that 13 of 18 of the subjects preferred the low-dose dust-mite therapy to placebo. They also reported that active therapy resulted in a significant increase in morning peak nasal inspiratory flows and reduction in sensitivity to nasal provocation. However, the statistical methods used by the investigators to reach these conclusions have been challenged.¹⁰

There is clearly a disparity in the reported efficacy of sublingual immunotherapy in comparison of this study with these recent reports. In this study doses were administered that were several times those that would be used in the highest-dose injection immunotherapy and as high as those in the studies reporting positive results. One difference in this study is the choice of extract used. Whether this difference in allergen used accounts for the difference in results cannot be determined from the available data. Perhaps more critical was the practice of expectorating the residual extract rather than swallowing it. In the two papers that reported what appears to be clear-cut efficacy of high-dose sublingual therapy, subjects swallowed the extract.^{4, 5} In these studies the favorable response may have been related to absorption of the extract farther down the gastrointestinal tract.

In this study high-dose sublingual therapy with cat extract was no more effective than placebo (histamine) therapy in reducing the symptoms of allergic rhinitis or nasal obstruction as measured by the blockage index when subjects were exposed to an apartment containing dander. There were also no significant changes in immediate skin test reactivity to cat extract or in levels of cat-specific IgG or IgE with the active treatment.

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