Evidence Table 1: Costs and Work Performance

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Blanc, Trupin, Eisner, et al., 2001	Design: Population-based telephone survey Intervention(s): NA Duration of study treatment: NA Dates: May 28-July 21, 1999 Location: Northern California rural, suburban, and urban regions Setting: Community Type(s) of providers: NA	No. of subjects at start: 5,304 contacts made with individual households; 1,411 refused; 227 excluded (language); 254 excluded (no asthma or rhinitis) Dropouts/withdrawals: NA No. of subjects at end: 125 asthma; 175 rhinitis (and no asthma) Inclusion criteria: Age 18-50; self-reported physician-diagnosed asthma (asthma group) or self- or physician-diagnosed "allergic rhinitis, sinusitis or hay fever" or "chronic post-nasal drip" (rhinitis group) Exclusion criteria: Emphysema or cystic fibrosis Age: NR Sex: 72% women Race: 74% White, 16% Latino, 9% Asian/Other, 2% Black Other: Smoking status: Current 16% Former 28% Never 57% Insured for healthcare: 89%	1) Severity of respiratory symptoms (self-reported) 2) Medication use 3) Quality of life (SF-12) 4) Health care utilization 5) Employment status 6) Work effectiveness	1) Severity of respiratory symptoms (self-reported): Severe: 22% Moderate: 49% Mild: 29% 2) Medication use: Past 2 weeks: Rx inhaler: 9% Rx nasal spray: 25% Antihistamine: 59% Ever use steroids for breathing: 13% 3) Quality of life (SF-12): Functional status scores (mean ± SD): SF-12 physical component: 49 ± 10 SF-12 mental component: 48 ± 11 Activity limitations due to condition (in previous month): 30% 4) Health care utilization, past 12 months, for condition: Urgent care visit: 32% ED visit: 6% 5) Employment status: Labor force participation since onset: 97% Labor force participation given onset < 18 years of age: 99% Changed jobs or duties due to condition: 18% Currently employed: 23% 6) Work effectiveness (last 4 weeks): Any partial or complete lost work days: 23% Any partial lost work days: 20% Any complete lost work days: 13% Self-rated effectiveness on job < 90%: 36%	Quality Scoring: Population similar: Yes Intervention(s) described: No Comorbidities described: Yes Diagnosis by MD: No Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 1b Notes: Survey failed to screen for COPD (only emphysema). Study designed to compare asthma group to rhinitis-only group. No comparison possible to subjects with no respiratory illness.

Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Burton, Conti, Chen, et al., 2001	Design: Prospective survey of customer service representatives, weekly productivity data and Health Risk Appraisal (HRA) information from employer, and pollen counts in the community. To measure productivity impact of AR and its treatment Intervention(s): NA Duration of study treatment: NA Dates: June 1998 through October 1998 Location: Elgin, IL Setting: Large employer Type(s) of providers: NA	No. of subjects at start: Surveys sent to 1600 telephone customer service representatives in June 1998; 54% (634 subjects) completed and returned. The follow-up survey sent out in October 1998 was completed by 72% (459 subjects). Of the study population, HRA information was available for 299 in the AR group and 269 in the non-AR group. Dropouts/withdrawals: NR No. of subjects at end: 634 subjects were included in analyses of productivity Inclusion criteria: NR Exclusion criteria: NR Age: 20.5% < 25; 36.1% 25-34; 23.3% 35-44; 20.3% 45+ Sex: 88.6% women Race: Asian: 2.4%; Black:7.7%; White: 81.4%; Hispanic: 8.4%; Native American: 0.2%	1) Proportion of patients with self-reported AR who reported using no medications, OTC medications, or prescription medications 2) Likelihood of meeting the productivity standard during weeks when the pollen count was high 3) Impact of allergies on meeting the productivity standard before or after allergy season 4) Impact of allergies on meeting the productivity standard during the allergy season 5) Impact of no medication among those with allergies on productivity during the allergy season 6) Impact of using antihistamines (sedating or nonsedating) on productivity during the allergy season 7) Impact of type of antihistamine on productivity during the allergy season	1) 21.7% reported no medication use for AR; 41.6% reported OTC medication use; and 36.7% reported prescription medication use. 2) 7% fewer employees with allergies met the productivity standard when pollen counts were high compared with employees without allergies 3) Employees with or without allergies met the productivity standard as often before and after the allergy season 4) 5% fewer employees with allergies met the productivity standard during allergy season compared with employees without allergies 5) 10% fewer employees with allergies who reported using no medication met the productivity standard compared to employees without allergies 6) 3% fewer employees who reported using nonsedating or sedating antihistamines met the productivity standard compared to employees without allergies 7) No difference in productivity was observed between those reporting the use of sedating or nonsedating antihistamines among those who used medication	Quality Scoring: Population similar: Yes Intervention(s) described: No Comorbidities described: Yes Diagnosis by MD: No Objectively confirmed: Not applicable Outcome measures valid: Yes Level of evidence: 4 Notes: Weekly productivity was measured as a dichotomous variable classified as either meeting or not meeting the overall productivity standard. As the final measure, the average of all weekly scores was computed. Those meeting the weekly productivity standard more than half the time were classified as meeting the productivity standard. The results on medication type and productivity are misleading. Instead of reporting the % reduction in the likelihood of meeting the productivity standard, the authors report these percentages as the percent reduction in productivity. This interpretation is carried out through the discussion when making a case for the cost-benefit of providing pharmacy coverage for people with AR.

Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Cockburn, Bailit, Berndt, et al., 1999a **and** **Cockburn, Bailit, Berndt, et al., 1999b**	Design: Retrospective analysis of claims data and daily work output records To test the impact of antihistamine use on productivity, work output observations of insurance claims processors were classified into periods directly preceding and following the date on which the prescription was filled. Time periods of 3, 5, 7, 10, and 14 days were tested. Intervention(s): NA Duration of study treatment: NA Dates: January 1993-July 1995 Location: NR Setting: Community, large insurance company Type(s) of providers: NA	No. of subjects at start: Health claims for 5,888 individuals Dropouts/withdrawals: NA No. of subjects at end: After removing outliers, 183,301 observations on daily work output were available for 682 individuals Inclusion criteria: Individuals with prescription claim(s) for antihistamines Exclusion criteria: Age: Mean, 32 Sex: 94% female Race: NR Other:	1) Effect of antihistamines (all types combined) on average level of productivity 2) Effect of sedating and nonsedating antihistamines on average level of productivity 3) Effect of sedating antihistamines on average level of productivity when extending the analysis time period 4) Daily cost of lost output based on hourly pay of $11.50 5) Net monetary benefit of treatment with non-sedating antihistamines compared to sedating antihistamines	1) When not controlling for the type of antihistamine, there was not a statistical difference in productivity during the 3-day period prior to filling the prescription or the 3-day period following the filling of a prescription for an antihistamine. 2) During the 3-day period after filling a prescription for a sedating antihistamine, workers were on average 7.8% less productive ($p < 0.01$). Conversely, during the 3-day period after filling a prescription for a nonsedating antihistamine, workers were 5.2% more productive on average ($p < 0.01$). 3) When extending the time period during which productivity is measured following a sedating antihistamine, the negative effect on productivity remains significant ($p < 0.01$) out to 14 days (max period tested). However, the size of the effect lessened to 3.1%. 4) Daily cost of lost output: $9 per day (ranging from $7 to $11) 5) Net monetary benefit of treatment with non-sedating antihistamines compared to sedating antihistamines: $7.50- $8 per day assuming an incremental cost of $1-$1.50/day for nonsedating antihistamines	Quality Scoring: Population similar: Yes Intervention(s) described: No Comorbidities described: No Diagnosis by MD: No Objectively confirmed: Not applicable Outcome measures valid: Yes Level of evidence: 4 Note: Study limitation: Claims for prescription drugs could have been prescribed for dependants, not employees.

Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Crystal-Peters, Crown, Goetzel, et al., 2000	Design: Cost of illness study (indirect costs only) based on a synthesis of data from: 1) 1995 National Health Interview Survey; 2) Bureau of Labor Statistics Intervention(s): NA Duration of study treatment: NA Dates: 1995 Location: US Setting: Community Type(s) of providers: NA	No. of subjects at start: NA Dropouts/withdrawals: NA No. of subjects at end: NA Inclusion criteria: Respondents with self-reported diagnostic information that was coded as allergic rhinitis Exclusion criteria: Age: Of those reporting AR, 18.2% < 18, 72.9% 18-64, 8.9% ≥ 65 Sex: Of those reporting AR, 53.6% women Race: NR	1) Prevalence of AR 2) Prevalence of AR by age group 3) Average annual number and total number of work days lost per person with AR 4) Indirect costs of lost work days 5) Total number of at-work reduced activity days 6) Indirect costs of at-work productivity losses 7) Indirect costs of reduced activity due to sedating antihistamines 8) Total indirect costs of AR	1) Prevalence of AR: 9.8% (25.7 million) 2) Prevalence of AR by age group: < 18yo: 6.6%; 18-64yo: 11.7%; ≥ 65yo: 9.8% 3) Average annual number and total number of work days lost per person with AR: 0.24 days per year, 3.6 million lost work days 4) Indirect costs of lost work days: $445.3 million ($1995) 5) Total number of at-work reduced activity days: Nearly 3 million at-work reduced activity days 6) Indirect costs of at-work productivity losses: $92.8 million ($1995) 7) Indirect costs of reduced activity due to sedating antihistamines: $4.6 billion ($1998) 8) Total indirect costs of AR: $5.2 billion ($1998)	Quality Scoring: Population similar: Yes Intervention(s) described: No Comorbidities described: No Diagnosis by MD: No Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 2b Notes: Assumptions used in cost calculations: 1) At-work productivity losses were based on NHIS-reported number of days that respondents cut down on usual activities by more than half of the day and were valued at 25% of the respondent's daily salary. 2) Assumed that at-work reduced activity days reported in NHIS do not consider the effects of sedating antihistamines. 3) To assign indirect costs of reduced productivity due to sedating antihistamines, it was assumed based on unpublished survey data that 82% of AR patients use some treatment, and that 57% use OTC sedating antihistamines. 4) 1989 Gallup poll: People with AR who used sedating (OTC) antihistamines reported a 25% reduction in productivity for 14 work days per year. This analysis double-counts productivity losses. It uses

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Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
					NHIS data to estimate lost productivity due to missed work days and at-work reduced productivity days. It assumes that reduced activity resulting from sedating antihistamines is not included in these estimates. Therefore, it uses the results from the 1989 Gallup poll and unpublished survey data to estimate indirect costs resulting from the use of sedating antihistamines.
Cuffel, Wamboldt, Borish, et al., 1999	Design: Retrospective analysis of health care claims This analysis was designed to: 1) estimate the prevalence of coexistent AR, depression and anxiety disorder; 2) estimate the effects of the comorbid conditions on costs; and 3) determine whether treatment of AR had an impact on overall costs when these conditions were comorbid. Intervention(s): NA Duration of study treatment: NA Dates: 1995 Location: US Setting: NA Type(s) of providers: NA	No. of subjects at start: Claims data from 600,000 persons Dropouts/withdrawals: NA No. of subjects at end: 13% (85,298) with AR diagnosis; 9.3% (59,529) with diagnosis of depression and 2.2% (14,582) with diagnosis of anxiety Inclusion criteria: Diagnosis of AR based on ≥ 2 prescriptions for allergy medication or diagnosis of AR Exclusion criteria: None specified Age: 0-17yo: 16.1%; 18-34yo: 17.6%; 35-44yo: 21.3%, 45-54yo: 25.6%, 55-64yo: 18.9%; ≥65yo: 0.4% Sex: 61% women Race: NR	1) Prevalence of AR 2) Proportion of AR patients with depression or anxiety disorder or both conditions 3) Odds ratio (OR) of a depressive disorder among people with AR compared to people without AR 4) Odds ratio (OR) of a anxiety disorder among people with AR compared to people without AR 5) Additional annual expense from having a diagnosis of AR and depression versus a diagnosis of either AR or depression alone 6) Additional annual expense from having a diagnosis of AR and anxiety disorder versus a diagnosis of either AR or	1) 13.3% (85,298/641,205) 2) Depression, 12%; anxiety disorder, 1.5%; depression and anxiety disorder, 1.5% 3) OR = 1.7 (95% CI, 1.63-1.73) 4) OR = 1.41 (95% CI, 1.35-1.47) 5) $363 additional per person per year 6) $207 additional per person per year	Quality Scoring: Population similar: Yes Intervention(s) described: No Comorbidities described: No Diagnosis by MD: No Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 2b

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Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
			anxiety disorder alone		
			7) Economic impact of AR treatment on total costs when AR and depression were comorbid	7) $83 reduction per person per year	
			8) Economic impact of AR treatment on total costs when AR and anxiety disorder were comorbid	8) $141 reduction per person per year	
Donahue, Greineder, Connor-Lacke, et al., 1999	Design: Retrospective analysis based on HMO claims data Intervention(s): NA Duration of study treatment: NA Dates: April 1988 through December 1994 Location: Northeast US Setting: Staff model HMO Type(s) of providers: NA	No. of subjects at start: 122,196 diagnosed with asthma or rhinitis; of which 2,677 (2%) received ≥ 1 immunotherapy injection Dropouts/withdrawals: NA No. of subjects at end: 603 met all duration of membership, pharmacy coverage, and automated record eligibility requirements and were deemed to have actually received an immunotherapy injection Inclusion criteria: Subjects were required to have a minimum of 4 years of continuous enrollment in the HMO. Medical records were used to confirm the accuracy of asthma and rhinitis diagnoses. Exclusion criteria: Age: 7% age < 10 years; 15% age 10-29; 55% age 20-39; 23% age ≥ 40 Sex: 56% women Race: NR	1) Median duration of immunotherapy (2-6 years of follow-up per patient) 2) Distribution of number of treatments per person 3) Correlates of duration of therapy 4) Compliance with immunotherapy (see Notes for definition)	1) 2.7 years. Bivariate analyses showed that duration did not differ by age or gender, but duration was longest for patients with both asthma and rhinitis. Duration was similar among those with cat, ragweed and other allergens, but was shorter among patients with undocumented allergen. 2) The distribution was bimodal with peaks at ~5 and ~65 injections per patient, 23% had no injections after the first month. 3) Multivariate analyses showed that duration of immunotherapy was shortest among females, those aged 10-20 years, and those for whom the allergen type was not documented. 4) Of those with sufficient follow-up for assessment, 33% were classified as completing immunotherapy. 43% of those with both asthma and rhinitis completed therapy compared to 28% of those with rhinitis and 13% of those with asthma only. Patients with ragweed allergen were more likely to complete treatment and those with undocumented allergen were less likely.	Quality Scoring: Population similar: No Intervention(s) described: No Comorbidities described: Yes Diagnosis by MD: No Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 2b Note: Compliance with immunotherapy was evaluated by determining the proportion of patients who received at least 50% of the recommended number of injections in each interval according to the following recommendations: ≥ 20 injections in 1st 6 months, ≥ 30 injections in 1st year, an additional 31 injections over next 2.5 years, and a total of ≥ 61 injections over 3.5 years.

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Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
		Diagnoses: 58% had rhinitis without asthma, 39% had rhinitis plus asthma, 3% had only asthma Allergens: 6% cat (no ragweed) 45% ragweed (no cat) 20% other or combination 29% no documented	5) Total cost of immuno-therapy (allergy testing, immunotherapy visits, visits for adverse reactions). 6) Immunotherapy and nonimmunotherapy costs for people who completed therapy compared to those who did not compete therapy	5) $438 per person-year: $212 for people with asthma, $416 for people with rhinitis, and $496 for people with both conditions. 6) $698 per person-year among those who completed immunotherapy vs. $247 for those who did not. Non-immunotherapy costs were $508 among people who completed immunotherapy and $421 among people who did not.	
Fell, Mabry, and Mabry, 1997	Design: Case series, survey Patients administered the survey were asked to rate their nasal symptoms and QOL before undergoing immunotherapy and at the time they completed the survey. Intervention(s): Immunotherapy Duration of study treatment: NA Dates: NR Location: Texas Setting: Outpatient Type(s) of providers: Patients from 1 provider represented	No. of subjects at start: 60 Dropouts/withdrawals: 0 No. of subjects at end: 60 Inclusion criteria: patients with IgE-mediated allergy who had undergone 1or more years of immunotherapy Exclusion criteria: NR Age: Men: ages 27-70; women: ages 29-72 Sex: 60% men Race: NR	1) Nasal symptoms currently and before immunotherapy. 2) General health currently and before immunotherapy. 3) Tolerance of exercise, outdoor activities, participation in social activities and energy level for every day activities currently and before immunotherapy. 4) Productivity at work currently and before immunotherapy and causes for changes in productivity. 5) Work days missed currently and before immunotherapy.	1) 92% reported a signif icant improvement in symptoms 2) 62% reported that their general health was much better since beginning immunotherapy. 3) 38% reported an increase in exercise tolerance. Of the 34 patients who reported regularly participating in outdoor activities, 74% were better able to perform these activities; 63% reported improvement in their social lives, and 55% reported an increased energy level. 4) Of the 56 patients who were employed, 59% reported that their allergies caused them to be less productive at work, and all of these patients reported increased productivity since beginning immunotherapy. 5) 31 of 56 (55%) reported missing work as a consequence of allergies. Prior to beginning immunotherapy, 29 of the 31 missed between 1 and 6 days of work over a 6-month period. The other 2 patients reported missing 12-18	Quality Scoring: Population similar: Yes Intervention(s) described: No Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 4 Note: These results are limited by recall bias and selection bias as only patients who continued immunotherapy were included in the survey and all were under the care of the 2nd author. Furthermore, it was not reported how these patients were selected to participate in the survey. In addition, no statistical testing was used to compare responses.

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Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
				work days within 6 months. Compared to the period before immunotherapy, patients missed work 4.2 fewer days after initiation of immunotherapy.	
			6) Number of physician visits to treat severe allergy symptoms or infections currently and before immunotherapy.	6) The 63% of patients making frequent physician visits for allergies prior to immunotherapy had a decrease in the number of office visits by 3.8 per 6-month period after initiation of immunotherapy.	
			7) Quantity of medications currently and before immunotherapy.	7) 63% were able to decrease the amount of each medication taken. Of the 36 people who reported taking more than 3 courses of antibiotics per year, 89% were able to decrease antibiotic use by at least 50% since starting immunotherapy.	
			8) Patients' assessment of whether immunotherapy was worthwhile and time until they noticed a benefit of immunotherapy.	8) 92% reported that they felt that immunotherapy was worthwhile and the average amount of time they received immunotherapy before noting a benefit was 4.2 months when excluding one patient who reported 24 months.	

Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Gilmore, Alexander, Mueller, et al., 1996	Design: Case-control study using a large managed care database Intervention(s): NA Duration of study treatment: NA Dates: 1992-1993 Location: Washington state Setting: Community, staff-model HMO Type(s) of providers: NR	No. of subjects at start: NA Dropouts/withdrawals: NA No. of subjects at end: 3,394 incident visits for traumatic work-related injury Inclusion criteria: Cases: people who had a clinic or emergency room visit for an acute work-related injury in 1992-1993 Controls: matched to cases on sex, decade of birth date, and employer Case:Control Ratio: 1:2 Exclusion criteria: NA Age: 18 years or older Sex: 58.2% male Race: NR	1) Odds Ratio for increased risk of work-related injury within 30 days following use of antihistamines	1) Open wounds and contusions: OR = 1.5 (95%CI: 1.1 to 1.9); burns: OR = 3.1 (95%CI: 1.0-9.7); and fractures: OR = 1.7 (95%CI: 0.9-3.3).	Quality Scoring: Population similar: Yes Intervention(s) described: No Comorbidities described: No Diagnosis by MD: No Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 3b Notes: Antihistamines in this study were almost always sedating, as non-sedating antihistamines were not available on the formulary during the study period. Limitation of analysis: Exposure to medication was based on purchase of medication within 30 days prior to the date of injury. However, misclassification was not expected to differ between cases and controls.

Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Keith, Haddon, and Birch, 2000	Design: RCT, parallel-group, method of randomization not described Intervention(s): 1) Intranasal budesonide delivered as a dry powder (Rhinocort® Turbuhaler® 400 µg), once per day (n = 121) 2) Intranasal budesonide delivered as an aqueous spray (Rhinocort® Aqua® 256 µg), once per day (n = 121) Duration of study treatment: 4 weeks Loratidine and sodium cromoglycate or naphazoline HCl-antazoline phosphate eyedrops "provided for rescue" (instructions for using not described) Trial preceded by 7- to 10-day placebo run-in period Dates: 1993 ragweed pollen season Location: Canada Setting: Allergy clinic Type(s) of providers: NR	No. of subjects at start: 242 (randomized and received treatment) Dropouts/withdrawals: No. of subjects at end: 242 received treatment, 241 completed both willingness-to-pay questionnaires Inclusion criteria: Age ≥ 18 years; positive skin prick test to ragweed (≥ 3 mm); symptoms of rhinitis or a clear exacerbation of perennial rhinitis symptoms during ≥ 1 previous ragweed season Exclusion criteria: None specified Age: 36 Sex: 54.5% female Race: NR	1) Costs: Included costs for study and rescue meds; any immunotherapy received; unscheduled visits to physician and services provided at such visits; visits to other physicians or hospital outpatient departments; and time off work or school 2) Benefits: Indirectly assessed by willingness-to-pay questionnaire administered at beginning and end of study 3) Cost-benefit analysis (including sensitivity analysis)	1) Costs: Cost data were provided in figures. Therefore, exact cost estimates are not available from the article. 2) Benefits: Prior to treatment, subjects were willing to pay an average of $15.89 (1993 Canadian$) per week for an allergy treatment that would relieve all symptoms. Following treatment, subjects were willing to pay an average of $12.95 (1993 Canadian$) per week to take the drug they had been using during subsequent allergy seasons. The reduction in willingness-to-pay was significant. 3) Cost-benefit analysis (including sensitivity analysis): The net benefit was significantly higher than costs incurred by $5.80 per week. The net benefit was highest ($7.39) among those who felt they had fewer symptoms than in previous ragweed seasons. When excluding the time lost from work or school from the calculation of costs, the net benefit was higher at $8.30 per week. In the sensitivity analysis, the estimates that were most sensitive to change were the cost of study medication, days missed from work or school and rescue medications. Only when the cost of each was at its highest assumed value was the net benefit negative.	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: Mo Level of evidence: 4 Note: Double-dummy blinding technique employed.

Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Kessler, Almeida, Berglund, et al., 2001	Design: Population-based daily diary survey used to estimate indirect costs of AR Intervention(s): NA Duration of study treatment: NA Dates: March 1996 to May 1997 Location: US Setting: Community Type(s) of providers: NA	No. of subjects at start: The National Survey of Daily Experience (NSDE) (n = 3,032) was a substudy of the MacArthur Foundation Midlife Development in the US Survey (MIDUS). 83% of the target sample (n = 1,242) consented by telephone to participate. Dropouts/withdrawals: NA No. of subjects at end: 114 w/out AR, 625 with self-reported AR Inclusion criteria: Age 25 to 74; self-reported "hay fever or other seasonal allergies" among a list of conditions Exclusion criteria: None specified Age: Of those with allergic rhinitis: 35.5% 25-34, 34.7% 35-49,29.7% ≥ 50 Sex: 60.5% women Race: NR	1) Associations between impaired work quality and sociodemographic variables 2) Associations between impaired work quantity and sociodemographic variables 3) Average monthly indirect cost during periods of high pollen/mold exposure per person 4) Projected US annual indirect cost of AR during high pollen/mold exposure	1) Impaired work quality was inversely related to age, higher in the western areas of the US, and lower in the fall than other seasons. 2) Impaired work quantity was higher in women and higher in the western areas of the US 3) $156.27 SE = $20.04 ($1997) 4) $7.7 billion ($1997)	Quality Scoring: Population similar: Yes Intervention(s) described: No Comorbidities described: No Diagnosis by MD: No Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 1b Notes: Assumptions used in cost calculations: 1) Data on work impairment (work quality and work quantity) was collected using self-administered diaries during 8 consecutive days (periods were randomly assigned). 2) Impaired work quality was measured using yes/no response options. Work quantity was measured on a 0-10 scale, then dichotomized as impaired (0-5) and not impaired (6-10). 3) Individual-level wage data were combined with results from regression analyses to estimate indirect costs. It was assumed that impaired work quality was equal to 25% of the respondent's daily wage and impaired work quantity was equal to 75% of daily wage.

Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Kozma, Schulz, Sclar, et al., 1996	Design: Secondary analysis of data from previously reported RCT (see Notes) Intervention(s): 1) Fluticasone propionate nasal spray, 2 sprays per nostril, once per day (total dose 200 µg) (n = 78) 2) Terfenadine 60 mg bid (n = 77) Duration of study treatment: 14 days No mention of rescue med Trial preceded by 4- to 7-day run-in period Dates: NR Location: Texas Setting: Allergy clinic Type(s) of providers: NR	No. of subjects at start: 232 in original trial; 77 subjects randomized to placebo were excluded from the cost-effectiveness analysis Dropouts/withdrawals: No. of subjects at end: 155 Inclusion criteria: Based on four 0-100 point visual analog scales for sneezing, nasal obstruction, rhinorrhea, and nasal itching, patients had to have had a combined score ≥ 200 on 4 of 7 days prior to the intervention Exclusion criteria: NR Age: 39 years (mean) Sex: 52% female Race: White: 81.3%; Black: 3.2%; Hispanic: 15.5%; Other: 0%	1) Efficacy: 1a) Patient-assessed symptom severity: sneezing, nasal obstruction, rhinorrhea, and nasal itching graded daily using 0- to 100-point visual analog scales 1b) Patient global assessment of efficacy: overall response to treatment graded at end of trial on scale of 1 (significant improvement) to 7 (significant worsening) 2) Costs: Included only direct cost for study med (average wholesale price) 3) Cost-efficacy analysis (including sensitivity analysis)	1) Efficacy: 1a) There were no differences in total symptom severity scores prior to treatment. However, scores were significantly lower in the fluticasone group during the treatment period (159 vs 201, p = 0.003). The average decrease in scores between baseline and treatment periods was also greater for the fluticasone arm (-116 vs -80, p = 0.007). 1b) More patients in the fluticasone arm indicated that they improved during the treatment period (mild, moderate or significant improvement) compared to patients in the terfenadine arm (85% vs 69%, p = 0.007). 5% in the fluticasone arm and 2% in the terfenadine arm reported worsening. A greater proportion of patients in the terfenadine arm reported no change (29% vs 9%). When the criteria used to indicate improvement included only those reporting significant or moderate improvement, there was not a significant difference between treatment arms (64% vs 53%, p = 0.154). When only a significant improvement was used as the criterion, more patients in the fluticasone arm were deemed to have improved (38% vs. 19%, p = 0.007). 2) Cost of terfenadine during study period: $24.81; cost of fluticasone during study period: $18.14 3) Incremental cost-effectiveness ratios were not reported as fluticasone was found to be less costly and more effective than terfenadine when the standard for improvement included only those indicating significant	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: No Outcome measures valid: No Level of evidence: 2b Notes: Efficacy assessed through a secondary analysis of data from a previously published trial (van Bavel J, Findlay S, Hampel F, et al. Intranasal fluticasone propionate is more effective than terfenadine tablets for seasonal allergic rhinitis. Arch Intern Med 1994;154:2699-704). Original trial included a placebo arm, which was not included in this re-analysis. Double-dummy blinding technique employed in original trial.

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Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
				improvement or when the standard for improvement included those indicating significant, moderate or mild improvement.	
Lee, Cummins, and Okamoto, 2001	Design: Retrospective analysis of health care claims Intervention(s): NA Duration of study treatment: NA Dates: 1997 and 1998 Location: US Setting: National managed care organization Type(s) of providers: NA	No. of subjects at start: > 16 million people in data set Dropouts/withdrawals: NA No. of subjects at end: 202,426 Inclusion criteria: People diagnosed with AR during 1997 or 1998 and with at least one prescription claim within the 12-month period following AR diagnosis. All prescription claims within the 12-month period following the first prescription claim were analyzed. Exclusion criteria: Patients who were not continuously enrolled during the study period Age: Mean, 34 Sex: 61.4% women Race: NR Geographic region: Midwest: 27.7% Northeast: 12.0% Southeast: 51.8% West: 9.0%	1) Proportion of patients who received treatment with second-generation antihistamines ± nasal steroids, plus breakdown by treatment 2) Prevalence of comorbid conditions 3) Average annual charges by department 4) Total average annual charges 5) Proportion of total costs attributed to prescription drugs and outpatient medical services	1) Treatment included second-generation antihistamine and/or nasal steroid: 90.7%; Monotherapy with second-generation antihistamines: 41.4%; Monotherapy with nasal steroids: 19.7%; Combination therapy with second-generation antihistamines and nasal steroids: 29.7% 2) Upper respiratory infection: 32.2%; Lower respiratory infection: 3.3%; depression: 6.5%; sinusitis: 34.2%; Asthma: 14.8%; emphysema: 0.2%; COPD: 0.9%; otitis media: 11.5% 3) Inpatient: $8.28; outpatient: $216.31; ancillary: $4.43; emergency: $0.16; pharmacy-related: $236.02 4) $465.21 5) Prescription drugs: 51%; outpatient medical services: 46%	Quality Scoring: Population similar: Yes Intervention(s) described: No Comorbidities described: No Diagnosis by MD: No Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 2c Notes: Patients' treatment was classified based on initial treatment selection. Switches or augmentations were not considered.

Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Leickly, Sears-Ewald, and Ownby, 1989	Design: RCT, parallel-group Intervention(s): 1) Terfenadine 60 mg twice per day (n = 10) 2) Chlorpheniramine 4 mg + pseudoephedrine 60 mg, one capsule in morning and two at night (n = 9) Patients in both groups permitted to use nasal cromolyn as rescue med, if study med failed to relieve symptoms adequately Duration of study treatment: 38 days (during ragweed season) Dates: August- September 1986 Location: Detroit, MI Setting: Allergy clinic Type(s) of providers: NR	No. of subjects at start: 20 Dropouts/withdrawals: 1 No. of subjects at end: 19 Inclusion criteria: History of late summer-early fall ragweed-induced allergic rhinitis for at least 2 years and a positive skin test to ragweed Exclusion criteria: Perennial allergic rhinitis, poorly controlled asthma, daily systemic steroid use, or long period of absence from study location Age: Mean, 32 years; range, 18-59 Sex: 53% women Race: NR	1) Daily cost to druggist for study meds (based on average wholesale prices, December 1986) 2) Patient-assessed symptom severity: sneezing; stuffy nose; runny nose; red, itchy nose; cough/wheeze; and shortness of breath graded twice daily on scale of 0 (none) to 6 (very severe) 3) Adverse effects: drowsiness and irritability graded twice daily on scale of 0 (none) to 6 (very severe); GI complaints noted, but not scored 4) Treatment compliance 5) Patient global evaluation of efficacy of treatment: experience during study rated relative to previous ragweed seasons 6) Patient satisfaction: pts asked at end of trial whether they would use the study med again	1) Daily cost to druggist for study meds: $0.92 for terfenadine, $0.37 for chlorpheniramine/pseudoephedrine 2) Patient-assessed symptom severity: No significant differences in any individual symptom (p-values from 0.32 to 0.90) or combined symptoms (p = 0.97) 3) Adverse effects: No significant difference in any individual adverse effect (p-values from 0.07 to 0.77), but terfenadine had significantly fewer total adverse effects (p = 0.03). 4) Treatment compliance: 1 patient in the terfenadine group reported 3 days of noncompliance 5) Patient global evaluation of efficacy of treatment: 6 of 10 in the terfenadine group and 8 of 9 in the chlorpheniramine/ pseudoephedrine group stated that this was their 'best year'. 6) Patient satisfaction: 7 of 10 patients treated with terfenadine would stated that they would use the medication again; 8 of 9 chlorpheniramine/ pseudoephedrine patients reported that they would use the medication again.	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 4 Note: Unable to determine how they calculated their symptom scores. Scores were collected twice daily using a 0-6 scale. They state that the average symptom scores represent the total score for the group for that symptom divided by the number of days in the study, providing an average symptoms treatment group score per day. If they did add up the scores for pts in each arm of the trial (n = 9 and n = 10) and then divide by the number of days, these results will not be valid because (1) there are more patients in one group versus the other (2) because observations are not on a per-patient basis but a per-day basis.

Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Liao, Leahy, and Cummins, 2001	Design: Retrospective analysis of health care claims Intervention(s): NA Duration of study treatment: NA Dates: 1999 Location: US Setting: National managed care organization Type(s) of providers: NA	No. of subjects at start: ~13 million people in data set Dropouts/withdrawals: NA No. of subjects at end: 105,696 Inclusion criteria: People diagnosed with AR during 1999 with at least one prescription claim for a nonsedating antihistamine within the 12-month period following AR diagnosis. Exclusion criteria: NR Age: Mean, 36 (SD 19); 16% age < 12; 10% age 13-18; 39% age 19-45; 29% age 46-65; 7% age > 65 Sex: 61.8% women Race: NR Geographic Region: Midwest: 14.1% Northeast: 13.9% Southeast: 63.9% West: 8.1%	1) Proportion of patients who received treatment with second-generation antihistamines ± nasal steroids, plus breakdown by treatment. Patients' treatment was classified based on initial treatment selection. Switches or augmentations were not considered. 2) Prevalence of comorbid conditions 3) Average annual charges by department 4) Total average annual charges 5) Proportion of total costs attributed to prescription drugs and outpatient medical services	1) Treatment included second-generation antihistamine and/or nasal steroid: 66.3%; Monotherapy with second-generation antihistamines: 24.8%; Monotherapy with nasal steroids: 12.0%; Combination therapy with second-generation antihistamines and nasal steroids: 29.5% 2) Prevalence of comorbid conditions: Upper respiratory infection: 29.0%; lower respiratory infection: 4.7%; depression: 7.4%; sinusitis: 32.0; asthma: 18.4%; emphysema: 0.3%; COPD: 6.9%; otitis media: 8.9% 3) Average annual charges by department: inpatient: $14.71; outpatient: $358.84; ancillary: $5.44; emergency: $0.30; pharmacy-related: $171.32 4) Total average annual charges: $550.61 5) Proportion of total costs attributed to prescription drugs and outpatient medical services: Prescription drugs: 31%; Outpatient medical services: 65%	Quality Scoring: Population similar: No Intervention(s) described: No Comorbidities described: Yes Diagnosis by MD: No Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 3b Notes: The results are not consistent with the inclusion criteria. The inclusion criteria defined cases as patients with a prescription claim for a nonsedating antihistamine, yet in the results a proportion of patients received monotherapy with steroids or neither steroids nor nonsedating antihistamines. Also, this study was intended to update the results of the study by Lee, Cummins, and Okamoto (2001), above. However, there are substantial differences between the results of these study for some outcomes such as the proportion of pts receiving neither nasal steroids nor nonsedating antihistamines (33.7% vs. 9.3%), the proportion receiving nasal steroids only (12.0% vs. 19.7%), and average costs for pharmaceuticals ($171.32 vs. $236.02). The authors attribute these differences to differences in the study populations.

Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Malone, Lawson, Smith, et al., 1997	Design: Cost of illness study based on data from the 1987 National Medical Expenditure Survey (NMES) Intervention(s): NA Duration of study treatment: NA Dates: 1987 Location: US Setting: Community Type(s) of providers: Allergist, 17%; ENT, 4%; GP or family practitioner, 6%; internist, 3%; pediatrician, 9%; nurse, 24%; other, 20%; not certain, 10%	No. of subjects at start: 36,259 respondents to NMES Dropouts/withdrawals: No. of subjects at end: Inclusion criteria: Non-institutionalized civilians in the US Exclusion criteria: Federal, military, and Department of Veterans Affairs populations, plus residents of nursing homes and other institutions Age: NR Sex: 45% male (of respondents with AR) Race: Native American: 328,921 (1%) Asian/Pacific: 606,762 (1%) Black: 4,215,059 (11%) White: 32,728,023 (84%) Other: 1,116,999 (3%)	1) Prevalence of AR 2) Proportion of AR patients who sought medical treatment 3) Number and cost of prescriptions for AR 4) Number and cost of office or clinic visits to medical providers for AR 5) Number and cost of outpatient hospital visits for AR 6) Number and cost of emergency room visits for AR 7) Number of missed work days and associated productivity loss 8) Number of missed school days and associated productivity loss 9) Productivity loss associated with reduced activity days 10) Total direct cost of AR 11) Total indirect cost of AR 12) Total direct and indirect cost of AR	1) Prevalence of AR: 38.9 million (26.7 million adults and 12.3 million children) 2) Proportion of AR patients who sought medical treatment: 12.1% (4.7 million persons) 3) Number and cost of prescriptions for AR: 11.5 million prescriptions, $184 million ($1987), $301 million ($1994) 4) Number and cost of office or clinic visits to medical providers for AR: 16.7 million visits, $418 million ($1987), $648 million ($1994) 5) Number and cost of outpatient hospital visits for AR: 734,000 visits, $96 million ($1987), $180 million ($1994) 6) Number and cost of emergency room visits for AR: 101,000 visits, $9.5 million ($1987), 17.7 million ($1994) 7) Number of missed work days and associated productivity loss: 811,000 missed work days, $37 million ($1987), $47 million ($1994) 8) Number of missed school days and associated productivity loss: 824,000 missed school days, $13 million ($1987), $17 million ($1994) 9) Productivity loss associated with reduced activity days: 4,230,000 reduced activity days, $17 million ($1987), $23 million ($1994) 10) Total direct cost of AR: $708 million ($1987), $ 1.15 billion ($1994)	Quality Scoring: Population similar: Yes Intervention(s) described: No Comorbidities described: No Diagnosis by MD: No Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 3b Notes: Assumptions used in cost calculations: 1) Restricted activity days collected in NMES were valued at 25% of the respondent's daily salary. 2) Restricted activity days for those less than 18 years of age were not included. 3) Indirect costs for missed school days based on parent's income. 4) Cost of OTC medications not included.

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Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
				11) Total indirect cost of AR: $67 million ($1987), $ 86 million ($1994) 12) Total direct and indirect cost of AR: $775 million ($1987), $ 1.23 billion ($1994)	
Manor, Matthews, and Power, 2001	Design: Longitudinal survey of a 1958 birth cohort administered at ages 23 and 33 Intervention(s): NA Duration of study treatment: NA Dates: Surveys administered in 1981 and 1991 Location: England, Wales, and Scotland Setting: Community Type(s) of providers: NR	No. of subjects at start: At age 23: n = 12,525 Dropouts/withdrawals: 1,252 No. of subjects at end: At age 33: n = 11,273 Inclusion criteria: Born in England, Wales, or Scotland during one week in March 1958 Exclusion criteria: NA Age: Survey administered when respondents were 23 and 33 years of age Sex: 50% male Race: NR	1) Prevalence of hay fever at age 23 and age 33 in men and women 2) Relationships between 2 global health measures and (self-rated health and limiting longstanding illness) and specific health problems. Self-rated health was grouped into 2 categories: fair/poor and good/excellent. Limiting longstanding illness was determined by asking whether respondents had a longstanding illness, disability, or infirmity that limited their daily activities in any way compared to people of their same age. Hay fever was one of the specific health problems examined. Others included psychological distress, respiratory problems, obesity, asthma, backache, eczema, diabetes, epilepsy, cancer, heart trouble, high blood pressure, arthritis, and menstrual or other gynecologic problems. 3) Association between changes in self-reported	1) Prevalence of hay fever by age and sex: Age 23: men 16.6%; women 16.4% Age 33: men 15.6%; women 16.3% 2) Self-rated health and limiting illness were associated with all specific health problems except among men for hay fever and obesity. In women, those who reported hay fever were more likely to report fair/poor health - lowest odd ratio reported for any health condition [OR = 1.47 (age 23) and 1.33 (age 33)]. The association between reporting longstanding illness and hay fever was significant in men and women at age 23 (OR = 1.38 and 1.98, respectively), but only for women at age 33 (OR = 1.74). These associations were considered weak. 3) No association between changes in self-rated health and changes in	Quality Scoring: Population similar: Yes Intervention(s) described: No Comorbidities described: No Diagnosis by MD: No Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 1b Notes:

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Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
			health and changes in specific health problems reported	reporting hay fever or eczema were found. Significant associations were found for other health problems.	
Mc-Menamin, 1994	Design: Cost of illness study based on a synthesis of data from multiple sources: 1) 1988 National Health Interview Survey; 2) 1985 National Ambulatory Medical Care Survey; 3) 1989 Gallup Poll; 4) National Health Accounts from the Health Care Financing Administration 5) wage data from US Dept of Labor Intervention(s): NA Duration of study treatment: NA Dates: Vary Location: US Setting: Community Type(s) of providers: NA	No. of subjects at start: NA Dropouts/withdrawals: NA No. of subjects at end: NA Inclusion criteria: NA Exclusion criteria: Federal, military, and Department of Veterans Affairs populations, plus residents of nursing homes and other institutions Age: NR Sex: NR Race: NR	1) Prevalence estimate from NHIS: no. of people reporting hay fever in 1988 2) Number and cost of physicians' office visits for AR 3) Cost of medications for AR 4) Direct medical costs for AR (physician visits and medications) 5) Number of lost work days 6) Indirect costs of AR 7) Total costs (direct + indirect)	1) Prevalence estimate from NHIS: no. of people reporting hay fever in 1988: 22.4 million; 9.3% prevalence rate 2) Number and cost of physicians' office visits for AR: 9.8 million visits, $881 million ($1990) 3) Cost of medications for AR: $276 million ($1990) 4) Direct medical costs for AR (physician visits and medications): $1.16 billion ($1990) 5) Number of lost work days: 3.4 million 6) Indirect costs of AR: $639 million ($1990) 7) Total costs (direct + indirect): $1.8 billion ($1990)	Quality Scoring: Population similar: Not adequately described Intervention(s) described: No Comorbidities described: No Diagnosis by MD: No Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 3b Notes: Assumptions used in cost calculations: 1) 5% growth in population from 1985 to 1990. 2) 1989 Gallup poll: People with AR who used sedating (OTC) antihistamines reported a 25% reduction in productivity for 14 work days per year. 3) Proportion Treated with OTC antihistamines: 1989 Gallup poll: 50%. 4) Medication costs were based on the ratio of prescription and OTC medication costs to total physician costs as estimated in the National Health Accounts for HCFA (37.93%). 5) Cost of office visit: $50, cost of office visit with tests: $100 6) Average daily earnings: $96.05. 7) Productivity losses based on (1) total lost work days; (2) 25% of wage earners' reduced activity days; (3) 25% of home workers reduced activity days less 5%.

Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Meltzer, Casale, Nathan, et al., 1999	Design: RCT, parallel-group, method of randomization not described Intervention(s): 1) Fexofenadine 180 mg once per day (n = 275) 2) Fexofenadine 120 mg once per day (n = 284) 3) Placebo (n = 286) Duration of study treatment: 2 weeks No mention of rescue med Trial preceded by 1-week placebo run-in period Dates: August-November 1997 Location: US Setting: Community Type(s) of providers: NR	No. of subjects at start: 845 Dropouts/withdrawals: No. of subjects at end: 845 (610 eligible for inclusion in analyses of work impairment, 238 for classroom impairment) Inclusion criteria: Age 12-65; moderate to severe seasonal AR; history of AR during previous 2 fall seasons; positive skin prick test; symptom score ≥ 6 (max score: 16), with 2 or more symptoms rated as moderate-to-severe. After 1-week placebo run-in period, patients needed a symptom score ≥5 with ≥ 2 individual symptoms rated as moderate or severe. Exclusion criteria: Patients with individual symptoms rated as very severe; URI within 30 days of study; lack of response to antihistamines; clinically significant underlying medical disorder; receipt of immunotherapy; pregnancy; inability to read or understand English Age: Mean, 32-33 Sex: 64.6% female Race: 88.2% Caucasian; 11.8% Other Average no. of years since onset of seasonal AR: 17	1) Disease-specific quality of life: assessed using the Rhinoconjunctivities Quality of Life Questionnaire (RQLQ) at baseline and at 1 and 2 weeks 2) Performance impairment due to allergy symptoms: assessed using the Work Productivity and Activity Impairment (WPAI) instrument at baseline and at 1 and 2 weeks 3) Overall health impressions/generic quality of life: measured using 3 generic domains of the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) (Role-Physical, General Health Perceptions, Change in Health)	1) Disease-specific quality of life: Mean overall RQLQ score at baseline: 2.7; patients treated with both doses of fexofenadine experienced greater improvement in overall RQLQ scores. The 180-mg group reported greater improvement than placebo for all 7 RQLQ domains. The 120-mg group reported greater than placebo for 4 of the 7 RQLQ domains: practical problems, nasal symptoms, eye symptoms, and emotions. 2) Performance impairment due to allergy symptoms: Overall work impairment significantly decreased 7.1% in the 120-mg group and 8.7% in the 180-mg group, compared to a 1.8% reduction in the placebo group. There were also significant reductions in both fexofenadine groups relative to placebo in activity impairment. There were no significant differences between treatment groups in the percentage of time missed from work. There were also no significant differences in classroom impairment measures. 3) Overall health impressions/generic quality of life: There were significant improvements in both fexofenadine groups as measured by the SF-36 Role-Physical domain compared to placebo. Significantly more patients treated with fexofenadine reported an improvement in health from baseline to Week 1 compared to placebo. However, there was not a significant difference between treatment groups from week 1 to week 2.	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: Yes Level of evidence: 1b Notes:

Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Ray, Baraniuk, Thamer, et al., 1999	Design: Cost of illness study based on data from 1994 National Hospital Discharge Survey, 1994 National Ambulatory Medical Care Survey, 1994 National Hospital Ambulatory Medical Care Survey, 1994 National Survey of Ambulatory Surgery, 1987 National Medical Expenditure Survey, and estimates gathered from 4 experts using a 3-round modified consensus Delphi procedure The study objective was to estimate direct medical costs associated with treatment of allergic rhinoconjuctivitis. The analysis was based on the assumption that AR is a predisposing factor for other airway disorders. The Delphi procedure was used to obtain estimates of the proportion of patients with specific airway disorders who would also be assumed to have allergic rhinoconjunctivitis (AR/AC). Intervention(s): NA Duration of study treatment: NA Dates: 1994 data extrapolated to 1996 values Location: US Setting: All medical settings Type(s) of providers: All	No. of subjects at start: NR Dropouts/withdrawals: NA No. of subjects at end: NR Inclusion criteria: All survey records with a primary diagnosis of AR or atopic conjunctivitis were attributed to AR/AC Exclusion criteria: Federal, military, and Department of Veterans Affairs populations, plus residents of nursing homes and other institutions Age: NR Sex: NR Race: NR	1) Total number of outpatient physician visits attributed to AR/AC in US 2) Total number of hospital outpatient visits attributed to AR/AC in US 3) Total number of emergency department visits attributed to AR/AC in US 4) Total number of hospitalizations attributed to AR/AC in US 5) Total medical costs attributed to AR/AC in US Costs were estimated by the expert panel. These estimated costs were multiplied by the total number of encounters for each of 10 airway disorders (e.g. chronic otitis media, sinusitis, asthma) to estimate resource use attributable to AR/AC	1) Total number of outpatient physician visits attributed to AR/AC in US: 24,200,183 outpatient physician visits 2) Total number of hospital outpatient visits attributed to AR/AC in US: 1,410,779 hospital outpatient visits 3) Total number of emergency department visits attributed to AR/AC in US: 1,887,448 emergency department visits 4) Total number of hospitalizations attributed to AR/AC in US: 97,349 hospitalizations 5) Total medical costs attributed to AR/AC in US: $5.93 billion ($1987), of which 31.4% was for treatment of AR/AC coded as the primary diagnosis, 25% for comorbid chronic otitis media or eustachian tube disorders, and 17% for comorbid sinusitis and 17% for comorbid asthma	Quality Scoring: Population similar: Yes Intervention(s) described: No Comorbidities described: Yes Diagnosis by MD: No Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 4 Notes: This study may overestimate the cost of allergic rhinoconjunctivitis because the total cost of visits that have a primary diagnosis of 1 of 10 airway diseases were attributed to allergic rhinoconjunctivitis. It is also likely to overestimate the number of inpatient/outpatient/ER encounters because even though AR may be assumed to be a secondary diagnosis in many cases where another diagnosis is the primary, exacerbation or treatment of the principal diagnosis precipitated the medical encounter. For example, the majority of hospital costs were attributable to the assumption that 30% of those with asthma would have AR.

Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Reilly, Tanner, and Meltzer, 1996	Design: Validation study of the Allergy-specific Work Productivity and Activity Impairment (WPAI-AS) using data from 2 multicenter, double-blind, randomized, placebo-controlled trials Intervention(s): 1) Terfenadine 2) Fexofenadine 3) Placebo Duration of study treatment: Dates: 1993 autumn allergy season for the work/activity impairment cohort (Study 1) and 1994 spring allergy season for the classroom impairment cohort (Study 2) Location: US Setting: Allergy clinic Type(s) of providers: NR	No. of subjects at start: 574 in the intent-to-treat dataset for Study 1, 422 completed WPAI-AS at baseline, week 1, and week 2; 962 in the intent-to-treat dataset for Study 2, 241 were students who completed Classroom WPAI-AS at baseline, week 1, and week 2 Dropouts/withdrawals: NR No. of subjects at end: NR Inclusion criteria: Moderate to severe AR Exclusion criteria: Patients with asthma were NOT specifically excluded, but patients with severe asthma were not eligible because patients taking concomitant corticosteroids or cromolyn medications were excluded Age (mean): Study 1, 33; Study 2, 22.8 Sex: Study 1, 63% female; Study 2, 51.5% female Race: Study 1, 84.8% Caucasian; Study 2, 84.2% Caucasian Years of seasonal AR: Study 1, 17.5; Study 2, 12.6	1) Discriminative validity: Correlations between time missed from work or classroom and total symptom score at baseline and weeks 1 and 2. 2) Discriminative validity: Correlations between impairment measures and total symptom score at baseline and weeks 1 and 2. 3) Discriminative validity: Results of regression analysis for total symptom scores on the prediction of work and activity impairment 4) Discriminative validity: Results of regression analysis for total symptom scores on the prediction of classroom impairment 5) Evaluative validity: Correlation between average change in total symptom scores and change in time missed from work or classroom 6) Evaluative validity: Correlation between changes in total symptom scores and work and classroom impairment measures 7) Evaluative validity: Results of regression	1) Correlations were generally low: work: r = 0.11 to 0.16; classroom: r = 0.13 to 0.27 2) Correlations were higher than with time missed measures: work: r = 0.30 to r = 0.55; classroom: r = 0.25 to 0.41 3) Higher total symptom scores were significant predictors of greater work and activity impairment, but not time missed from work at all time points. 4) Higher total symptom scores were significant predictors of classroom impairment at all time points. Higher total symptom scores were also predictive of more classroom time missed at weeks 1 and 2. 5) There was virtually no correlation (work: r = -0.06; classroom: r = 0.05 to 0.14). 6) Correlations were positive (work: r = 0.35 to 0.42; classroom: r = 0.24 to 0.27) 7) Average change in total symptom score was a significant predictor of all	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: Yes Level of evidence: 4 Note: The discriminative and evaluative validity of the WPAI-AS impairment measures (work impairment, overall work impairment, activity impairment, classroom impairment and overall classroom impairment) was established. Because absenteeism from work and school was relatively low (1.7% for work and 4.7% for classroom), establishing the validity of work time missed and classroom time missed was not possible.

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Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
			analysis for changes on total symptom score and changes in work and classroom impairment measures	impairment measures except work or classroom time missed.	
			8) Responsiveness: changes in mean total symptom scores and WPAI-AS scores for the 5% of patients with the most improvement and the 5% of patients with the least improvement	8) Among the 5% of patients with the most improvement, the level of work and classroom impairment decreased dramatically. Among the 5% of patients with the least improvement, the level of work and classroom impairment generally increased or stayed about the same.	
			9) Responsiveness: changes in total symptom scores and impairment measures for responders and nonresponders (as measured by physician evaluation)	9) For responders in Study 1 and Study 2, total symptom scores and impairment measures decreased dramatically. For nonresponders in Study 1 and Study 2, symptom scores and impairment measures either decreased slightly or stayed about the same.	
			10) Sample size implications	10) To detect a 5% difference in overall work impairment, 201 patients per treatment group would be necessary for 80% power and 5% Type 1 error for a 2-sided hypothesis test. To detect a 5% difference in overall classroom impairment, 192 patients per treatment group would be necessary.	

Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Revicki, Leidy, Brennan-Diemer, et al., 1998	Design: Cross-sectional surveys for instrument development The objective of the study was to design a preference-weighted instrument for rhinitis that could be used to construct rhinitis symptom-adjusted life years (distinct from quality-adjusted life years) in order to quantify outcomes of care for cost-effectiveness analyses. Intervention(s): NA Duration of study treatment: NA Dates: NR Location: Baltimore Setting: Allergy clinic Type(s) of providers: NR	No. of subjects at start: 100 patients, of whom 20 were randomly selected to be retested at 2 weeks to evaluate test-retest reliability Dropouts/withdrawals: NR No. of subjects at end: 100 Inclusion criteria: Receiving care at the Johns Hopkins University Asthma and Allergy Center Exclusion criteria: NR Age: Mean: 36.9 years Sex: 60% women Race: 77% Caucasian; 15% African-American; 8% Asian or other ethnic group Other: Mean duration of illness: 21 years Mean age of onset: 16 years Concurrent diagnosis of asthma: 52% <u>Clinical and health-related measures:</u> To evaluate concurrent and construct validities with the Rhinitis Symptom Utility Index (RSUI), 6 additional measures were used: (1) physician-reported disease severity; (2) disability days; (3) disease-specific quality of life using the RQLQ; (4) generic health utility using the Health Utilities Index Mark 2 (HUI2); (5) Visual Analog Scale (VAS); and (6) Standard Gamble (SG)	1) Average number of days over the previous month when the patient was in bed most or all of the day, had restricted activity for at least ½ day, and the number of days the patient missed school or work 2) RSUI scores 3) Reproducibility of RSUI over 2 weeks. 4) Construct validity of the RSUI 5) Correlations between the RSUI and total and subscale scores for the RQLQ.	1) Average number of bed disability days: 0.63; restricted activity days: 2.49; and missed work days: 0.45. 2) RSUI scores ranged from 0.15 to 1.0. Most scores were > 0.70. The mean was 0.72 (SD 0.23), the median score was 0.78. 3) Intraclass correlation coefficient (ICC) was 0.40. (ICCs for RQLQ ranged from 0.17 to 0.77 due to instability of allergic rhinitis symptoms over time). 4) The RSUI was able to discriminate between levels of disease severity. The mean RSUI for none/mild allergic rhinitis was 0.79 and the mean RSUI for the moderate/severe group was 0.67 ($p < 0.05$). Mean RSUI scores were also higher for patients with HUI2 scores ≥ 0.75 (0.76) than patients with HUI2 scores 0.75 (0.57). Also, mean RSUI scores were higher for patients with no bed disability days (0.76) compared to patients with ≥ 1 bed disability day (0.62). 5) Correlation between the RSUI and total score was -0.67 ($p = 0.0001$). Correlation between the RSUI and each subscale was -0.47 for activity limitations, -0.58 for sleep, -0.51 for non-hay fever symptoms, -0.61 for eye symptoms, -0.69 for nasal symptoms, -0.49 for emotional symptoms, and -	Quality Scoring: Population similar: Yes Intervention(s) described: Not applicable Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: Yes Level of evidence: 4

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Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
		Multiattribute utility assessment methods were used to derive the preference weighting scheme to estimate the RSUI score.		0.61 for practical problems (p = 0.0001 for each).	
Ross, 1996	Design: Cost of illness study (indirect costs only) based on a synthesis of data from multiple sources: 1) 1983-1985 survey from US Department of Health and Human Services; 2) 1994 Statistical Abstract of the United States; and 3) 1989 Gallup Poll The study was designed to estimate the indirect costs associated with the use of first-generation, sedating antihistamines. Intervention(s): NA Duration of study treatment: NA Dates: 1983-1986 prevalence estimates; 1993 wages Location: US Setting: Community Type(s) of providers: NR	No. of subjects at start: NA Dropouts/withdrawals: NA No. of subjects at end: NA Inclusion criteria: Member of US work force Exclusion criteria: NA Age: NR Sex: 51.6% men, Race: NR	1) Prevalence estimate – no. of people with AR in US workforce 2) Prevalence estimate – no. of people with AR classified into 1 of 11 employment categories for men and women 3) Lost productivity due to treatment of AR with sedating (OTC) antihistamines using Assumption #2 (see Notes) 4) Lost productivity if 10%, 20%, 30% of workers with AR lost 1 day of work per year due to AR	1) 12.6 million 2) 11.1 million 3) $3.79 billion ($2.39 billion for men and $1.40 billion for women) 4) 10%: $108 million; 20%: $216 million; 30%: $324 million	Quality Scoring: Population similar: Yes Intervention(s) described: No Comorbidities described: No Diagnosis by MD: No Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 3b Notes: Assumptions used in cost calculations: 1) 5% growth in population during previous decade 2) Reduced productivity: 1989 Gallup poll: People with AR who used sedating (OTC) antihistamines reported a 25% reduction in productivity for 14 work days per year. 3) Proportion Treated with OTC antihistamines: 1989 Gallup poll: 50%

Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Santilli, Nathan, Glassheim, et al., 2001	Design: Survey Intervention(s): NA Duration of study treatment: NA Dates: NR Location: Bridgeport, CT; Colorado Springs, CO; Fresno, CA Setting: Private allergy practices Type(s) of providers: Specialists	No. of subjects at start: 175 Dropouts/withdrawals: 0 No. of subjects at end: 175 Inclusion criteria: Immunotherapy for one allergen or a combination of pollens, molds, mites and animal dander for at least 1 year Exclusion criteria: NR Age: NR Sex: 68% female Race: NR Other: Average duration of immunotherapy 3.3 years	1) Rhinitis Outcomes Questionnaire (ROQ) consisting of 26 symptom questions each scored using a 0 to 5 Likert scale. A total score of 130 is possible, representing the most severe combination of allergy symptoms. 2) Percent of patients reporting that immunotherapy was effective 3) Change in antibiotic use, emergency room visits, days lost from work or school, and hospital admissions 4) Change in number of daily medications	1) Prior to immunotherapy, the average score on the ROQ was 52. The average score decreased to 25 following immunotherapy. 2) 81% reported that they believed immunotherapy was effective, and 19% of patients were unsure. 3) Patients reported a 67% decrease in antibiotic use, 68% decrease in emergency room visits, a 75% decrease in days lost from work or school, and a 79% decrease in hospital admissions. 4) Patients did not report a decrease in the number of daily medications after immunotherapy.	Quality Scoring: Population similar: Not adequately described Intervention(s) described: No Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: Yes Level of evidence: 4 Note: Patients who discontinued immunotherapy prior to 1 year were not included in the study. Also, the study is limited by recall bias, as patients completed the survey twice at one sitting (once to recall symptoms prior to immunotherapy and once to evaluate current symptoms). The absolute numbers of patients reporting antibiotic use, ER visits, lost work/school days, or hospital admission were not reported, and no statistical tests were used for comparisons.

Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Santos, Cifaldi, Gregory, et al., 1999 **Study 1 (= retro-spective review of annual medical costs of treating allergic rhinitis)**	Design: Retrospective analysis based on HMO claims data Intervention(s): None – billing encounter data analyzed to compute utilization of HMO system resources (specifically, service encounters and prescriptions) over a 1-year period for selected cohorts of patients with and without allergic rhinitis Duration of study treatment: NA Dates: 1996 Location: New Mexico Setting: Community, network model HMO Type(s) of providers: NR	No. of subjects at start: 15,872 (7936 allergic rhinitis patients + 7936 age- and sex-matched non-allergic rhinitis controls) Dropouts/withdrawals: NA No. of subjects at end: 15,872 Inclusion criteria: Age 12-64; HMO member in 1996 with continuous enrollment from 1994 to 1995; evidence of allergies based on one of the following: a visit for an allergen skin test, an ICD-9-CM code of allergic rhinitis, or a prescription for an allergy medication during the spring or fall allergy seasons Exclusion criteria: NR Age: mean: ~41 years Sex: 58% women Race: NR	1) Total cost to the HMO for medical care provided to the AR group and the matched control group in 1996 2) Cost of prescription medication to HMO for AR group and matched control group in 1996 3) Among the AR group, costs and distribution of prescriptions for allergic rhinitis 4) Average AR prescription costs per person with AR 5) Percent of AR population who filled at least one prescription.	1) AR group: $5.38 million; matched control group: $3.46 million 2) <u>All medication</u>: AR group: $2.06 million; matched control group: $1.05 million. <u>AR medication only</u>: AR group: $1.08 million; matched control group: $0.22 million <u>AR medication as a % of total Rx cost</u> AR group: 53%, matched control group: 21% 3) <u>Antibiotics</u>: 34.6% of AR prescriptions, 12.9% of total medication costs; <u>Oral Steroids</u>: 4.7% of AR prescriptions, 0.3% of total medication costs; <u>Antihistamines</u>: 29.4% of AR prescriptions; 21.8% of total medication costs; <u>Nasal Anti-inflammatory</u>: 27.2% of AR prescriptions; 16.5% of total medication costs; <u>Combination/cold</u>: 4.0% of AR prescriptions, 1.1% of total medication costs. 4) <u>All AR medications</u>: $190.70; <u>Antibiotics</u>: $68.49; <u>Oral Steroids</u>: $10.06; <u>Antihistamines</u>: $187.00; <u>Nasal Anti-inflammatory</u>: $125.30; <u>Combination/cold</u>: $42.71 5) 72%	Quality Scoring: Population similar: Yes Intervention(s) described: No Comorbidities described: No Diagnosis by MD: No Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 4 Notes: Assumptions used in cost estimation: 1) Relative value units (RVUs) were used to estimate costs for the HMO ($38.82/RVU in 1996 US$). 2) Prescription drug prices based on October 1997 AWP plus dispensing fee

Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Santos, Cifaldi, Gregory, et al., 1999 **Study 2 (= prospective RCT comparing two types of clinics for treating patients with allergic rhinitis)**	Design: RCT, parallel-group, method of randomization not described Intervention(s): 1) Intervention clinics – used practice guidelines designed to improved and standardize treatment of patients with allergic rhinitis; interventions/ practice guidelines used not described (n = 247 patients) 2) Control clinics – did not alter diagnostic and treatment practices (n = 255 patients) Duration of study treatment: 4 weeks Dates: 1996 fall allergy season Location: New Mexico Setting: Community, network model HMO Type(s) of providers: NR	No. of subjects at start: 502 Dropouts/withdrawals: NR No. of subjects at end: Inclusion criteria: Age 12-65; HMO members for ≥ 12 months prior to start of intervention; present evidence of fall allergies involving nasal symptoms Exclusion criteria: NR Age: NR Sex: NR Race: NR	1) Direct medical costs: included service encounters, prescriptions, and OTC medications (recorded by patients in daily symptom diaries) 2) Indirect costs: Estimated by measuring declines in work and school productivity using the Work Productivity and Activity Impairment Index – Allergy Specific (WPAI-AS) 3) Patient-assessed symptom severity: stuffy nose, sneezing, runny nose, itchy nose/palate/ throat, and itchy/watery eyes graded daily on scale of 0 (no symptoms) to 4 (physician visit needed); these data supplemented (how?) by data gathered in enrollment survey and periodic phone surveys 4) Behavior index – measured compliance with suggested preventive behavior (medical compliance, avoiding smoke, wearing a dust mask, etc.); scores ranged from 0 (no action) to 11 (maximum); not clear when assessed 5) Quality of life: assessed using an index "based on items from the Rhinoconjunctivitis Quality	1) Direct medical costs: Total direct medical costs: Intervention group: $56,515; Control group: $58,402 Direct medical costs per person: Intervention group: $229; Control group: $229 2) Indirect costs (productivity/activity impairment): Total indirect costs: Intervention group: $16,561; Control group: $21,372 Indirect costs per person: Intervention group: $67; Control group: $84 3) Patient-assessed symptom severity: Intervention group vs. control group: Stuffy nose: 1.60 vs 1.55; Sneezing: 1.02 vs 0.97; Runny Nose: 1.15 vs 1.10; Itchy Nose/Palate/Throat: 1.16 vs 1.02; Itchy/Watery Eyes: 1.27 vs 1.09 4) Average behavior index score: Intervention group: 4.60; Control group: 4.30 5) Quality of life measured using the RQLQ Index: Intervention Group: 2.9; Control group: 2.4	Quality Scoring: Population similar: Not adequately described Intervention(s) described: No Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 4 Notes: Results of statistical comparisons were not reported to compare differences in costs or patient outcomes. Not relevant to key question about correlating symptom outcomes/disease-specific quality of life with workplace performance data – estimates of statistical variation (SD or SE) are not reported, nor are the results of statistical comparisons

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Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
			of Life Questionnaire (RQLQ)"; scores ranged from 0 to 10, with higher scores indicating lower quality of life		
Schädlich and Brecht, 2000	Design: Cost-effectiveness analysis using a model based on secondary data. Separate models were developed for seasonal and perennial allergic rhinitis. Intervention(s): Specific immunotherapy (SIT) for 3 years versus pharmacologic treatment Duration of study treatment: Model was based on a 10-year follow-up period Dates: NA Location: Germany Setting: NA Type(s) of providers: NA	No. of subjects at start: NA Dropouts/withdrawals: NA No. of subjects at end: NA Inclusion criteria: NA Exclusion criteria: NA Age: NR Sex: NR Race: NR Cost-Effectiveness Model: Time period: model was based on a 10-year period. Health Outcome: the presence or absence of asthma symptoms at 10 years. Clinical trial, observational, and epidemiological data were used to model the health outcome. Costs: Costs in the model were valued from 3 perspectives: society, the healthcare system, and the statutory health insurance provider (SHI). Cost estimates were derived from a variety of sources including public pharmacies for the cost of drugs and allergen extracts, government payment schedules, and published estimates. Costs were discounted at 5% per annum.	1) Break-even point of accumulated costs and cost difference at 10 years between SIT and pharmacologic treatment 2) Incremental number of patients free from asthma due to SIT 3) Cost per additional patient free from asthma symptoms at 10 years 4) Results of sensitivity analyses	1) In the base-case analysis, cumulative costs in both arms were equal during year 7. At 10 years, cumulative costs in the SIT arm were approximately DM670 (DM; DM 1 = $US 0.5764, 1997 values) lower in the SIT group. 2) Out of 1000 hypothetical patients, the model showed that 161 additional patients were free from asthma symptoms at 10 years. 3) In the best case scenario for pollen allergy, the break even point for costs was reached at 1 year, resulting in a cost savings of DM 3,620 at 10 years with 212 additional patients free from asthma. In the worst case scenario, the break even point was never reached, resulting in additional costs in the SIT arm of DM 1,420 at 10 years with 88 additional patients free from asthma. 4) Sensitivity analyses: The following variables had an important effect on cost-effectiveness: a) Direct medical cost of anti-allergic pharmacotherapy (symptomatic treatment); b) Cost of SIT; c) Increase in asthma prevalence with symptomatic treatment of allergic rhinitis.	Quality Scoring: Population similar: Yes Intervention(s) described: No Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: No Outcome measures valid: No Level of evidence: 1b Note: 100% compliance with immunotherapy was assumed, the measure of effectiveness modeled was the additional patient free of asthma symptoms based on cumulative incidence and remission rates from different published sources for SIT and symptomatic treatment.

Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Stahl, van Rompay, Wang, et al., 2000	Design: Retrospective cost-minimization analysis based on data from a randomized, double-blind, parallel group study Intervention(s): 1) Budesonide 256µg once daily 2) Fluticasone 200 µg once daily 3) Placebo Duration of study treatment: 6 weeks Dates: November 1994 to July 1995 Location: Canada and Spain Setting: Allergy clinic Type(s) of providers: NR	No. of subjects at start: 314 Dropouts/withdrawals: NR No. of subjects at end: NR Inclusion criteria: Perennial allergic rhinitis Exclusion criteria: None specified Age: NR Sex: NR Race: NR	1) Cost of study drugs for 12 months in 1998 Canadian dollars 2) Cost of medical management (physician visits, comedication, laboratory tests/ examinations) of perennial AR for 12 months in 1998 Canadian dollars based on expert opinion 3) Cost of medical management due to lack of efficacy and side effects over 12 months in 1998 Canadian dollars 4) Treatment cost for both active treatment study arms (placebo was not considered a relevant comparator and was not included in the cost minimization analysis)	1) Budesonide: $95.80; fluticasone: $214.01; difference = $118.21 2) Physician visits: $114.23; laboratory tests/examinations: $48.23; co-medications: $38.96; total = $201.41 3) Lack of efficacy: $75.18; side effects: $17.46 4) Because effectiveness and side effect profiles for both medications were not different, the difference in costs is attributable to the difference in drug costs. The total 12-month cost for budesonide was estimated at $389.85 and the total 12-month cost for fluticasone was estimated at $508.06. Difference = $118.21.	Quality Scoring: Population similar: Not adequately similar Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: No Outcome measures valid: No Level of evidence: 4 Notes: The clinical data used in the study included all patients from Canada and Spain. However, the cost-minimization analysis was conducted using practice patterns (from an expert panel) and costs from Canada. Drug costs for study medications determined the results.

Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Storms, Meltzer, Nathan, et al., 1997	Design: Population-based mail surveys Intervention(s): NA Duration of study treatment: NA Dates: 1993 Location: US Setting: Co mmunity Type(s) of providers: NR	No. of subjects at start: Surveys initially sent to 15,000 households; 66.3% responded; a sample of 1450 persons were sent a 2nd survey to gather further information about AR; 73.4% responded Dropouts/withdrawals: NA No. of subjects at end: 481 respondents Inclusion criteria: Self-reported seasonal or perennial AR and ≥ 7 days of symptoms during previous year Exclusion criteria: Respondents who selected one of the following options as best describing their nasal/ocular symptoms that lasted ≥ 7 days during previous year: common cold, an allergy only when exposed to certain triggers, sinus problems, or other condition Age: 11.9% < 18; 20.6% 18-34; 33.5% 35-49; 19.1% 50-64; 10.8% ≥ 65 Sex: 56% female Race: 93% white	1) Proportion who reported not taking medications for AR, proportion filling a prescription for AR, proportion reporting an average monthly expenditure for OTC medications for AR 2) Proportion reporting any missed work or school days or unable to perform normal activities 3) Proportion who sought treatment from a physician for AR symptoms 4) Average per-patient expenditure on prescription and OTC medications for AR 5) Total US expenditures for prescription and OTC medications for AR 6) Total US expenditures for physician visits for AR 7) Total direct medical costs for AR	1) No medication: 13.5%; prescription medication: 45%; OTC medication: 69%. 2) 5% 3) 63% (22.6 million people) 4) Prescription: $56 ($1993); OTC: $56 ($1993) 5) Prescription: $907 million ($1993); OTC: $1.39 billion ($1993); Total: $2.3 billion 6) $1.13 billion ($1993) 7) $3.4 billion ($1993)	Quality Scoring: Population similar: Yes Intervention(s) described: No Comorbidities described: No Diagnosis by MD: No Objectively confirmed Not applicable Outcome measures valid: No Level of evidence: 4 Notes: It is not clear whether self-reported "expenses" represent total costs or out-of-pocket expenditures. Assumptions used in cost calculations: 1) Cost of office visit: $50. Assumed that physician visits did not include any diagnostic tests. 2) Self-reported expenses equal to direct medical costs.

Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Sussman, Mason, Compton, et al., 1999	Design: RCT, parallel-group, method of randomization not described Interventions: 1) Fexofenadine 60 mg + pseudoephedrine 120 mg (extended-release), twice per day (n = 215) 2) Fexofenadine 60 mg twice per day (n = 218) 3) Pseudoephedrine 120 mg (extended-release) twice per day (n = 218) Duration of study treatment: 14-20 days Rescue med not permitted Trial preceded by a 3- to 5-day placebo run-in period; no other washout period described Dates: NR Location: Canada Setting: Allergy clinic Type(s) of providers: NR	No. of subjects at start: 710 were screened for study; 651 randomized and treated with study drug(s) Dropouts/withdrawals: 9.7% discontinued the study; 2.8% due to adverse events; 3.8% due to subject/investigator decision. No. of subjects at end: 651 included in intent-to-treat analysis Inclusion criteria: Age 12-65; history of ragweed allergy confirmed by a positive skin prick test; evidence of a clinical response to antihistamines. At the initial visit, subjects had to have a total symptom score ≥ 6 for the previous 12 hours, with nasal congestion and ≥ 2 symptoms rated as moderate or severe. After the placebo lead-in phase, subjects had to have a total symptom score ≥ 6, moderate or severe nasal congestion, and at least 2 symptoms rated as moderate or severe for 2 of the 3 most recent evening assessments. Exclusion criteria: History of alcoholism or drug abuse; hypersensitivity to terfenadine, fexofenadine, or pseudoephedrine; URI or sinusitis within 30 days of 1st study visit; pregnant or lactating women; any symptoms rated as very severe Age: Mean ~33 years Sex: 57.8% female	1) Patient-assessed symptom severity: sneezing; rhinorrhea; itchy nose, palate, and/or throat; itchy, watery, or red eyes; and nasal congestion graded twice each day (7 PM and bedtime) on scale of 0 (symptom absent) to 4 (symptom so severe as to warrant an immediate visit to the physician). 2) Adverse events: Patients "were required to record any adverse events" 3) Work-related productivity: Assessed using the Work Productivity Activities Index (WPAI), completed at baseline and at end of treatment	1) Patient-assessed symptom severity: When using the efficacy endpoint used to evaluate all symptoms except nasal congestion, symptoms were improved to a greater extent with combination therapy than with pseudoephedrine alone, but not when compared with fexofenadine alone. When using the efficacy endpoint to evaluate nasal congestion symptoms, again, there was a significant improvement in the combination therapy arm compared to pseudoephedrine, but not compared to fexofenadine alone. 2) Adverse events: 43% of patients experienced ≥ 1 adverse event. There was no difference between the combination (51.2%) and pseudoephedrine only (45.4%) groups. However, the incidence of adverse events was significantly lower in the fexofenadine group (32.6%). The most frequently reported events were headache and insomnia. 3) Work-related productivity: At baseline, all patients reported an average of 44% impairment in daily activities. Working patients reported a 1.8% loss in work time, 38.7% work impairment, and 39.3% overall work impairment during the placebo lead-in phase. After treatment, daily activity impairment decreased by 9.8% in the fexofenadine group, 7.9% in the pseudoephedrine group, and 13% in the combination therapy group. Among working patients, there was a significant improvement in work productivity in the combination group (9.3%) compared to the pseudoephedrine group (6.2%). There was no improvement between the	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: Yes Level of evidence: 4 Note: Double-dummy blinding technique employed.

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Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
		Race: White: 86.9%; Black: 5.4%; Asian: 6.4%; Multiracial: 1.2% Other: Average years since first episode of seasonal AR: ~15.3 years.		combination and fexofenadine group (8.1%). Overall work productivity in the combination (8.5%) and the fexofenadine (8.0%) groups increased compared to the pseudoephedrine group (4.9%).	
Tanner, Reilly, Meltzer, et al., 1999	Design: Results of 2 RCTs pooled, both parallel-group, method of randomization not described Intervention(s): 1) Fexofenadine 60 mg bid (n = 389) 2) Placebo (n = 387) 3) (See Notes) Duration of study treatment: 2 weeks Use of meds with antihistamine or decongestant activity, corticosteroids, and immunotherapy in changing doses prohibited during trial No run-in/washout period described; patient using meds with antihistamine or decongestant activity within 48 hours, corticosteroids within 30 days, or immunotherapy in changing doses within 60 days excluded Dates: Spring 1994 Location: US	No. of subjects at start: 1957 randomized; 1948 had baseline and at least one other QOL assessment; 776 of these assigned to analyzed interventions (fexofenadine 60 mg bid and placebo) Dropouts/withdrawals: No. of subjects at end: 1948 Inclusion criteria: Diagnosis of moderate to severe seasonal allergic rhinitis based on a positive skin prick test within previous 15 months; ≥ 2 of the following symptoms rated as moderate or severe by the investigator: sneezing, rhinorrhea, itchy nose, palate and/or throat; or itchy, watery eyes; history of positive response to previous antihistamine use Exclusion criteria: Symptoms rated as very severe; pregnant or lactating women; significant hepatic, neurologic, endocrine, or major systemic disease Age (mean): Study 1, 32 (range, 11-65); Study 2, 33 (range, 12-68) Sex: Study 1, 58% femal; Study	1) Disease-specific quality of life: assessed using the Rhinoconjunctivities Quality of Life Questionnaire (RQLQ) at baseline and at 1 and 2 weeks 2) Performance impairment (at work and in classroom) due to allergy symptoms: assessed using the Allergy-Specific Work Productivity and Activity Impairment Questionnaire (WPAI-AS) at baseline and at 1 and 2 weeks 3) Generic quality of life: measured using 3 generic domains of the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36) (Role-Physical, General Health Perceptions, Change in Health)	1) Disease-specific quality of life: Average overall RQLQ score at baseline: 2.7; linear regression revealed significantly lower mean RQLQ scores at weeks 1 and 2 in the fexofenadine group compared to the placebo group. At week 1, patients randomized to fexofenadine had significant reductions in all RQLQ domains except sleep. By week 2, a significant reduction remained in the following domains only: activity, practical problems and nasal symptom scores. 2) Performance impairment due to allergy symptoms: Patients taking fexofenadine had significant reductions in the percentage of daily activity impairment at weeks 1 and 2. By week 2, patients taking fexofenadine had greater reductions in the percentage of overall work impairment. At baseline, only approximately 3% of usual work time was missed due to allergy symptoms. There was not a significant difference in the percent of usual work time missed between treatment groups at Week 1 or Week 2. Reductions in classroom time missed, classroom impairment or overall impairment in the classroom were significantly lower in the fexofenadine group at Week 1, but there was no difference at Week 2.	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: Yes Level of evidence: 4 Notes: Unspecified range of fexofenadine doses tested in original trials; present analysis considers 60-mg bid dose vs. placebo. No separate publications referenced for 2 RCTs here pooled.

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Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Setting: 32 centers throughout the US Type(s) of providers: NR	2, 55% female Race: Study 1, 85% Caucasian, 15% Other; Study 2, 80% Caucasian, 20% Other Average number of years of seasonal allergic rhinitis: Study 1, 16; Study 2, 17		3) Generic quality of life: No significant differences on the generic QOL measures were detected between treatment groups at any time point.	
Trotter, 2000	Design: Retrospective analysis of prescription claims Intervention(s): NA Duration of study treatment: NA Dates: April 1997 - April 1998 Location: US Setting: Outpatient Type(s) of providers: NR	No. of subjects at start: Prescription records from > 60 million people Dropouts/withdrawals: NA No. of subjects at end: 121,524 patients met inclusion criteria Inclusion criteria: Claim for initial prescription for = 1 of the following medications: azelastine, fexofenadine, loratadine, fluticasone, beclomethasone, or cetirizine. Initiating therapy was defined as the absence of a prior prescription claim for the AR medications or other medications, including antihistamines, nasal steroids, and medications for cough/cold. Patients had to be eligible for prescription plan benefits for the full study year. Exclusion criteria: NR Age: NR Sex: NR Race: NR	1) Average number of prescriptions received annually 2) Total prescription costs for AR drugs for patients initiating therapy with various AR medications 3) Percentage of patients receiving monotherapy with each medication	1) Average number of prescriptions received annually: Azelastine 2.2 Beclomethasone 2.4 Cetirizine 2.5 Fluticasone 2.6 Loratadine NR Fexofenadine 2.7 2) Total prescription costs for AR drugs for patients initiating therapy with various AR medications: Azelastine $111 Beclomethasone $118-$129 Cetirizine $134 Fluticasone $137 Loratadine $171 Fexofenadine $222 3) Percentage of patients receiving monotherapy with each medication: Azelastine 46.6% Beclomethasone 43.3% Cetirizine 46.2% Fluticasone 38.1% Loratadine 40.3% Fexofenadine 38.9%	Quality Scoring: Population similar: Not adequately described Intervention(s) described: No Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: No Outcome measures valid: No Level of evidence: 2b Notes: The study aim was to estimate the total cost of treatment for patients initiating treatment with selected medications. Assumption used in cost estimation: Unit size (e.g., no of tablets, inhalations) of each prescription was combined with average wholesale price to estimate medication costs. It is not clear whether 12 months of data were available beyond the date on which the initial AR medication was filled because the claims used in the analysis covered only a 13-month period. Therefore, patients who filled their first AR

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Evidence Table 1: Costs and Work Performance (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
					medication 6 months into the study period may have had data available for only 7 months, not 1 year.
Yawn, Yunginger, Wollan, et al., 1999	Design: Analysis of population-based registry of patients with asthma The study was designed to estimate the prevalence and incremental medical care charges (not including medications) of AR among patients with asthma. Intervention(s): NA Duration of study treatment: NA Dates: Charge data, 1987-1996 Location: Olmstead County, Minnesota Setting: Community Type(s) of providers: NA	No. of subjects at start: Random sample of 1245 patients with asthma Dropouts/withdrawals: Patients > 65 years were excluded from analysis No. of subjects at end: Analysis of charge data was based on 1065 patients; analysis of clinical data was based on 1245 patients Inclusion criteria: Diagnosed with "definite asthma" based on patient history or clinical findings Exclusion criteria: Bullous emphysema or pulmonary fibroses on chest radiograph; PiZZ α_1-antitrypsin; cystic fibrosis; other major chest disease Age: Mean, 31 (in 1987); median, 24 Sex: 53% male Race: NR	1) Proportion of asthma patients diagnosed with AR 2) Tri-mean (dollars/year) for patients with asthma only (total medical care charges not including medications) 3) Tri-mean (dollars/year) for patients with asthma and AR (total medical care charges not including medications) 4) Tri-mean (dollars/year) for patients with asthma only (total medical care charges not including medications), stratified by gender 5) Tri-mean (dollars/year) for patients with asthma and AR (total medical care charges not including medications), stratified by gender	1) 52.4% with concomitant AR 2) $249.89 ($1987) 3) $335.82 ($1987) 4) $160.26 for men ($1987) $392.18 for women ($1987) 5) $226.93 for men ($1987) $543.96 for women ($1987)	Quality Scoring: Population similar: Yes Intervention(s) described: ?? Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: No Outcome measures valid: No Level of evidence: 1b Notes: Annual medical charges were computed for each patient and adjusted to 1987 dollars using the Medical Consumer Price Index. Charges did not include charges for medication. The 'tri-mean' is computed as the mean of the 1st quartile (Q_1), 2 times the median (Q_2), and the 3rd quartile (Q_3): (tri-mean = $(Q_1+2Q_2+Q_3)/4$).

[†] Quality scoring criteria were as follows:
Population similar: Was the study population described and reasonably similar to an adult working US population? (Yes [described and similar], No [described, but not similar], Not adequately described)
Intervention(s) described: Were the intervention protocols referenced or described in sufficient detail to replicate? (Yes, No)
Comorbidities described: Was the presence of comorbid asthma (or other upper respiratory conditions) described in the study population? (Yes, No)
Diagnosis by MD: Was the diagnosis of allergic rhinitis based on physician diagnosis? (Yes, No, Not applicable [asthma patients only])
Objectively confirmed: If physician-diagnosed, was the diagnosis supported by objective evidence of allergy (e.g., skin prick or serum IgE antibody testing)? (Yes, No, Not applicable)

Outcome measures valid: Were the main outcomes of interest to us measured in a way that has been demonstrated empirically to be valid and reliable (e.g., using a standardized scale such the RQLQ or SF-36)? (Yes, No, Not adequately described)
Level of evidence: Based on Oxford Center for Evidence-Based Medicine Levels of Evidence (1a, 1b, 1c, 2a, 2b, 2c, 3a, 3b, 4, 5)

Evidence Table 2: Environmental Measures

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Antonicelli, Bilò, Pucci, et al., 1991	Design: RCT, crossover Interventions: 1) HEPA filter (Enviracaire®) + routine house cleaning. HEPA filter device placed in bedroom and used 24 hours/day for 8 weeks. 2) Routine house cleaning alone. Duration of study treatment: 8 weeks each treatment period; no washout between periods Dates: 10/1988-2/1989 Location: Italy Setting: NR Type(s) of providers: NR	No. of subjects at start: 9 Dropouts/withdrawals: 0 No. of subjects at end: 9 Inclusion criteria: Rhinitis and mild asthma; dust mite sensitivity by skin test Exclusion criteria: Long-term corticosteroid therapy, immunotherapy Age: 16 (range 10-28) Sex: 7 male; 3 female (misreported?) Race: NR Other:	1) Allergen levels: dust collected monthly from bedroom floor on day after usual room cleaning 2) Patient-assessed symptom severity: rhinitis, cough, and dyspnea graded daily on scale of 0 (asymptomatic) to 3 (maximum symptoms) 3) Use of symptomatic medication (terfenadine tablets, salbutamol inhalations): recorded daily in study diaries 4) Spirometry (morning and evening peak flow rates, FEV1, and bronchial reactivity [metacholine challenge test])	1) Allergen levels: Results reported graphically; no significant differences between groups in floor samples. 2) Patient-assessed symptom severity: Results reported graphically; significant period effect on rhinitis symptoms but no intervention effect. No significant effects on cough, wheezing. 3) Use of symptomatic medication: Results reported graphically; no significant effect. 4) Spirometry: Not abstracted	Quality Scoring: Population similar: No Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: No Blinding adequate: Not applicable Dropouts described: Yes Intention-to-treat: Yes Note: No assessment of carry-over effect, period effect, or treatment-by-period interaction. Statistical power not addressed.

Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Bahir, Goldberg, Mekori, et al., 1997	Design: RCT, parallel-group Interventions: 1) Acaricide (Acardust® = esdepallethin 0.9% and piperonyl butoxide 7.2%) + continuous avoidance measures (n = 13). Acaricide applied twice to mattress and floors (at start of study and at 3 months); avoidance measures described below. 2) Placebo acaricide (applied to mattress and floor at start of study and at 3 months) + continuous avoidance measures (described below) (n = 17) 3) Continuous avoidance measures only (described below) (n = 16) Avoidance measures (all 3 groups): Start of trial: Change bed-clothes, mattresses, rugs, curtains, upholstered furniture, toys, etc. Every object prone to accumulate dust to be removed. Pillows or blankets made of goose, feather, or wool forbidden. Synthetic pillows and blankets only. Daily: wash floors and dust furniture with damp cloth; shake bedclothes outside bedroom and leave on window sill Weekly: vacuum mattresses on both sides; thoroughly clean shelves, pictures,	No. of subjects at start: 62 Dropouts/withdrawals: 16 No. of subjects at end: 46 Inclusion criteria: Mild to moderate asthma by ATS criteria; duration ≥ 1 year; reversible airway disease document by FEV1 or PEF Exclusion criteria: Respiratory tract infection, steroid use, or sodium cromoglycate within past month; immunotherapy or hospitalization for asthma in past 6 months Age: Range, 6-16.5 Sex: NR Race: NR Other:	1) Allergen levels: dust collected by vacuum and analyzed by investigators; allergenicity of dust graded on scale of 0 (none) to 4 (strong) 2) Spirometry (FEV1, peak flow rates) 3) Patient-assessed symptom severity: quality of sleep, dyspnea, wheezing, cough, sputum, rhinitis, and sneezing graded daily on scale of 0-12 4) Use of $ß_2$-agonists and concurrent medication (topical steroids, cromoglycate): recorded by patients daily 5) Parents' global assessment of severity of asthma at end of study compared to beginning (same, better, worse)	1) Allergen levels: Baseline and f/u; p = ns Gp1: 3.6 ± 0.7; 3.3 ± 0.9 Gp2: 3.3 ± 0.6; 2.9 ± 0.8 Gp3: 3.5 ± 0.6; 2.7 ± 0.8 2) Spirometry: Not abstracted 3) Patient-assessed symptom severity: Reported graphically; p = ns 4) Use of $ß_2$-agonists and concurrent medication: Reported graphically; p = ns 5) Parents' global assessment of severity of asthma at end of study compared to beginning; p = ns Gp 1: 7 better; 6 same; 0 worse Gp 2: 9 better; 8 same; 0 worse Gp 3: 6 better; 9 same; 1 worse	Quality Scoring: Population similar: No Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Not applicable Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Note: Power: 80% power to detect a 0.75 difference in house dust mite antigen.

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Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	furniture, walls, drawers, and cupboards; change bed sheets and wash them in washing machine at 60° C or hotter Monthly: Wash blankets and pillows at 60° C or hotter Duration of study treatment: 6 months Trial preceded by 2-week run-in period Dates: NR Location: Israel Setting: Pediatric Health Centers Type(s) of providers: NR				
Burr, Dean, Merrett, et al., 1980	Design: RCT, parallel-group Interventions: 1) Avoidance measures (n = 26), as follows: mattress vacuumed at start of trial and weekly thereafter; blankets and sheets laundered at start, and blankets beaten in open air at least once every 2 weeks; sheets, pillow -cases, and other washable bedding laundered weekly; feather pillows replaced with synthetic pillows or enclosed in impervious cover; all pillows beaten weekly in open air; quilts and eiderdowns removed unless < 6 months old and washable; soft toys removed or washed, brushed,	No. of subjects at start: 55 Dropouts/withdrawals: 2 No. of subjects at end: 53 Inclusion criteria: Asthma; positive skin test for dust mites Exclusion criteria: "Asthma seemed to be exacerbated by other allergens" Age: 9 (range, 4.5-14) Sex: 36 male; 17 female Race: NR Other:	1) Spirometry (morning and evening peak flow rates) 2) Mother and investigator global evaluation of efficacy: at end of trial (8 weeks), clinician assessed child's progress "in light of the mother's report of symptoms and the changes in physical signs and lung function;" child's condition graded as much better, better, same, worse, or much worse 3) Allergen levels: dust samples obtained from bedding of treated group at start of trial and from	1) Spirometry: Not abstracted 2) Mother and investigator global evaluation of efficacy: Intervention: 5/26 much better; 11/26 better Control: 6/27 much better; 9/27 better 3) Allergen levels: Only reported pre-post for intervention group. Between-group comparisons not made.	Quality Scoring: Population similar: No Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Not applicable Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: No Blinding adequate: Not applicable Dropouts described: Yes Intention-to-treat: No *(continued on next page)*

Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	or vacuumed every week; bedroom carpets vacuumed several times every week; upholstery vacuumed every 2 weeks. 2) Placebo avoidance measures (n = 27), as follows: importance of dust in living room emphasized; living room dusted daily using special duster, and other rooms similarly dusted once per week; spray-on polish recommended before each dusting; upholstered chairs in living room vacuumed or brushed at least twice a week; carpet in living room vacuumed daily. Duration of study treatment: 8 weeks Trial preceded by 1-week run-in period, during which baseline data collected Dates: NR Location: UK Setting: Pediatric outpatient clinic Type(s) of providers: Pediatricians		both groups at end of trial; collected using special suction device		Note: Power not addressed

Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Burr, Neale, Dean, et al., 1980	Design: RCT, crossover Interventions: 1) Avoidance measures, as follows: each child issued with new sleeping bag, pillow, and blankets (if required); mattress completely enclosed in impervious plastic bag; all other bedding either enclosed in impervious bags or removed; carpets in bedroom vacuumed several times every week. 2) No special avoidance measures. Duration of study treatment: 1 month each treatment period; no washout between periods Dates: NR Location: UK Setting: Pediatric outpatient clinic Type(s) of providers: Pediatricians	No. of subjects at start: 21 Dropouts/withdrawals: 0 No. of subjects at end: 21 Inclusion criteria: Asthma; positive skin test for dust mites Exclusion criteria: "Asthma seemed to be exacerbated by other allergens" Age: NR, but is a subset of Burr, Dean, Merrett, et al., 1980, above Sex: NR, but is a subset of Burr, Dean, Merrett, et al., 1980, above Race: NR Other:	1) Spirometry (morning and evening peak flow rates) 2) Mother's global evaluation of efficacy: at end of treatment period, mother asked whether child's asthma better or worse 3) Allergen levels: mites contained in bedding counted at end of each treatment period	1) Spirometry: Not abstracted 2) Mother's global evaluation of efficacy: Intervention period compared to control: 6 improved, 14 no change, 1 worse (no test for significance) 3) Allergen levels: Not meaningfully reported	Quality Scoring: Population similar: No Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Not applicable Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: No Blinding adequate: Not applicable Dropouts described: Yes Intention-to-treat: Can't determine Notes: All patients had participated in trial by Burr, Dean, Merrett, et al., 1980, described above. No assessment of carry-over effect, period effect, or treatment-by-period interaction. Power not addressed.

Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Carswell, Birmingham, Oliver, et al., 1996	Design: RCT, parallel-group Interventions: 1) Acaricide (Acarosan®) + avoidance measures (n = 35). At start of trial, Acarosan® powder (benzyl benzoate 5%) applied to bedroom carpet and Acarosan® foam (benzyl benzoate 1.6%) applied to mattresses, duvets, pillows, and any upholstered furniture. All items thoroughly vacuumed with Medivac® vacuum before application of acaricide, 24 hours later, and 4 weeks later. Allergen exclusion covers (Intervent®) fitted to mattresses, duvets, and pillows and left in place for 24 weeks. All bed linens to be washed at 60° C each week. Softy toys removed or washed at 60° C. 2) Placebo acaricide + placebo avoidance measures (n = 35). At start of trial, placebo powder (chalk dust) applied to bedroom carpet and water spray applied to mattresses, duvets, pillows, and any upholstered furniture. All items thoroughly vacuumed with Medivac® vacuum before application, 24 hours later, and 4 weeks later. Placebo covers (cotton) fitted to mattresses, duvets, and pillows and left in place for 24 weeks. All bed linens to be washed at 40° C each week. Softy toys removed or washed at 40° C.	No. of subjects at start: 70 randomized; 62 started treatment Dropouts/withdrawals: 19 No. of subjects at end: 51 (49 completers) Inclusion criteria: Asthma (wheezing, breathlessness); skin test positive for house-dust mite; high dust-mite antigen in mattress Exclusion criteria: Cat allergen sensitive and cat in house; no duvet or not sleeping in single bed Age: 9.8 (range, 7-10) Sex: 44 males; 26 females Race: NR Other:	1) Allergen levels: dust collected by vacuum and Petri dishes "from potentially mite allergen-rich sites" pretreatment and at 2, 6, 14 and 24 weeks 2) Spirometry (peak flow rates) 3) Bronchial histamine sensitivity 4) Patient-assessed symptom severity: presence/absence of asthma symptoms of wheeze, cough, activity impairment, and sleep disturbance recorded whenever peak flow rates measured (3 times per day during four different 2-week periods) 5) Use of symptomatic medication: recorded whenever peak flow rates measured (3 times per day during four different 2-week periods)	1) Allergen levels: Mattress: Median change, $p < 0.0001$ Intervention: 480 ng Control: 215 ng Carpets: reported graphically; no significant difference 2) Spirometry: Not abstracted 3) Bronchial histamine sensitivity: Not abstracted 4) Patient-assessed symptom severity: results reported graphically; total symptoms decreased significantly more in the intervention group (about 30% fewer patients with symptoms vs. no change in control, $p<0.05$). No significant difference in individual symptoms of daytime wheeze and cough. 5) Use of symptomatic medication: 50% of intervention patients took medication vs. 80% in control group, $p< 0.02$. (From graph: about a 30% difference in bronchodilator use and about 20% difference in inhaled steroid use.)	Quality Scoring: Population similar: No Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Not applicable Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Notes: 10 subjects excluded because of incomplete treatment or non-adherence. Power: a priori sample size calculation showing 50 completers needed. Looked at potential confounders and found no difference except fewer cats in placebo group.

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Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Duration of study treatment: 24 weeks Dates: NR Location: UK Setting: Schools Type(s) of providers: Family practitioners				
Chang, Becker, Ferguson, et al., 1996	Design: RCT, parallel-group Interventions: 1) Acaracide (Acarosan® = benzyl benzoate) + avoidance measures (n = 12). Acaracide applied once at start of study to carpet in bedroom, carpet in most commonly used room, and mattress; avoidance measures described below. 2) Avoidance measures only (described below) (n = 14) Avoidance measures (both groups): Vacuum home at least once per week, wash bedding in hot water (> 58° C), and encase mattresses and pillows with vinyl covers Duration of study treatment: 3 months Trial preceded by 1-month run-in period, during which allergen levels tested; patients completed diary cards for 1 month pre-trial	No. of subjects at start: 26 Dropouts/withdrawals: 0 No. of subjects at end: 26 Inclusion criteria: Asthma; dust-mite sensitivity by skin test; mite allergens > 1 µg/g of dust from mattress or bedroom floor Exclusion criteria: None specified Age: 11 children, 15 adults Sex: NR Race: NR Other:	1) Allergen levels (mattress and floor): dust collected by vacuum at baseline, 1 week, and 1 and 3 months 2) Patient-assessed symptom severity: cough, wheeze, and breathless-ness graded daily on score of 0 (no symptoms) to 3 (severe) 3) Spirometry (FEV1, morning peak expiratory flow rate, evening peak expiratory flow rate) 4) Methacholine inhalation test	1) Allergen levels (baseline; 3 months): Mattress: p = ns Gp 1: 2.17 ± 2.64; 0.06 ± 1.12 Gp 2: 1.68 ± 2.22; 0.28 ± 1.32 Floor: $p < 0.05$ Gp 1: 2.38 ± 2.24; 0.50 ± 1.71 Gp 2: 2.05 ± 2.05; 1.10 ± 2.17 2) Patient-assessed symptom severity (baseline; 1; 2; and 3 months): p = ns Gp 1: 1.5 ± 2.1; 1.5 ± 1.9; 1.6 ± 2.2; 1.1 ± 1.7 Gp 2: 0.6 ± 0.8; 1.2 ± 1.6; 0.7 ± 1.7; 0.4 ± 0.5 3) Spirometry: Not abstracted 4) Methacholine inhalation test: Not abstracted	Quality Scoring: Population similar: Yes Intervention(s) describe: Yes Comorbidities described: Yes Diagnosis by MD: Not applicable Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: No Blinding adequate: Not applicable Dropouts described: No Intention-to-treat: Can't determine Notes: Important baseline differences between groups in symptoms. Power: not addressed.

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Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Dates: 12/1993-4/1994 Location: Canada Setting: NR (subset of participants in another study) Type(s) of providers: NR				
Chen and Hsieh, 1996	Design: RCT, parallel-group Interventions: 1) Avoidance measures (n = 29). Patients provided with new Microstop®-treated mattresses, quilts, pillows, bed linens, and quilt covers. 2) Placebo avoidance measures (n = 29). Patients provided with new non-Microstop®-treated mattresses, quilts, pillows, bed linens, and quilt covers. 3) No avoidance measures (n = 15). Patients continue to use their regular bedding. Duration of study treatment: 12 months Trial preceded by run-in period of at least 1 month, during which baseline data collected Dates: 1/1994 - 4/1995 Location: Taiwan Setting: Allergy clinic at Women and Childrens Hospital	No. of subjects at start: 73 Dropouts/withdrawals: 29 No. of subjects at end: 44 Inclusion criteria: Asthma and positive to house dust-mite Exclusion criteria: Pets, immunotherapy, inhaled steroids Age: 8.23 ± 2.56 Sex: 55 male; 18 female Race: NR Other:	1) Allergen levels: dust samples collected by vacuum from mattress, quilt, and pillows at baseline and after 1, 2, 3, 6, 9, and 12 months 2) Patient-assessed symptom severity: asthma symptoms of sleep disturbance, chest tightness on awakening, daytime symptoms, and cough graded twice daily on scale of 0 (none) to 4 (severe [different definitions for various specific outcomes]) 3) Spirometry (morning and evening peak flow rates)	1) Allergen levels: (reported graphically) Mattress: Intervention showed significant decreases compared to baseline. Placebo groups did not show significant decreases. No between-group differences reported. Quilt: Intervention and placebo avoidance showed significant differences compared to baseline. No between-group differences reported. Pillow: Intervention showed lower mite count compared to placebo and control groups (p = not significant). 2) Patient-assessed symptom severity: (reported graphically). Intervention group showed significantly decreased symptoms compared to baseline for 10 of 12 months. No between-group comparisons reported. 3) Spirometry: Not abstracted	Quality Scoring: Population similar: No Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Not applicable Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Notes: Power: no discussion. High number of dropouts. No between-group comparisons.

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Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Type(s) of providers: NR				
Clooster-man, Hofland, Lukassen, et al., 1997	Design: RCT, parallel-group, randomization stratified by type of floor covering (textile vs. smooth) and initial FEV1 Interventions: 1) Acaracide (Acarosan® = benzyl benzoate) + avoidance measures (n = 16). Acaricide applied to bedroom and living room floors once at start of study; avoidance measures consisted of encasing mattresses, pillows, and duvets in covers impermeable to house dust mites and house dust mite allergens. 2) Placebo acaracide (water) + placebo avoidance measures (cotton covers permeable to house dust mites and house dust mite allergens (n = 13). Patients in both groups were instructed to vacuum bedroom and living room floors and wash bedding once per week. Duration of study treatment: 6 weeks Trial preceded by 2-week baseline period Dates: 1993 Location: The Netherlands Setting: Recruited from	No. of subjects at start: 29 Dropouts/withdrawals: 11 (5 treatment, 6 placebo) No. of subjects at end: 18 (11 treatment, 7 placebo) Inclusion criteria: Positive skin test for house dust mite; skin test reaction to dogs, cats, and *Spergillus fumigatus* < reaction to house dust mite; (all patients had mild symptoms of asthma but this was not an inclusion criteria) Exclusion criteria: Confirmed diagnosis of asthma; history of receiving anti-inflammatory medication; peak flow variability > 15% or FEV1 increase by > 15% after salbutamol Age: Gp 1: 32.4 ± 11.5; Gp 2: 23.5 ± 6.3 (p = 0.04) Sex: 17/29 women Race: NR Other:	1) Spirometry (peak flow rates, peak flow variability) 2) Patient-assessed symptom severity: cough, breathlessness, wheezing, expectoration, tiredness, and disturbed sleep (due to cough, wheeze, or breathlessness) graded on scale of 0 (no symptoms) to 10 (severe symptoms)	1) Spirometry: Not abstracted 2) Patient-assessed symptom severity: Selected symptoms (sleep, breathlessness, wheeze, overall score) reported graphically; no data given for other symptoms; only within-group p-values given. Between-group differences given for only one symptom (wheeze) at one time point, week 5 (Gp 1 change from baseline of -0.31 ± 0.1 vs Gp 2 +0.53 ± 0.24; p = "significant").	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: No Objectively confirmed: Yes Outcome measures valid: No (?) Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: No Blinding adequate: Not applicable Dropouts described: Yes Intention-to-treat: No Notes: Stratification and randomization resulted in unbalanced distribution of patients to treatment groups. Appear to be important baseline differences in symptoms and demos. Patients were minimally symptomatic. Sample size based on peak flow; 80% power to detect a 15 l/min difference; no post-hoc power calculation on symptoms.

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Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	patients referred for skin testing Type(s) of providers: General practitioners				
Clooster-man, Schermer, Bijl-Hofland, et al., 1999	Design: RCT, parallel-group Interventions: 1) Acaracide (Acarosan® = benzyl benzoate) + avoidance measures (n = 76). Acaricide applied to carpets and rugs in bedroom and living room once at start of study; avoidance measures consisted of encasing mattresses, pillows, and duvets in covers impermeable to house dust mites and house dust mite allergens. 2) Placebo acaracide (water) + placebo avoidance measures (cotton covers permeable to house dust mites and house dust mite allergens (n = 81). Duration of study treatment: 20 weeks Trial preceded by 4-week baseline period During trial, patients used only bronchodilators, and in a standardized way; exacerbations treated with prednisone and, if necessary, antibiotics in a standardized way Dates: 10/1993-9/1996	No. of subjects at start: 258 eligible; 204 randomized Dropouts/withdrawals: 58 No. of subjects at end: 146; 157 ITT Inclusion criteria: Asthma; positive skin test for house dust mite; FEV1 > 50% and > 65% after salbutamol; PC20 = 8 mg/ml or reversibility of obstruction after salbutamol Exclusion criteria: Oral steroids; inhaled corticosteroids dependency; skin test reactivity to pets > reaction to dust mite if pets in house Age: Gp 1: 32.7 ± 11; Gp 2: 33.9 ± 11.1 Sex: 82 men; 75 women Race: NR Other:	1) Allergen levels: dust collected by vacuum from mattress and floors at baseline and at 8, 14, and 20 weeks 2) Spirometry (peak flow rates, peak flow variability, FEV1, bronchial hyper-responsiveness) 3) Patient-assessed symptom severity: cough, breathlessness, wheezing, expectoration, tiredness, and disturbed sleep (due to cough, wheeze, or breathlessness) graded on scale of 0 (no symptoms) to 10 (severe symptoms)	1) Allergen levels: Reported graphically (Der P 1): Mattress: ng/g, p = 0.0001 Gp 1: 860 (95% CI, 537-1376), declined by 90.6% Gp 2: 931 (95% CI, 602-1439), declined by 31.5% Bedroom floor (p = 0.883) and living room floor (p = 0.9422) – only graphical 2) Spirometry: Not abstracted 3) Patient-assessed symptom severity: Reported graphically only; no significant differences, p = 0.5474	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Not applicable Objectively confirmed: Not applicable Outcome measures valid: No (?) Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: No Blinding adequate: Not applicable Dropouts described: Yes Intention-to-treat: Yes Note: Power not addressed

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Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Location: The Netherlands Setting: Allergy laboratory records with GP and Pulmonologists Type(s) of providers: General practitioners and pulmonologists				
Dietemann, Bessot, Hoyet, et al., 1993	Design: RCT, parallel-group Interventions: 1) Acaracide (Acarosan® = benzyl benzoate) (n = 11). Applied to all mattresses and upholsteries in home and to all carpets and rugs at the start of the trial and once again after an interval of at least 6 months. 2) Placebo acaracide, applied as above (n = 12). Duration of study treatment: 1 year Dates: NR Location: France Setting: Chest clinic Type(s) of providers: Pulmonologists?	No. of subjects at start: 26 Dropouts/withdrawals: 3 No. of subjects at end: 23 Inclusion criteria: Definite history of asthma; positive skin test to *Dermatophagoides pteronssinus*; RAST for Dp > 3 using pharmacia screening system; Acarex value ≥ ++ Exclusion criteria: None specified Age: 35 ± 14.9 Sex: 12 men; 12 women Race: NR Other:	1) Investigator-assessed symptom severity ("clinical scores"): graded every 3 months during clinic visits on scale of 0 = no asthmatic episodes, 1 = at least one asthmatic episode per month, 2 = at least one asthmatic episode per week, 3 = at least one asthmatic episode per day,] 2) Patient-assessed symptom severity: graded every 3 months during clinic visits on VAS scale of 0 (severe dyspnea) to 10 (no dyspnea) 3) Medication use: graded every 3 months during clinic visits on following scale: 0 = no medication; 1 = no more than 4 inhalations per day of ß2-agonists or disodium cromoglycate intake or both; 2 = continuous bronchodilator treatment with ß2-agonists, with or without long-acting theophylline (twice per day), and beclomethasone	1) Investigator-assessed symptom severity ("clinical scores"): Baseline and % change, p = ns Gp 1: 2.54 (95% CI, ± 1.5); -45% Gp 2: 2.0 (95% CI, ± 0.4); -41% 2) Patient-assessed symptom severity: Baseline and % change, p = ns Gp 1: 5.7 (95% CI, ± 0.84); +36% Gp 2: 5.0 (95% CI, ± 0.78); +46.6% 3) Medication use: Baseline and % change, p = ns Gp 1: 2.27 (95% CI, ± 0.66); -12% Gp 2: 1.92 (95% CI, ± 0.50); -19.8% 4) Spirometry: Not abstracted 5) Allergen levels: Baseline µg/g and % change of Der p I + Der f I Mattress: p = ns Gp 1: 43.53 (95% CI, ± 24.6); -19.7% Gp 2: 84.66 (95% CI, ± 52.5); -17% Upholstery elements: p = ns Gp 1: 30.4 (95% CI, ± 31.5); -67% Gp 2: 40.0 (95% CI, ± 18.4); - 61% Carpets: p = ns Gp 1: 4.95 (95% CI, ± 3.23); -74% Gp 2: 13.0 (95% CI, ± 6.6); -27%	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Not applicable Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not applicable Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Notes: No diary recording of symptoms. Symptom outcomes based on data collected at 3-monthly clinic visits. Power not addressed.

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Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
			dipropionate at dose ≤ 1000 µg/day; 3 = ß2-agonist inhalation with or without long-acting theophylline, and beclomethasone dipropionate at dose ≥ 1000 µg/day 4) Spirometry (FEV1, FVC, FEF 25-75, peak flow rates) 5) Allergen levels: dust collected by vacuum from mattresses, carpets, and upholstery at baseline and 12 months		
Dorward, Colloff, MacKay, et al., 1988	Design: RCT, parallel-group Interventions: 1) Avoidance measures (n = 9). Mattresses and bedroom carpets soaked with liquid nitrogen at start of trial. Entire surface of bed vacuumed weekly. Blankets, pillows, and duvets cleaned at the start of trial; sheets and pillow cases washed weekly; blankets and upper sheets or duvets folded back each morning to allow mattress to air. Hard surfaces damp-dusted weekly. Plants, soft toys, cushions, and upholstered furniture removed from bedroom. 2) No avoidance measures (n = 9). Patients instructed to continue with their normal cleaning activities.	No. of subjects at start: 21 Dropouts/withdrawals: 3 No. of subjects at end: 18 Inclusion criteria: Stable asthma; positive skin test to house dust-mite; FEV1 >60% predicted Exclusion criteria: Requirement for oral steroids, theophylline, sodium cromoglycate or dog or cat at home Age: 25.6 (range 13-48) intervention; 24.8 control (range 14-53) Sex: 8 males; 10 females Race: NR Other:	1) Patient-assessed symptom severity: presence/absence and duration of wheezing recorded daily; overall severity of asthma graded daily on 10-cm linear analog scale 2) Use of salbutamol inhaler: number of puffs used recorded daily 3) Spirometry (morning and evening peak flow rates) 4) Bronchial reactivity (PC_{20} histamine values) 5) Allergen levels: dust samples collected from mattresses and carpets at baseline and at 4 and 8 weeks	1) Patient-assessed symptom severity: (reported graphically as mean % change) Wheezing hours decreased significantly in intervention group (about -50% vs. + 10%, $p < 0.05$); wheezing days did not differ (about -20% vs. 0%); asthma severity decreased but not significantly different (about -45% vs. +10%). 2) Use of salbutamol inhaler: No significant difference (about -10% vs. +10%) 3) Spirometry: Not abstracted 4) Bronchial reactivity: Not abstracted 5) Allergen levels: (Mattress, # intact mites/0.25 m2/min) Intervention: 6.56 ± 6.25 baseline; 0.33 ± 1.33 8 weeks, $p< 0.01$ for within-group change Control: 7.0 ± 6.98 baseline; 4.22 ±	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Not applicable Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: No Blinding adequate: Not applicable Dropouts described: Yes Intention-to-treat: No Note: Power: no discussion *(continued on next page)*

Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Duration of study treatment: 8 weeks Trial preceded by 2- to 3-week run-in period Dates: 1/1984 – 6/1984 Location: Scotland Setting: Hospital respiratory clinic Type(s) of providers: NR		6) IgE and allergen-specific IgE antibody levels	4.94 8 weeks , p > 0.05 for within-group change No between-group comparison made 6) IgE and allergen-specific IgE antibody levels: Not abstracted	
Frederick, Warner, Jessop, et al., 1997	Design: RCT, crossover Interventions: 1) Avoidance measures, consisting of encasing mattresses, pillows, and duvets in covers impermeable to house dust mites and house dust mite allergens (Intervent®). Patients instructed to wipe down covers with a damp cloth once per week. 2) Placebo avoidance measures (polycotton covers, no weekly wipe-down). Duration of study treatment: 3 months each treatment period, with a 1-month washout between periods Trial preceded by 2-week run-in period Dates: 11/1992 – 11/993 Location: UK	No. of subjects at start: 31 Dropouts/withdrawals: 0 No. of subjects at end: 31 Inclusion criteria: Documented perennial asthma; positive skin test or RAST ≥ grade 3 to house dust mite Exclusion criteria: None specified Age: 9 (range 5-15) Sex: 20 male; 11 female Race: NR Other:	1) Allergen levels: dust collected from mattress, duvet, and pillow at baseline and end of each period 2) Patient-assessed symptom severity: asthma last night, daytime wheeze, and exercise tolerance measured (twice?) daily on scale of 0-3 (not described) 3) Spirometry (morning and evening peak flow rates, FEV1, PC_{20}) 4) Use of bronchodilator (ß2-agonist): recorded daily by patients in diary 5) Blood assays (ECP, EPX, EPO, sIL-2R)	1) Allergen levels: Median ng/g (with range), baseline and 3 months: Mattress: (active and placebo crossover), p = 0.0012 Gp 1 (active): 12,403 (616-24,138); 1,246 (0-66,667) Gp 2 (active): 8,500 (354-50,000); 1,086 (0-6,452) Gp 1 (placebo): 7,275 (100-30,519); 2,737 9(53-97,143) Gp 2 (placebo): 14,759 (0-82,500); 13,500 (900-63,830) Duvet (p < 0.000) and pillow (p < 0.0001) antigen levels also decreased significantly 2) Patient-assessed symptom severity: Baseline; month 3; median and (range) Asthma: p = ns Active: 0.2 (0-1.9); 0.1 (0-0.8) Placebo: 0.09 (0-2.5); 0.09 (0-1.7) Asthma, wheeze, and exercise tolerance did not differ significantly between groups 3) Spirometry: Not abstracted 4) Use of bronchodilator (ß2-agonist):	Quality Scoring: Population similar: No Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Not applicable Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: No Double-blind: No Blinding adequate: Not applicable Dropouts described: Yes Intention-to-treat: Yes Notes: Intervention bias (i.e., no weekly wipe-down in placebo group); could lead to unblinding. No assessment of period effect or treatment-by-period interaction.

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Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Setting: General Pediatric Hospital Type(s) of providers: ?			Baseline; 3 months, median µg (range) Active: 120 (0-986); 80 (0-312) Placebo: 60 (0-542); 40 (0-372) 5) Blood assays: Not abstracted	Power not addressed.
Geller-Bernstein, Pibourdin, Dornelas, et al., 1995	Design: RCT, parallel-group Interventions: 1) Acaricide (Acardust® = esdepallethin 0.9% and piperonyl butoxide 7.2%), applied at baseline and 3 months to mattress (and more widely throughout bedroom?) (n = 17) 2) Placebo acaricide, applied as above (n = 15) Subjects in both groups cleaned their bedrooms regularly using the same procedures (change of bedsheet every week, change of blanket every month, daily dust removal with damp cloth, and weekly vacuuming of carpets and furniture). Duration of study treatment: 6 months Trial preceded by 1-month run-in period Dates: NR Location: Israel Setting: Pediatric Allergy Clinic Type(s) of providers: ?	No. of subjects at start: 35 Dropouts/withdrawals: 3 No. of subjects at end: 32 Inclusion criteria: Age 4-12 with asthma or rhinitis severe enough to require continuous medications for the 3 months prior to entry; in asthmatics, a peak flow or FEV1 ≥ 15% below predicted; positive skin test to house dust mite; Acarex test ≥ 2+ in child's mattress dust Exclusion criteria: Allergy due to non-house dust mite allergens; use of an acaricide w/in 3 months of study entry Age: Gp 1: 9.7 ± 2.6; Gp 2: 8.1 ± 2.6 Sex: 23 male; 12 female Race: NR Other:	1) Patient-assessed symptom severity (diary data): asthma severity, nasal secretion, nasal obstruction, sneezing, ocular pruritus, and lacrimation graded twice weekly (so text; abstract has "daily") on scale of 0 (no symptoms) to 3 (severe symptoms) 2) Patient-assessed symptom severity (clinic visits): disruption of daily activities, wheezing frequency, severity of rhinitis symptoms, frequency of rhinitis crisis graded at monthly clinic visits on scale of 0 (no symptoms/less than once per month) to 3 (severe symptoms/permanently) 3) Investigator-assessed symptom severity (monthly clinic visits) 4) Use of concurrent medication: recorded by patients in diary (frequency unclear) 5) Adverse events: patients instructed to record "any unusual events, symptoms or other	Outcomes reported monthly; data reported below are for baseline and 6 months. 1) Patient-assessed symptom severity (diary data): means (no variance given), p = 0.001? Gp 1: 34.83; 5.47 Gp 2: 29.88; 6.60 2) Patient-assessed symptom severity (clinic visits): means (no variance given) Daily Activity Disruption (p = 0.02) Gp 1: 1.17; 0.13 Gp 2: 0.94; 0.27 Wheezing frequency (p = 0.10) Gp 1: 1.94; 0.67 Gp 2: 2.06; 0.73 Nasal secretion – graphical results only, p = 0.01 favoring Acardust® Other rhinitis symptoms – graphical results only, p = 0.02 favoring Acardust® 3) Investigator-assessed symptom severity (monthly clinic visits): Not abstracted 4) Use of concurrent medication: Graphical results only, p = 0.01 favoring Acardust® 5) Adverse events: None	Quality Scoring: Population similar: No Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Notes: Poorly reported trial. Often difficult to know whether outcomes reported are based on patient-diary or clinic-visit data. 32 patients had rhinitis; 31 had asthma. Power not addressed.

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Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
			illnesses" in their diaries 6) Patient/parent monthly global evaluation of asthma severity: graded at monthly clinic visits using VAS from 0-100 mm 7) Investigator monthly global evaluation of asthma severity 8) Investigator final global evaluation of improvement (6 months) 9) Spirometry (morning and evening peak flow, PFF, FEV1) 10) Blood tests (total and dust mite farinae-specific IgE levels) 11) Allergen levels: dust collected by vacuum from mattress at baseline and 2, 3, 4, and 6 months	6) Patient/parent monthly global evaluation of asthma severity: Graphical results only, p = 0.001 favoring Acardust® 7) Investigator monthly global evaluation of asthma severity: Not abstracted 8) Investigator final global evaluation of improvement (6 months): Not abstracted 9) Spirometry: Not abstracted 10) Blood tests: Not abstracted 11) Allergen levels: p = 0.02 Gp 1: 10.05 ± 13.74; 4.15 ± 6.51 Gp 2: 6.01 ± 8.01; 3.01 ± 4.33	

Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Gillies, Littlewood, and Sarsfield, 1987	Design: RCT, parallel-group Interventions: 1) Avoidance measures (n = 13). Mattress completely enclosed by special cover; pillows enclosed in plastic covers; soft toys and pets excluded from bedroom; synthetic bedding used; damp-dusting performed weekly; bed, mattress, and bed base vacuumed thoroughly (interval not specified). 2) No avoidance measures (n = 12). Patients instructed to continue their normal domestic cleaning practice. Duration of study treatment: 6 weeks (controlled portion of trial) Dates: 11/1984?-4/1985? Location: UK Setting: NR Type(s) of providers: NR	No. of subjects at start: 26 Dropouts/withdrawals: 1 No. of subjects at end: 25 Inclusion criteria: Children; mild to moderate asthma; positive skin test to dust mite allergen Exclusion criteria: Requiring regular asthma medication Age: 9.7 (range 6-16) Sex: NR Race: NR Other:	1) Allergen levels: dust collected from mattresses using a standard dusting technique at baseline and 6 weeks 2) Total and allergen-specific IgE antibody levels 3) Bronchial reactivity (PC_{20} histamine values) 4) Patient-assessed symptom severity: day- and nighttime cough and wheeze and daytime activity recorded daily 5) Use of bronchodilators: recorded daily 6) Spirometry (morning and evening peak flow rates)	1) Allergen levels: Mattress (dust mite counts mites/m2, baseline - 6 weeks) Intervention: 40.0 ± 64.24; 1.23 ± 1.74 Control: 21.75 ± 20.3; 10.33 ± 16.22 (no between-group statistical comparison) 2) Total IgE antibody levels: Not abstracted 3) Bronchial reactivity: Not abstracted 4) Patient-assessed symptom severity: reported in text as "no significant changes in …[symptom scores, medication requirements]…" 5) Use of bronchodilators: reported in text as "no significant changes in …[symptom scores, medication requirements]…" 6) Spirometry: Not abstracted	Quality Scoring: Population similar: No Intervention(s) described: No Comorbidities described: Yes Diagnosis by MD: Not applicable Objectively confirmed: Not applicable Outcome measures valid: ?? Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: ?? Blinding adequate: ?? Dropouts described: ?? Intention-to-treat: ?? Notes: All patients employed avoidance measures during weeks 7-12. Power: no discussion Poorly reported trial. No data given for symptoms, no between-group comparisons.

Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Huss, Huss, Squire, et al., 1994	Design: RCT, parallel-group Interventions: 1) Acaracide (Acarosan® = benzyl benzoate) + avoidance measures (n = 6). Acaracide applied to bedroom and living room carpets at baseline and 6 months; avoidance measures described below. 2) Placebo acaracide (applied as above) + avoidance measures (described below) (n = 6) Avoidance measures: patients in both groups had already (at start of trial) implemented avoidance measures such as encasing mattresses, box springs, and pillows in allergen-impermeable covers and washing bed linens in hot water. During trial, were instructed to vacuum carpets weekly. Duration of study treatment: 1 year Dates: 10/1990-11/1991 Location: US Setting: NR Type(s) of providers: NR	No. of subjects at start: 12 Dropouts/withdrawals: 0 No. of subjects at end: 12 Inclusion criteria: Symptomatic asthma using standardized criteria; positive skin test to house dust mite; high levels of house dust mite in carpets Exclusion criteria: "Significant" severity to dog, cat, feathers, or other potentially relevant indoor allergens Age: 44; (range 25-65) Sex: 4 male; 8 female Race: 10 white; 1 black; 1 other Other:	1) Allergen levels: collected from bedroom and living room carpets by vacuum at baseline and at 3, 6, 9, and 12 months 2) Spirometry (morning and evening peak flow, FEV1, FEF_{25-75}, peak flow variability) 3) Experience using acaracide/difficulty of use/time involved: assessed by interview at end of study (12 months) 4) Patient global assessment of efficacy: graded once, at 12 months; patient asked whether he/she felt treatment had improved his/her asthma (yes/no/unsure) 5) Patient global assessment of adverse events: graded once, at 12 months; patient asked whether he/she had felt any adverse effects as result of treatment (yes/no) 6) Medication use: Not clear how assessed	1) Allergen levels: Results shown graphically; no within-group or between-group differences. 2) Spirometry: Not abstracted 3) Experience using acaracide/difficulty of use/time involved: Not abstracted 4) Patient global assessment of efficacy: Not reported by group 5) Patient global assessment of adverse events: No adverse events reported. 6) Medication use: No data reported; statement of "not significantly different"	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Not applicable Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: No Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Yes Notes: Small sample size (6 patients per group). Very little patient-assessed symptom data reported. No daily recording of symptoms. Power not addressed.

Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Kniest, Young, Van Praag, et al., 1991	Design: Controlled trial (patients assigned "arbitrarily" – doesn't say randomly), parallel-group, matched-pairs design (matched by age, IgE and skin testing to house dust mite, symptoms, guanine exposure and dwelling) Interventions: 1) Acaracide (Acarosan® = benzyl benzoate) + avoidance measures (n = 10). Acaracide applied to all textile objects in home (carpets, padded furniture, upholstery, mattresses, stuffed animals) at baseline and 6 months; avoidance measures described below. 2) Placebo acaracide (applied as above) + avoidance measures (described below) (n = 10) Avoidance measures (both groups): Described as "normal but intensive household cleaning" Duration of study treatment: 1 year Dates: 6/1988 – 6/1989 Location: The Netherlands Setting: Allergy Department Type(s) of providers: NR	No. of subjects at start: 20 Dropouts/withdrawals: 0 No. of subjects at end: 20 Inclusion criteria: House dust mite induced perennial rhinitis more evident than other allergic symptoms Exclusion criteria: None specified Age: 20; (range 12-35) Sex: NR Race: NR Other:	1) Patient-assessed symptom severity: itching of eye and nose, sneezing, nose secretion, nose bleeding, eye irritation, and nasal blockage graded daily on scale of 0 (no symptoms) to 3 (symptoms present for more than 2 hours) 2) Medication use: use of steroid nasal spray, cromoglycate nasal spray, and terfenadine recorded daily 3) Physician global evaluation of efficacy 4) Blood tests (IgE, eosinophils) 5) Allergen levels: dust collected from all textile objects in home by vacuum at baseline and at 3, 6, and 12 months	1) Patient-assessed symptom severity: Gp 1 improved more than Gp 2 (p = 0.025, matched-pairs analysis, subject level scores given) 2) Medication use: No between-group differences in medication index (no p-value or means reported) 3) Physician global evaluation of efficacy: Not abstracted 4) Blood tests (IgE, eosinophils): Not abstracted 5) Allergen levels: Graphical results given; guanine exposure dropped more for group 1 (70% of baseline) than group 2 (97% of baseline; p = 0.45, matched-pairs analysis)	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 3b Randomized: No Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Yes Notes: Uncertain if truly randomized. Concealment: NR Power not addressed.

Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Kooistra, Pasch, and Reed, 1978	Design: RCT, crossover; groups matched for skin test sensitivity to ragweed and *Alternaria* Interventions: 1) Air conditioning + home air cleaner (Space Gard®, removes particles 6.0 µ and larger with 99% efficiency) 2) Air conditioning + placebo air cleaner (no filter) Duration of study treatment: 4 weeks each treatment period; no wash-out between periods Dates: 8/10/1976-10/4/1976 Location: USA Setting: Allergy clinic? Type(s) of providers: Allergists?	No. of subjects at start: 20 Dropouts/withdrawals: 0 No. of subjects at end: 20 Inclusion criteria: ≥ 5-year history of seasonal hay fever symptoms; skin test ≥ 2+ for ragweed extract Exclusion criteria: Significant allergy to house dust mite, or animal dander; nasal polyps. No patients were using corticosteroids. None had had immunotherapy in past 2 years. Age: Range 15-68 Sex: 11 men; 9 women Race: NR Other:	1) Patient-assessed symptom severity: duration of sneezing, nasal congestion, and itchy eyes, and amount of medication used, recorded for 3 periods each day (day = 8 AM to 5 PM; evening = 5-10 PM; night = 10 PM to 8 AM); values of 0-3 assigned (by investigators?) to each parameter 2) Pollen concentrations (indoor and outdoor): recorded at 2 and 4 weeks during each study period	1) Patient-assessed symptom severity: (difference between cleaner out – cleaner in) Daytime: 0.15 (4% reduction); p = ns Evening: 0.03 (.9% reduction); p = ns Night: 0.35 (14% reduction); p = 0.0007 Total 24 hours: 0.52 (6% reduction); p = 0.06 2) Pollen concentrations: Results seem uninterpretable given the crossover design. Outdoor allergen levels differ between filter-in and filter-out time periods.	Quality Scoring: Population similar: Not adequately described Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: No Dropouts described: Yes Intention-to-treat: Yes Notes: No statistical test for period effect. Treatment-by-period interaction assessed: "order of placement of the air cleaner (first half or second half) . . . had no statistical effect on the symptoms of hay fever." Power not addressed. All patients had allergic rhinitis; 6 had symptoms of mild asthma.

Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Korsgaard, 1983	Design: RCT, parallel-group Interventions: 1) Avoidance measures (n = 23), as follows: mattresses vacuumed twice a week; bedding replaced with new synthetic quilts and pillows; bed linen changed and washed twice a week; bedroom floor changed, if necessary, to linoleum or wood and cleaned twice a week; bedroom thoroughly aired for at least 20 minutes every day, and one window left half-open for 24 hours; window in living room open for at least 20 minutes every day; indoor clothes drying to be avoided, if possible; no flowers or plants in bedroom; water-vapor producing activities to be followed by thorough airing 2) No special avoidance measures (n = 23) Duration of study treatment: 12 weeks Trial preceded by 12-week run-in period Dates: 12/1979-3/1981 Location: Denmark Setting: Hospital Chest Clinic Type(s) of providers: NR	No. of subjects at start: 46 Dropouts/withdrawals: 0 No. of subjects at end: 46 Inclusion criteria: Asthma; positive skin test to house dust mites; RAST class ≥ 3 to house dust mite; positive bronchial provocation test to house dust mite Exclusion criteria: Skin test reaction to other indoor allergens (e.g., mold); unable to safely use B2 agonists Age: Median 30 (range 21-34) Sex: 32 men; 14 women Race: NR Other:	1) Adherence to prescribed avoidance measures: assessed by questionnaire at baseline and 12 weeks 2) Spirometry (morning and evening peak flow) 3) Medication use (terbutaline spray): assessed a) by weighing container when exchanged for a new one (every 4 weeks), and b) by daily diary recordings 4) Patient-assessed symptom score: shortness of breath, coughing, and wheezing graded on scale of 0-3 (not described) twice daily (once for 24 hours overall and once for nighttime only) 5) Indoor absolute humidity: measured during weeks -8, -4, 1, 5, 9, and 12 6) Allergen levels: dust collected from mattress and bedroom and living room floors (frequency not reported)	1) Adherence to prescribed avoidance measures: Intervention group increased cleaning of bed linen, mattress, bedroom and living room floor, and airing of the bedroom significantly. 2) Spirometry: Not abstracted 3) Medication use (terbutaline spray): Baseline (12 weeks); 12 weeks following intervention, median (IQR); p = 0.163 Gp 1: 0.54 g/month (0.26-2.29); 0.33 (0.09-1.33) Gp 2: 0.71 g/month (0.42-1.15); 0.40 (0.14-1.41) 4) Patient-assessed symptom score: Baseline (12 weeks); 12 weeks following intervention, median (IQR); 24 hour score: p = 0.0184 Gp 1: 9.0 (5.5-14.5); 3.0 (1.0-10.5) Gp 2: 9.0 (3.0-16.5); 7.5 (2.0-10.5) Night score: p = 0.0716 Gp 1: 5.0 (0.0-8.5); 0.5 (0.0-4.0) Gp 2: 4.0 (0.0-9.5); 3.0 (0.0-7.0) 5) Indoor absolute humidity: Not abstracted 6) Allergen levels: median (IQR) in 0.10 g of dust Mattress: p = 0.1532 Gp 1: 55 (23-346); 122 (18-230) Gp 2: 44 (5-398); 64 (8-378) Bedroom floor: p = 0.0001 Gp 1: 52 (8-204); 16 (5-30) Gp 2: 47 (6-201); 74 (21-463) Living room floor: p = 0.676 Gp 1: 6 (2-41); 14 (4-71) Gp 2: 8 (2-49); 8 (3-70)	Quality Scoring: Population similar: Yes Intervention(s) described: No Comorbidities described: Yes Diagnosis by MD: Not applicable Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: No Blinding adequate: Not applicable Dropouts described: Yes Intention-to-treat: Yes Notes: Power not addressed. 34 patients had allergic rhinitis.

Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Kroidl, Göbel, Balzer, et al., 1998	Design: RCT, parallel-group Interventions: 1) Acaracide (Acarosan®), applied (by patients) according to manufacturer's written instructions (n = 55). Applied at the start of trial and again at 6 months. 2) Placebo acaracide (as above, but without active ingredient [benzyl benzoate]) (n = 63). Duration of study treatment: 12 months Dates: NR Location: Germany Setting: NR Type(s) of providers: NR	No. of subjects at start: 118 Dropouts/withdrawals: 40 No. of subjects at end: 78 Inclusion criteria: Asthma requiring regular treatment; skin test and RAST positive for house dust mite Exclusion criteria: "Patients with other relevant allergies;" smoking within 5 years Age: Range 8-50 (mean not reported) Sex: 67 males; 51 females Race: NR Other:	1) Patient global evaluation of efficacy: at end of trial, symptoms assessed as "worse," "same," or "better" 2) Investigator global evaluation of efficacy 3) Allergen-specific IgE antibody levels 4) Skin reactivity 5) Bronchial reactivity	1) Patient global evaluation of efficacy: (reported graphically) – no significant difference (approximately 61% better in intervention group vs. 64% in control; p = 0.098) 2) Investigator global evaluation of efficacy: Not abstracted 3) Allergen-specific IgE antibody levels: Not abstracted 4) Skin reactivity: Not abstracted 5) Bronchial reactivity: Not abstracted	Quality Scoring: Population similar: Not adequately described Intervention(s) described: ?? Comorbidities described: Yes Diagnosis by MD: Not applicable Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Notes: No outcomes based on daily recording of symptoms. 70/118 patients had allergic rhinitis. Power: no discussion.

Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Marks, Tovey, Green, et al., 1994	Design: RCT, parallel-group Interventions: 1) Acaricide (Allersearch DMS®) + avoidance measures (n = 17). Acaricide applied once at start of study to both sides of mattress, pillows, duvet, and blankets, as well as to carpets and bedroom and living room furniture. Avoidance measures consisted of placing impermeable covers over mattress, pillows, and duvets. 2) Placebo acaricide (applied as above) (n = 18) Duration of study treatment: 6 months Trial preceded by a 3-month run-in period Dates: 1989-1990 Location: Australia Setting: Hospital asthma and allergy clinics; general practices Type(s) of providers: NR	No. of subjects at start: 35 Dropouts/withdrawals: 5 No. of subjects at end: 30 Inclusion criteria: Clinical diagnosis of asthma; reversible airflow obstruction; (all had positive skin tests to at least one inhaled allergen and all but two were positive to house dust mite) Exclusion criteria: None specified Age: mean 35 Sex: 18 female; 17 male Race: NR Other:	1) Allergen levels: dust samples collected from bed, bedroom floor, and living room floor at baseline and at 2 weeks, 3 months, and 6 months 2) Patient-assessed symptom severity: Symptoms assessed twice daily, as follows: a) Sleep disturbance due to asthma (0 = none, to 3 = awake most of the night); b) Chest tightness on awakening (0 = not present and didn't require extra bronchodilator during the night, to 2 = present); c) Duration and frequency of daytime wheeze and breathlessness (0 = none, to 3 = most or all of the day); d) Severity of daytime wheeze and breathless-ness (0 = none, to 2 = moderate to severe, distressing and/or had to limit activities); e) Cough (0 = none, to 2 = more than occasional). 3) Spirometry (peak flow rates, peak flow variability, FEV1, airway responsiveness [PD20 FEV1])	1) Allergen levels: Results presented graphically and as mean change. Over 3 sites (bed, bedroom floor, living room floor), Der p I levels decreased significantly at 2 weeks (p = 0.038) but not at 3 months (p = 0.33) or 6 months (p = 0.76) 2) Patient-assessed symptom severity: No significant differences at 1,3, or 6 months. 6-month mean change (95% CI), p = 0.20: Gp 1: 0.14 (-0.08-037) Gp 2: -0.06 (-0.31-0.19) 3) Spirometry: Not abstracted	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Not applicable Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: No Blinding adequate: Not applicable Dropouts described: yes Intention-to-treat: Can't determine Note: Power not addressed

Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Moon and Choi, 1999	Design: RCT, parallel-group Interventions: 1) "Routine care" (not defined) + avoidance measures (n = 15). Avoidance measures consisted of wrapping mattress in vinyl cover, washing top bedding cover in hot (55° C) water every 2 weeks, removing soft furniture from bedroom, and wet cleaning bedroom floor every day. 2) "Routine care" alone (n = 15). Other treatments continued including immunotherapy (52%) and symptomatic treatment (28%). Duration of study treatment: 4 weeks Dates: 7/1995-10-1995 Location: Korea Setting: Allergy clinic of University Hospital Type(s) of providers: Allergy clinic nurse	No. of subjects at start: 30 Dropouts/withdrawals: 1 No. of subjects at end: 29 Inclusion criteria: Allergic rhinitis; skin test ≥ 3+ to house dust mite; positive RAST; skin test for other "common inhalant allergens" was negative Exclusion criteria: None specified Age: 15.6 (range 6-31) Sex: 12 female; 17 male Race: NR Other:	1) Allergen levels: dust samples collected by vacuum from bedroom floor, bedding, and mattress at baseline and 1 month 2) Patient-assessed symptom severity: symptoms graded [daily or once at beginning and once at end??] as follows: Sneezing (0 = no sneezing attacks, to 3 = more than 10 sneezing attacks); Rhinorrhea (0 = no nose blowings, to 3 = more than 10 nose blowings); Nasal obstruction (0 = no nasal obstruction, to 3 nasal obstruction with predominant mouth breathing)	1) Allergen levels: $p<0.05$ Mean change Gp 1: -32.5 Gp 2: 15.8 2) Patient-assessed symptom severity: $p < 0.05$ Mean change Gp 1: -2.9 Gp 2: -0.3	Quality Scoring: Population similar: No Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: No Blinding adequate: Not applicable Dropouts described: Yes Intention-to-treat: No Note: Power not addressed

Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Reisman, Mauriello, Davis, et al., 1990	Design: RCT, crossover Interventions: 1) Active HEPA filter (ENVIRACAIRE® with active filter) placed in bedroom 2) Placebo HEPA filter (ENVIRACAIRE® with blank filter) placed in bedroom Duration of study treatment: 4 weeks each treatment period; no washout between periods Dates: Mid-Nov to March (year?) Location: US Setting: NR Type(s) of providers: NR	No. of subjects at start: 40 Dropouts/withdrawals: 8 No. of subjects at end: 32 Inclusion criteria: Perennial rhinitis; positive skin test to house dust or house dust mite Exclusion criteria: None specified Age: 27.5 (range 6-61) Sex: 12 male; 20 female Race: NR Other:	1) Airborne particle counts: measured at baseline, 4 weeks (end of 1st period), and 8 weeks (end of 2nd period) 2) Patient-assessed symptom severity: severity and duration of sneezing; nasal discharge; nasal congestion; itchy eyes, ears, nose, and throat; and asthma graded twice each day (for 7 AM to 7 PM and for 7 PM to 7 AM) on scale of 1 (mild/30 minutes) to 3 (severe/ more than 2 hours) 3) Medication use: graded (twice?) daily as follows: 1 = antihistamine or decongestant tablets; 2 = theophylline tablet; 3 = nasal or systemic steroid dose 4) Patient global evaluation of response: graded as “improved” or “no difference” at 4 and 8 weeks (end of each treatment period)	1) Airborne particle counts: Patient level data given; summary data given as % change without p value Gp 1: 73.4% decrease Gp 2: 3.6% increase 2) Patient-assessed symptom severity: For 7 individual symptoms and total symptoms compared separately for night- and daytime periods, there were no significant between-group differences (data presented for individual but not total scores) Analysis restricted to final 2-week period of placebo vs. active filter showed improvement for active filter on nasal congestion (p = 0.007) and upper airway itching (p = 0.017); data not reported, only p values given 3) Medication use: No significant differences; data not presented 4) Patient global evaluation of response: Active filter period: 11/32 improved Placebo filter period: 7/32 improved 14 found no difference	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Notes: Carry-over effect reduced by comparing last 2 weeks on treatment. No tests for period effect or treatment-by-period interaction. Power not addressed. 11 patients had asthma.

Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Shapiro, Wighton, Chinn, et al., 1999	Design: RCT, parallel-group Interventions: 1) Aggressive environmental control program (n = 22). Consisted of: application of dust mite impermeable covers to mattress, box spring, and pillow; laundry service delivery of a clean blanket and 4 sets of bed linens every months; and tannic acid acaricide application to bedroom and living room carpet every 2 months. Families instructed to dust and vacuum weekly and to avoid clutter. 2) Standard environmental control program (n = 22). Consisted of: general discussion of need to dust and vacuum house weekly and avoid clutter in the bedroom, and the application of placebo tannic acid acaricide every 2 months. Duration of study treatment: 1 year Trial preceded by 4-week run-in period Dates: NR Location: US Setting: Clinics serving low SES neighborhoods Type(s) of providers: NR	No. of subjects at start: 44 Dropouts/withdrawals: 8 No. of subjects at end: 36 Inclusion criteria: Mild to moderate persistent asthma by NHLBI criteria; ≥ 1 urgent care visit in past 6 months; albuterol use ≥ 5 times/month; positive methacholine challenge at ≤ 10 mg/ml; skin test positive to house dust mite Exclusion criteria: Already carrying out environmental control measures Age: 9.5 (range 6-15) Sex: 14 male; 22 female Race: 21 White; 9 African-American; 3 Asian-Pacific; 1 Hispanic; 2 other Other:	1) Parents' global evaluation of symptom severity: graded as mild, moderate, or severe at baseline, 6 months, and 12 months 2) Parents' global evaluation of quality of life: graded on scale of 0 (no symptoms) to 14 (many symptoms) at baseline, 6 months, and 12 months 3) Asthma exacerbations: measured in terms of hospitalizations, ED visits, and steroid bursts 4) Spirometry (FEV1, bronchial hyper-responsiveness (PD_{20}) 5) Allergen levels: dust collected from mattress, bedroom carpet, living room furniture and carpet, and kitchen floor at baseline and at 4, 8, and 12 months	1) Parents' global evaluation of symptom severity: "No significant changes from baseline"; no data or p-values given. 2) Parents' global evaluation of quality of life: "Similar for groups and did not change during the course of the year"; no data or p-values given 3) Asthma exacerbations: "Similar for the two groups" 4) Spirometry (FEV1, bronchial hyper-responsiveness (PD_{20}): Not abstracted 5) Allergen levels: Dust mite concentration categorized as low (<2 µg/g), moderate (2-<10 µg/g), or high (≥ 10 µg/g). 50% of Gp 1 and 16.7% of Gp 2 changed to a lower category (p = 0.03). Mean dust mite levels decreased 19.6% in Gp 1 and increased 33% in group 2 (p = 0.20).	Quality Scoring: Population similar: No Intervention(s) described: No Comorbidities described: Yes Diagnosis by MD: Not applicable Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Notes: No symptom data based on daily recordings. Investigators reported that "attempts to collect daily symptom and peak flow diaries were futile." Power not addressed.

Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Walshaw and Evans, 1986	Design: RCT, parallel-group Interventions: 1) Avoidance measures (n = 25). Mattress thoroughly vacuumed and covered with a plastic cover; cover to be damp-dusted at least weekly. Pillows also enclosed in plastic covers. Feather bedding replaced with synthetic polyester or avoided; woolen blankets replaced with cotton c ellular or polyester equivalents. All bedding to be washed at least weekly and/or shaken outside frequently. Bedroom carpet to be vacuumed at regular intervals or (preferably) replaced with linoleum, which was to be washed frequently. Soft furnishings and plants to be removed from bedroom. Bathroom door to be kept closed during and immediately after bathing, etc., and kitchen door during and immediately after cooking. Bedroom to be thoroughly ventilated on dry days only. Lounge floor to be vacuumed frequently. 2) No avoidance measures (n = 25). Duration of study treatment: 1 year Dates: 11/1982 – 4/1984 Location: UK Setting: Hospital-based chest	No. of subjects at start: 50 Dropouts/withdrawals: 8 No. of subjects at end: 42 Inclusion criteria: Adults with asthma; strongly positive skin test to house dust mite Exclusion criteria: Other chest disease Age: Intervention 33 ± 2 (SEM); Control 34 ± 2 (SEM) Sex: 22 male; 28 female Race: NR Other:	1) Allergen levels: dust samples collected at baseline and every 4 months thereafter from mattresses and bedroom and lounge floors using a modified hand-held vacuum 2) Relative humidity in the bedroom: measured at baseline and every 4 months thereafter 3) Spirometry (FEV1, FVC, peak flow rates) 4) Bronchial reactivity (PC_{20}) 5) Use of symptomatic medication (inhaled cromoglycate, broncho-dilators, and steroids; oral steroids): not clear how assessed 6) Patient- and investigator-assessed symptom severity: symptoms assessed at each 4-monthly clinic visit by means of a detailed history 7) Total IgE, IgA, IgM, and IgG antibody levels	1) Allergen levels: reported graphically, mattress and bedroom floor mite levels fell significantly for intervention group but not the control group; no between-group comparison given 2) Relative humidity in the bedroom: Fell significantly in 2 of 3 measures for intervention group and 1 of 3 measures for control group compared to baseline; no between-group comparisons 3) Spirometry: Not abstracted 4) Bronchial reactivity: Not abstracted 5) Use of symptomatic medication: Results stratified by RAST positive/negative. Only within-group analysis given. 6) Patient- and investigator-assessed symptom severity: (reported graphically) Results stratified by RAST positive/negative. Only the RAST positive intervention group showed improvement; no statistical tests reported; no between-group analysis reported. 7) Total IgE, IgA, IgM, and IgG antibody levels: Not abstracted	Quality Scoring: Population similar: No Intervention(s) described: No Comorbidities described: Yes Diagnosis by MD: Not applicable Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: No Blinding adequate: Not applicable Dropouts described: Yes Intention-to-treat: No Notes: Power: no discussion. Analysis is a multiple time points with no analysis for overall effect and no consideration of multiple testing.

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Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	clinics Type(s) of providers: NR				
Warburton, Niven, Pickering, et al., 1994	Design: RCT, crossover Interventions: 1) HEPA filter placed in main living room. Patients advised to leave unit running continuously and to keep external windows closed as much as possible. 2) Placebo HEPA filter (same external unit, internal HEPA and charcoal filters removed), employed as above. Duration of study treatment: Mean duration of active treatment was 30.3 days (range, 21-45); mean duration of placebo treatment was 24.0 days (range, 20-33) Trial preceded by run-in period of unspecified length Dates: NR Location: UK Setting: NR Type(s) of providers: NR	No. of subjects at start: 13 Dropouts/withdrawals: 1 No. of subjects at end: 12 Inclusion criteria: Volunteers with asthma; positive skin test to house dust mite antigen and to ≥ 1 of 3 fungal species Exclusion criteria: NR Age: 45.5 (range 19-64) Sex: 8 male, 4 female Race: NR Other:	1) Patient-assessed symptom severity: cough, phlegm production, wheeze, breathlessness, and chest tightness graded daily on visual analog scale; frequency of nocturnal wakening also recorded 2) Use of symptomatic medication (broncho-dilators): recorded daily 3) Spirometry (FEV1, FVC, morning and evening peak flow rates) 4) Bronchial reactivity (PD_{20}) 5) Airborne allergen levels: measured using Rotheroe and Mitchell pumps at height of 1.5 m in living room; measured at baseline and at end of each treatment period	1) Patient-assessed symptom severity: No significant difference in mean symptom scores for any individual symptom (no variance given for means) 2) Use of symptomatic medication: No significant difference in mean bronchodilator use (no variance given for means) 3) Spirometry: Not abstracted 4) Bronchial reactivity: Not abstracted 5) Airborne allergen levels: Intervention period: 0.038 ± 0.025 mg/m^{-3} Control period: 0.028 ± 0.015 mg/m^{-3} No significant difference	Quality Scoring: Population similar: Yes Intervention(s) described: No Comorbidities described: Yes Diagnosis by MD: Not applicable Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: No Dropouts described: Yes Intention-to-treat: No Notes: No assessment of carry-over effect, period effect, or treatment-by-period interaction. Power: no discussion.

Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Wood, Johnson, Van Natta, et al., 1998	Design: RCT, parallel-group Interventions: 1) Active HEPA filter (Envirocare® with active filter) in bedroom + avoidance measures (described below) (n = 18) 2) Placebo HEPA filter (Envirocare® with filter removed) in bedroom + avoidance measures (described below) (n = 17) Avoidance measures (both groups): bed fitted with impervious mattress and pillow covers; subjects instructed to wash bedding once a week and to keep cats from entering bedroom at all times Duration of study treatment: 3 months Trial preceded by 1-month baseline period Dates: NR Location: US Setting: Advertisement; University Allergy Clinic Type(s) of providers: NR	No. of subjects at start: 38 Dropouts/withdrawals: 3 No. of subjects at end: 35 Inclusion criteria: Adults with asthma or allergic rhinitis and symptoms associated with cat contact; symptoms requiring medication use on ≥ 50% of days; positive skin prick test and RAST to cat allergen; home with ≥ 1 cat Exclusion criteria: Severe asthma Age: 36.3 (range 23-60) Sex: 10 male; 25 female Race: NR Other:	1) Allergen levels: dust collected from carpet or upholstered furniture; air samples obtained with small portable pump 2) Patient-assessed symptom severity: nasal congestion, rhinorrhea, sneezing, coughing, wheezing, and chest tightness graded on scale of 0 (none) to 3 (severe) three times per day; sleep difficulty recorded daily (yes/no) 3) Medication use: recorded in daily diaries 4) Spirometry (morning and evening peak flow rates, FEV1, MCh reactivity, cat RAST levels)	1) Allergen levels: Baseline; 3-month Airborne Fel d 1, ng/m3; p = 0.045 for completers analysis; p = 0.152 for ITT Gp 1: 3.0 ± 1.1; 1.7 ± 1.7 Gp 2: 2.6 ± 1.2; 2.8 ± 1.8 Settled dust Fel d 1; ug/g; p = 0.407 completers analysis Gp 1: 10.1 ± 2.3; 10.5 ± 1.6 Gp 2: 11.8 ± 0.9; 10.6 ± 1.1 2) Patient-assessed symptom severity: Results presented separately for nasal and chest symptoms at 3 time periods (morning, afternoon, night). No significant between-group differences for any of the 6 comparisons Nasal am: Gp 1: 1.40 ± 0.60; 0.91 ± 0.61 Gp 2: 1.22 ± 0.63; 0.88 ± 0.64 p = 0.769 Nasal pm: Gp 1: 1.16 ± 0.62; 0.74 ± 0.59 Gp 2: 1.04 ± 0.58; 0.82 ± 0.66 p = 0.534 Nasal night: Gp 1: 1.01 ± 0.64; 0.67 ± 0.71 Gp 2: 0.70 ± 0.55; 0.64 ± 0.69 p = 0.138 Chest am: Gp 1: 0.82 ± 0.61; 0.29 ± 0.38 Gp 2: 0.86 ± 0.63; 0.55 ± 0.60 p = 0.388 Chest pm: Gp 1: 0.71 ± 0.60; 0.28 ± 0.39 Gp 2: 0.80 ± 0.59; 0.59 ± 0.56 p = 0.179 Chest night: Gp 1: 0.62 ± 0.62; 0.29 ± 0.49 Gp 2: 0.56 ± 0.53; 0.37 ± 0.60 p = 0.215 3) Medication use: Reported for nasal	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Yes Notes: 28/35 patients had asthma; 35/35 had allergic rhinitis Compliance: assessed using internal timers; machines operated at least 80% of the 3 months by 83% of intervention and 94% of placebo group. Post-hoc power analysis estimated 284-14,744 subjects needed depending on outcome addressed.

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Evidence Table 2: Environmental Measures (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
				and chest medications, prn and maintenance medications. No significant differences for any of the 4 comparisons. 4) Spirometry: Not abstracted	
Zwemer and Karibo, 1973	Design: RCT, crossover Interventions: 1) Pure-zone System® clean air head board (air filtering system built into head board of bed). 2) Placebo system (same as above, but with filter removed). Duration of study treatment: 2 weeks each treatment period Dates: Winter season Location: USA Setting: University practices Type(s) of providers: Pediatric allergists	No. of subjects at start: 18 Dropouts/withdrawals: 6 No. of subjects at end: 12 Inclusion criteria: Asthma; positive skin tests to house dust and other indoor allergenic materials; receiving hyposensitization and advised to practice environmental control Exclusion criteria: None Age: range 6-16 Sex: 7 male; 11 female Race: NR Other:	1) Patient-assessed symptom severity: day- and nighttime cough and wheezing graded daily on scale of 0 (none) to 6 (severe, intolerable); sick days (from school), number of asthma attacks, nights with normal sleep, and number of times awakened by symptoms also recorded daily 2) Use of symptomatic medication: recorded daily	1) Patient-assessed symptom severity: 7 excellent improvement; 4 good improvement; 1 fair improvement 2) Use of symptomatic medication: 5 reduced treatment	Quality Scoring: Population similar: No Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Not applicable Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 3b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: No Dropouts described: Yes Intention-to-treat: No Notes: No assessment of carry-over effect, period effect, or treatment-by-period interaction. Power: Not addressed Poorly reported; no analytic plan given and no statistics reported. Reports some failure of blinding (patients detected assignment).

[†] Quality scoring criteria were as follows:
Population similar: Was the study population described and reasonably similar to an adult working US population? (Yes [described and similar], No [described, but not similar], Not adequately described)
Intervention(s) described: Were the intervention protocols referenced or described in sufficient detail to replicate? (Yes, No)

Comorbidities described: Was the presence of comorbid asthma (or other upper respiratory conditions) described in the study population? (Yes, No)
Diagnosis by MD: Was the diagnosis of allergic rhinitis based on physician diagnosis? (Yes, No, Not applicable [asthma patients only])
Objectively confirmed: If physician-diagnosed, was the diagnosis supported by objective evidence of allergy (e.g., skin prick or serum IgE antibody testing)? (Yes, No, Not applicable)
Outcome measures valid: Were the main outcomes of interest to us measured in a way that has been demonstrated empirically to be valid and reliable (e.g., using a standardized scale such the RQLQ or SF-36)? (Yes, No, Not adequately described)
Level of evidence: Based on Oxford Center for Evidence-Based Medicine Levels of Evidence (1a, 1b, 1c, 2a, 2b, 2c, 3a, 3b, 4, 5)
Randomized: Was the study described as "randomized"? (Yes, No)
Allocation concealed: If the method for concealing allocation from the investigators was described, was it *adequate* (table of random numbers, computer-generated, coin tossing, etc.) or *inadequate* (alternating, date of birth, hospital number, etc.)? (Not described, Yes [described and adequate], No [described, but inadequate])
Double-blind: Was the study described as "double-blind"? (Yes, No)
Blinding adequate: If the method of double-blinding was described, was it *adequate* (e.g., identical placebo, active placebo, injection vs. tablet with double dummy) or *inadequate* (e.g., tablet vs. injection with no double dummy)? (Not described, Yes [described and adequate], No [described, but inadequate])
Dropouts described: Did the study describe dropouts and withdrawals so that all patients entering the trial could be accounted for? (Yes, No)
Intention-to-treat: Was the analysis performed according to the intention-to-treat principle? (Yes, No, Can't determine)

Evidence Table 3: Immunotherapy

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Alvarez-Cuesta, Cuesta-Herranz, Puyana-Ruiz, et al., 1994	Design: RCT, parallel-group Interventions: 1) Biologically standardized cat dander extract, quantified with monoclonal antibodies (100 biological units [BU] = 33 µg of *Fel d* I antigen, 650 µg of albumin, and 99 µg of *Fel d* Bd/K30 antigen) (n = 14). Gradually increasing doses administered twice weekly until dose of 13.2 µg of *Fel d* I or maximum tolerated dose reached; maintenance dose then repeated monthly with extract absorbed in aluminum hydroxide gel. Average maintenance dose 11.3 ± 4.7 µg of *Fel d* I (34.4 ± 14.3 BU); average total cumulative dose 170 µg *Fel d* I (515 BU). 2) Placebo (constituents not described) (n = 14) Duration of study treatment: 1 year Symptomatic medication permitted, but not described Dates: NR Location: Spain Setting: University hospitals Type(s) of providers: Specialists	No. of subjects at start: 28 Dropouts/withdrawals: 0 No. of subjects at end: 28 Inclusion criteria: Rhino-conjunctivits and asthma; 18+ months duration; exacerbated by exposure to cat; positive skin test and specific IgE to cat Exclusion criteria: Prior immunotherapy; sensitization to other perennial antigens (not specified); contraindication to immunotherapy Age: 15-65 years old; mean 24 active 29 placebo Sex: 6M/22F Race: NR Other:	1) Adverse reactions 2) Patient global evaluation of efficacy (PSE): at end of study, patients asked to grade their symptoms during direct contact with cats in relation to such symptoms before trial on scale of 0% (complete failure) to 100% (total success) 3) Patient-assessed symptom severity and use of symptomatic medication (combined in a single measure): unspecified symptoms graded daily on scale of 0-3 (not described); use of symptomatic medication recorded daily in study diaries 4) Skin reactivity 5) Conjunctival reactivity 6) Bronchial reactivity	1) Adverse reactions: 10 subjects had 14 "reactions," 7 local and 3 systemic. 2) Patient global evaluation of efficacy: Average 81.3 ± 15.5% improvement active vs. 20.7 ± 33.2% placebo; $p < 0.001$ 3) Patient-assessed symptom severity and use of symptomatic medication (combined in a single measure): 0.14 ± 0.35 active vs. 1.42 ± 0.51 placebo; $p < 0.001$ 4) Skin reactivity: Not abstracted 5) Conjunctival reactivity: Not abstracted 6) Bronchial reactivity: Not abstracted	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Not described Dropouts described: Yes Intention-to-treat: Yes Notes: Subjects also had to take environmental precautions for 12 months prior to immunotherapy, which included removing cat from home.

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Ariano, Kroon, Augeri, et al., 1999	Design: RCT, parallel-group Interventions: 1) Allergoid extract of *Parietaria* (wall pellitory) pollen (Purethal™-*Parietaria*) (n = 13). Glutaraldehyde-modified allergoid obtained from equal parts *Parietaria judaica* and *P. officinalis* pollens. Extract standardized to 20,000 AUeq per ml. Build-up phase: increasing doses (1,000; 2,000; 4,000; 6,000; 8,000; and 10,000 AUeq) injected each week. Maintenance phase: 10,000 AUeq injected each month. In event of AEs, dose repeated or temporarily reduced, according to international guidelines. 2) Placebo (same as above, except for allergen) (n = 12) Duration of study treatment: 1 year (RCT phase); trial followed by 2-year open study during which all patients received active treatment Symptomatic medication permitted: Loratadine or cetirizine (10 mg/day), beclomethasone nasal spray (100 µg/puff), and inhaled albuterol (100 µg/puff) Dates: October 1990-1991 Location: Presumably Italy, but not stated	No. of subjects at start: 25 Dropouts/withdrawals: 0 (at end of year 1) No. of subjects at end: 25 (end of year 1) Inclusion criteria: Single sensitization to *Parietaria* by skin test and RAST; 2 years of disease; rhinoconjunctivitis Exclusion criteria: Anatomic alteration of upper airway; immunodeficiency; malignancies; severe psychologic disorders; chronic steroids; beta-blockers; SIT in last 5 years; pregnant or lactating women Age: 13-62 (mean 32.1) Sex: 17 F Race: NR Other: 5 subjects had mild asthma (3 active, 2 placebo)	1) Adverse reactions: classified according to following scale: 1 = mild local = wheal/flare < 5 cm, granuloma persisting < 1 week, slight pain; 2 = moderate local = wheal/flare < 10 cm, granuloma persisting < 3 weeks; 3 = severe local = wheal/flare > 10 cm, granuloma persisting > 3 weeks, pain requiring medications; 4 = mild systemic = rhinitis, conjunctivitis, asthma, and urticaria not requiring treatment; 5 = severe systemic = as above (4), but requiring pharmacologic treatment 2) Patient-assessed symptom severity and medication use (combined in a single measure): sneezing, rhinorrhea, nasal obstruction, nasal/conjunctival itching, lacrimation, cough, and wheezing graded daily on scale of 0 (no symptom) to 2 (severe); use of symptomatic medication recorded in daily diaries (each dose recorded as score of 1) 3) Patient global evaluation of efficacy: assessed at 1 year in two ways: a) with a questionnaire on	1) Adverse reactions: Placebo: no systemic or local reactions Active: 2 moderate (asthma), 3 mild (rhinitis) systemic reactions. 5 mild, 3 moderate, 4 severe local reactions. All during buildup phase. 2) Patient-assessed symptom severity and medication use (combined in a single measure): Median symptom score after 1 year ~1,250 placebo and ~550 active (p = 0.02). However, baseline scores not given. (Values estimated from figure.) 3) Patient global evaluation of efficacy: (Active vs. Placebo) Frequency of symptoms: (p = 0.001) Decr-10 v 1 Unch-3 v 9 Incr- 0 v 2 Physical Performance (p = 0.043) Imp-6 v 1 Unch-6 v 9 Worse-1 v 2 Duration of symptoms (p = 0.024) Short-5 v 0 Unch-8 v 7 Leng-0 v 5 Satisfaction (p = 0.002) Yes-11 v 0 Indiff-1 v 0 No-1 v 11 VAS % improvement Active 31.6 v Placebo -15.0 (p = 0.01) 4) Skin reactivity: Not abstracted 5) Allergen-specific IgG_4 and IgE levels: Not abstracted	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Yes Notes: No histamine in placebo injection.

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Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Setting: Presumably academic Allergy and Immunology Department, but not stated Type(s) of providers: Presumably allergists		frequency of symptoms, physical performance, duration of complaints, and global satisfaction (each graded as "improved," "unchanged," or "worsened"); and b) with a visual analog scale running from + (clinical condition improved) to - (worsening of clinical condition) 4) Skin reactivity 5) Allergen-specific IgE and IgG4 antibody levels		
Arvidsson, Löwhagen, and Rak, 2002	Design: RCT, parallel-group Interventions: 1) Aluminum-adsorbed birch pollen (*Betula verrucosa*) extract (Alutard® SQ) (n = 24). Clustered protocol, with 14 gradually increasing doses (from 10 to 100,000 SQ-U) given over 7 to 8 weeks. Maintenance injections (100,000 SQ-U) given every 6 weeks for remainder of study. 2) Placebo (diluent + histamine dihydrochloride) (n = 25). Duration of study treatment: Up to 2 years over 2 pollen seasons Symptomatic medication permitted: Acrivastine capsule 8 mg; terbutaline inhalation 0.5 mg; salbutamol	No. of subjects at start: 49 Dropouts/withdrawals: 3 No. of subjects at end: 46 Inclusion criteria: History of birch pollen-induced symptoms from the upper airways; positive skin prick test (> 3 mm wheal) to *Betula verrucosa;* positive RAST; positive conjunctival provocation test Exclusion criteria: perennial symptoms from upper or lower airways; sensitivity to house dust mit or mold; previous treatment with SIT; treatment with topical steroids Age: mean 32 years (range 19 to 46 years) Sex: 59% women Race: NR	1) Patient-assessed symptom severity: evaluated in two ways: a) runny nose/sneezing, blocked nose, eye symptoms, and bronchial symptoms graded daily during pollen season on scale of 0 (none) to 3 (severe); and b) patient's perception of severity of symptoms graded once per week during pollen season on a VAS (0-10, end points not described) 2) Use of symptomatic medication: recorded daily during pollen season; scored as follows: 1 point: acrivastine capsule, terbutaline inhalation, or salbutamol inhalation; 2 points: sodium	1) Patient-assessed symptom severity: Median symptom scores 1st pollen season SIT 1.3 (range 0-5.2) Pl 2.1 (range 0.6-5.6) P=0.05 2nd pollen season SIT 2.6 (range 0-6.5) Pl 4.3 (range 2.4-9.1) P=0.005 2) Use of symptomatic medication: The placebo group used significantly more rescue medication than the active group during both seasons (p=0.004 in 1997 and p=0.004 in 1998) 3) Adverse reactions: SIT / placebo Total AE 71 / 81 # pts 22 / 20 general sx 40.7% / 46.7% respiratory (rhinitis or cough) 27.6% / 19.8% post-injection 4 / 7	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: No Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Notes: Long-term study *(continued on next page)*

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	inhalation 0.4 mg; and sodium cromoglycate eye drops (40 mg/ml) and nasal spray (5.2 mg/ml); if needed, patients could request topical steroids (budesonide nasal powder [100 µg/dose] or inhalation powder [200 µg/dose]) Dates: Treatment began Nov 1996 to Jan 1997; study ended June 1998 Location: Goteborg, Sweden Setting: Allergy clinic Type of providers: Allergists	Other: 21 patients also sensitive to grass pollen; 30 patients also sensitive to animal dander, but none had exposure to pets during the study	cromoglycate eye drop or nasal spray puff; 4 points: budesonide nasal powder or inhalation powder dose 3) Adverse reactions	(all mild)	
Bernstein, Tennenbaum, Georgakis, et al., 1976	Design: RCT, parallel-group (matched-pairs design) Interventions: 1) Alum-adsorbed Fraction A (partially purified derivative of aqueous ragweed extract) (n = 68). Cumulative dose of 24,000 PNU to be attained in 20 doses, but more injections required when large local or systemic reactions occurred. Goal for 1972 pre-season (injections given weekly) was to attain maximum individual dose of 6,000 PNU. During season, ½ of maximum pre-seasonal dose given every week. This dose continued every 4 weeks after end of season until 2 months prior to 1973 season, when maximum dose again reached at weekly intervals.	No. of subjects at start: 148 Dropouts/withdrawals: 17 13 lost to followup (10 P v 3 A); 4 serious systemic reaction No. of subjects at end: 131 completed 1972 season. Inclusion criteria: Definite seasonal history; clinical findings of ragweed hayfever 3+ years; no IT for at least 1 year; positive skin test to Fraction A Exclusion criteria: None specified Age: Mean age 30 Sex: 63 F Race: NR Other: 1/3 recipients had previous ragweed immunotherapy	1) Investigator global assessment of treatment response 2) Patient-assessed symptom severity: unspecified symptoms graded daily during pollen season on scale of 0 (no symptoms/ no significant symptoms) to 3 (significant symptoms not controlled by regular medication, but controlled by steroids) 3) Use of symptomatic medication: recorded daily during pollen season as 0 (no medication taken) or 1 (medication taken) 4) Immunologic parameters (hemagglutinating antibodies, RAST)	1) Investigator global assessment of treatment response: Not abstracted 2) Patient-assessed symptom severity: Assessed in only 112 patients. Data lost in mail on 19. Symptom Score (active v placebo): 1.097 v 1.378 ($p < 0.05$) 3) Use of symptomatic medication: Drug Score (active v placebo): 0.411 v 0.584 ($p < 0.05$) 4) Immunologic parameters (hemagglutinating antibodies, RAST): Not abstracted 5) Adverse reactions: Systemic effects in 17 patients (1.4% of injections) in active group and 6 patients in placebo group. Of these 6 active and 2 placebo treated patients had serious systemic reactions. 3 of 6 active group patients tolerated subsequent injections. Local reactions	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Notes: Results reported for 1st year of 2-year trial. No histamine in placebo.

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Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	2) Placebo (n = 63) Duration of study treatment: Approx. 2 years; protocol began with pre-seasonal treatment before 1972 ragweed season and extended through 1973 season Symptomatic medication permitted: Not described Dates: 1972 Ragweed season Location: Cincinatti, OH Setting: Academic immunology practice Type(s) of providers: Specialists		5) Adverse reactions	in 24 active group patients (2.3% of injections).	
Blainey, Phillips, Ollier, et al., 1984	Design: RCT, parallel-group Interventions: 1) Tyrosine-adsorbed extract of *Dermatophagoides pteronyssinus* (house dust mite) (Migen®) (n = 17). Build-up phase: 6 injections at weekly intervals, with doses increasing from 4 to 400 Noon units (10^{-6} g of whole allergen in ml of solution). Maintenance phase: 10 monthly injections at highest dose (400 Noon units), starting 4 weeks after last weekly injection. 2) Placebo (tyrosine-	No. of subjects at start: 39 Dropouts/withdrawals: 16 4 patients did not complete initial 6 weekly injection series (3 placebo patients withdrew for "social" reasons, 1 active patient had severe reaction). 10 patients withdrew during the monthly injection phase due to lack of response (9/18 placebo and 3 of 17 active). No. of subjects at end: 23 Inclusion criteria: Not specified, but all had history of perennial rhinitis exacerbated by dust from mattresses and bedding. All had positive ST or nasal provocation	1) Patient-assessed symptom scores (clinic visits): nasal blockage, sneezing, rhinorrhea, and sleep disturbance graded at each clinic visit on 10-cm visual analog scale running from "no symptoms" to "very severe symptoms" 2) Nasal reactivity 3) Total IgE, specific IgE, and specific IgG antibodies 4) Skin reactivity 5) Use of symptomatic	1) Patient-assessed symptom scores (clinic visits): No data. 2) Nasal reactivity: Not abstracted 3) Total IgE, specific IgE, and specific IgG antibodies: Not abstracted 4) Skin reactivity: Not abstracted 5) Use of symptomatic medication: (see Notes) No data. 6) Patient global evaluation of efficacy of treatment: 11 patients in active group and 5 patients in placebo group considered treatment effective ($p < 0.05$)	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No *(continued on next page)*

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	containing suspension) (n = 18) Duration of study treatment: 13 months (including 4-week run-in); final post-treatment results taken from 1 month after last maintenance treatment (14 months) Trial preceded by 4-week run-in phase during which patients were treated with beclomethasone dipropionate nasal spray and house dust mite avoidance measures Symptomatic medication permitted: Beclomethasone dipropionate or xylometazoline; patients "encouraged to reduce therapy if they felt able to do so without recurrence of troublesome symptoms" Dates: Enrollment over 2 successive years – not specified Location: London Setting: Not specified, but presumably academic respiratory unit Type(s) of providers: Specialists	study. All were non-responders to topical corticosteroids and avoidance measures. 15 patients had symptoms after contacting domestic animals or had seasonal exacerbation between May and August. Exclusion criteria: None specified Age: 17-36 (mean age 26) Sex: 20 F after initial 6 week injections. Race: NR Other:	medication: recorded daily in study diaries 6) Patient global evaluation of efficacy of treatment: assessed at end of study by asking patients, "Did your symptoms (blocked or runny nose and sneezing attacks) improve after the course of injections?" 7) Adverse reactions	7) Adverse reactions: 1 withdrawal for severe reaction. 5 patients in active group and 6 in placebo group with local reaction. Exacerbation of rhinitis or asthma in 3 active and 5 placebo patients.	Notes: Symptoms scored daily in study diaries, but results not reported because study participants "not thorough enough in completing their diary cards, particularly for drug usage." High dropout rate. No histamine in placebo.

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Bødtger, Poulsen, Jacobi, et al., 2002	Design: RCT, parallel-group Interventions: 1) Aluminum-adsorbed birch pollen (*Betula verrucosa*) extract (Alutard® SQ) (n = 17). Clustered protocol, with 11 injections of gradually increasing doses (from 10 to 100,000 SQ-U) given over 7 weeks. Dose modifications made in the event of local or systemic adverse reactions. Maintenance injections (100,000 SQ-U) given 2 and 6 weeks after maximum dose achieved, then every 8 weeks for remainder of treatment period. 2) Placebo (diluent with gradually increasing concentrations of histamine dihydrochloride) (n = 18). Duration of study treatment: 10 months (Jan to Nov); symptoms monitored for one allergy season (April-May); 1-year follow-up Symptomatic medication permitted: Acrivastine 8 mg; levocabastine eye drops (0.5 mg/ml) and nasal spray (50 µg/dose); and salbutamol inhalations (200 µg/dose); if necessary, a 1-week course of oral prednisone (12.5 mg/day) could be prescribed Dates: Jan 2000 through autumn 2001	No. of subjects at start: 35 Dropouts/withdrawals: 1 No. of subjects at end: 34 Inclusion criteria: At least 2 seasons of severe allergic symptoms in April and May (birch pollen season); poor symptom control in previous seasons on regular antiallergic treatment; positive skin prick tests (> 3 mm wheal) to *Betula verrucosa; positive RAST* Exclusion criteria: Previous SIT toward birch; lactation or pregnancy at start of injection therapy; perennial rhinitis or asthma; continuous use of systemic beta-blockers. Age: median 27 years (range 19 to 46) Sex: 60% women Race: NR Other: 14 patients had seasonal asthma symptoms; 20 patients had self-reported allergy to grass pollen	1) Patient-assessed symptom severity: symptoms of the nose, eyes, and lungs graded daily from 13 March to 21 May on scale of 0 (none) to 3 (severe) 2) Use of symptomatic medication: recorded in study diaries from 13 March to 21 May; scored as follows: 1 point: each drop or spray of levocabastine or inhalation of salbutamol; 2 points: each dose of acrivastine or prednisolone 3) Patient global evaluation of efficacy: assessed at 1-year follow-up in two ways: a) with a visual analog scale (not described) describing the overall severity of the pollen season; and b) with a non-validated questionnaire asking patients whether they had experienced any effect of treatment, a reduction in symptoms, a reduction in medication use, or increased well-being during the pollen season (yes/no for each question) 4) Conjunctival reactivity 5) Nasal reactivity 6) Skin reactivity	1) Patient-assessed symptom severity: IT 31.5 (6.0-50.0) Pl 44.0 (14.0-75) P < 0.05 2) Use of symptomatic medication: IT 52.0 (2.0-114.0) Pl 102 (2.0-186) P < 0.02 3) Patient global evaluation of efficacy: SIT (Y/N) Pl Effect of treatment 15/2 8/9 P < 0.03 Symptom decrease 14/3 8/9 p > 0.07 Medication reduced 10/7 5/12 P = 0.17 Increased well-being 14/3 5/12 P < 0.006 4) Conjunctival reactivity: Not abstracted 5) Nasal reactivity: Not abstracted 6) Skin reactivity: Not abstracted 7) Histamine release: Not abstracted 8) Total and specific IgE: Not abstracted 9) Adverse reactions: SIT placebo Grade 3-4 0 0 Grade 1-2 7 16 Immediate SE 7 14 Late SE 0 2	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: No Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Notes:

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Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Location: Copenhagen, Denmark Setting: Allergy clinic Type(s) of providers: Allergists		7) Histamine release 8) Total and specific IgE 9) Adverse reactions		
Bousquet, Frank, Soussana, et al., 1987	Design: RCT, parallel-group Interventions: 1) Formalinized high-molecular-weight mixed grass pollen allergoid (n = 40 or 39). Administered "using a rather aggressive protocol." Maximum dose reached in 9 injections (time frame not described). Mean total dose received 25,649.5 ± 17,704.3 PNU (range, 5,695 to 73,800). 2) Placebo (constituents not described) (n = 20 or 19). Duration of study treatment: NR (9 injections, but time frame not indicated); outcomes measured during single pollen season Symptomatic medication permitted: NR Dates: NR Location: Montpelier, France (Northern Mediterranean area) Setting: Allergy clinic Type(s) of providers: Allergists	No. of subjects at start: 59 Dropouts/withdrawals: 0 No. of subjects at end: 59 Inclusion criteria: Severe grass pollen-induced rhinitis; volunteers Exclusion criteria: None stated Age: 25.2 ± 12.1 years Sex: NR Race: NR Other:	1) Adverse reactions 2) Nasal reactivity 3) Patient-assessed symptom severity: nasal symptoms evaluated during peak of pollen season (May 1 to June 15); symptoms scored and scale used not described 4) Allergen-specific IgG antibody levels	1) Adverse reactions: 6/39 allergoid-treated pts had systemic reactions (5 mild, 1 urticaria with asthma requiring treatment) 1/20 placebo-treated pts had mild systemic reaction 2) Nasal reactivity: Not abstracted 3) Patient-assessed symptom severity: significantly reduced in allergoid group compared to placebo group (nasal symptom score 61± 35 versus 109 ± 33) 4) Allergen-specific IgG antibody levels: Not abstracted	Quality Scoring: Population similar: Yes Intervention(s) described: No Comorbidities described: No Diagnosis by MD: No Objectively confirmed: No Outcome measures valid: Not adequately described Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: No Blinding adequate: Not applicable Dropouts described: Yes Intention-to-treat: Can't determine Notes: No significant correlation between IgG titer and nasal provocation test or symptom scores. Article reports conflicting numbers of patients in the two treatment groups (n = 39 or 40 for allergoid group; n = 19 or 20 for placebo group).

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Bousquet, Hejjaoui, Skassa-Brociek, et al., 1987	Design: RCT, parallel-group Interventions: 1) Standardized orchard grass-pollen extract (n = 15). Treatment started in December or January. Rush protocol used, with rapid increase in allergen dose; maintenance dose (2 IR) reached in 4 days. Maintenance dose then given every week for 4 weeks, then every 2 weeks until April 1. Co-seasonal immunotherapy (dose reduced by half) then given every 2 weeks until October 1. 2) Mixed grass-pollen (six species) allergoid (n = 19). Treatment started in January or February. Rush protocol used, with rapid increase in allergoid doses over 3 days; doses subsequently increased weekly to reach maintenance dose of 1000 PNU. Increases stopped if/when systemic reaction or large local reaction (diameter > 10 cm) occurred, and maintenance dose defined as dose reached before this reaction. Maintenance dose then given every week for 4 weeks, then every 2 weeks until April 1. Co-seasonal immunotherapy (dose reduced by half) then given every 2 weeks. 3) Placebo (0.9% NaCl, 0.4% phenol, and 0.5 to 0.005 mg/ml histamine	No. of subjects at start: 45 Dropouts/withdrawals: 0 No. of subjects at end: 45 Inclusion criteria: Rhinitis during grass-pollen season; positive prick test (to 1/100 wt/vol standardized extract) and IgE (at RAST class 3 to 4) indicating allergy to orchard grass pollen Exclusion criteria: Multiple pollen allergy; previous specific immunotherapy to grass pollens; use of systemic corticosteroids Age: Mean 24.1 ± 10.1 years (range, 12 to 43) Sex: NR Race: NR Other: "More than half also had symptoms of asthma and/or conjunctivitis" asthma 71% conjunctivitis 58% "Duration of symptoms during pollen season ranged from 3 to 19 years"	1) Adverse reactions 2) Use of symptomatic medication: graded daily during pollen season, as follows: No medication: 0 Disodium cromoglycate nasal spray: 1 Beclomethasone nasal spray: 2 Terfenadine: 3 Oral prednisolone: 4 3) Patient-assessed symptom severity: symptoms graded daily during pollen season, as follows: No symptom: 0 > 5 episodes sneezing: 1 Nasal blockage: 1 or 2 Rhinorrhea: 1 or 2 Nasal pruritus: 1 4) Skin reactivity 5) Allergen-specific IgE and IgG	1) Adverse reactions: Allergoid group 37% Allergen group 20% Placebo group 0% 2) Use of symptomatic medication: Results presented in graph only (could be interpolated) Allergen < Placebo ($p < 0.01$) Allergoid < Placebo ($p < 0.05$) Allergen vs. Allergoid (p = NS) 3) Patient-assessed symptom severity: Results presented in graph only (could be interpolated) Allergen < Placebo ($p < 0.005$) Allergoid < Placebo ($p < 0.01$) Allergen vs. Allergoid (p = NS) 4) Skin reactivity: Not abstracted 5) Allergen-specific IgE and IgG: Not abstracted	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Yes Note: Only the placebo (3) versus allergoid (2) comparison was double-blind because of different protocol used for allergen group (1).

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Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	hydrochloride) (n = 11). Duration of study treatment: Approximately 10 months (December-September) Symptomatic medication permitted: Disodium cromoglycate nasal spray, beclomethasone nasal spray, terfenadine, oral prednisolone Dates: NR Location: Montpellier, France (Northern Mediterranean area) Setting: Allergy clinic Type(s) of providers: Allergists				
Bousquet, Hejjaoui, Soussana, et al., 1990	Design: RCT, parallel-group Interventions: 1) Formalinized high-molecular-weight allergoid prepared from a six grass-pollen extract, *high-dose schedule* (n = 20). Grasses were: *Dactylis glomerata, Festuca elatior, Holcus lanatus, Lolium perenne, Phleum pratense,* and *Poa pratensis.* Maximal single dose (10,000 PNU) achieved with 8th injection on day 28. This dose administered three times at weekly intervals, then reduced by ½ and administered every 2 weeks during allergy season. Mean cumulative dose received 45,433 ± 14,001 PNU.	No. of subjects at start: 57 Dropouts/withdrawals: 2? (unclear) No. of subjects at end: 55? (unclear) Inclusion criteria: Symptoms of rhinitis during grass-pollen season, positive prick test to 1/100 (wt/vol) standardized orchard-grass pollen extract; positive RAST to orchard-grass pollen Exclusion criteria: previous specific immunotherapy to pollen extract Age: 26.8 ± 10.4 years (range 11 to 45)	1) Adverse reactions 2) Patient-assessed symptom severity: symptoms of rhinitis (rhinorrhea, sneezing, and nasal obstruction), conjunctivitis (watery eyes, red eyes, and pruritus), and asthma (wheezing and shortness of breath) graded twice daily on scale of 0 to 5 (not described) 3) Use of symptomatic medication: recorded daily by patients in study diaries; system for scoring not described 4) Nasal reactivity	1) Adverse reactions: large local reactions (> 10cm diameter and lasting > 24hr) in 9 patients (4/19 low dose group; 5/20 high dose); mild systemic reactions (flushing of face, rhinitis, or urticaria; resolved w/o treatment) in 8 pts (3 placebo; 2 low dose; 3 high dose) severe reaction (urticaria, rhinitis, asthma w/o hypotension) 2) Patient-assessed symptom severity: Mean rhinitis symptom scores (± SD): High dose: 63.6 ± 32.5 Low dose: 57.8 ± 37.5 Placebo: 108.6 ± 33.2 $p < 0.005$, high dose vs. placebo; $p < 0.001$, low dose vs. placebo; p = NS, high dose vs. low dose Mean asthma symptom scores (± SD): High dose: 17.4 ± 20.2	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: No Intention-to-treat: Can't determine Note: Exact scores given for subgroups of pts with asthma *(continued on next page)*

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	2) Formalinized high-molecular-weight allergoid prepared from a six grass-pollen extract (as above), *low-dose schedule* (n = 19). Schedule as above, except maximal single dose 2,000 PNU. Mean cumulative dose received 10,570 ± 2,808 PNU. 3) Placebo (saline, phenol, and histamine dihydrochloride 0.005 to 0.5 mg/ml) (n = 18). Duration of study treatment: 6 weeks pre-season, plus maintenance treatment during single allergy season Symptomatic medication permitted: Nasal and ocular cromoglycate, nasal beclomethasone, terfenadine, oral corticosteroids, inhaled salbutamol, and theophylline; used according to a pre-specified protocol and only when symptoms present Dates: Spring 1987 Location: Montpelier, France Setting: Allergy clinic Type(s) of providers: Allergists	Sex: 24 men Race: NR Other:	5) Skin reactivity 6) Allergen-specific IgE and IgG antibody levels	Low dose: 12.8 ± 16.8 Placebo: 54.8 ± 23.0 p < 0.001, high dose and low dose vs. placebo; p = NS, high dose vs. low dose 3) Use of symptomatic medication: Mean medication score (± SD) High dose: 38.6 ± 37.6 Low dose: 35.3 ± 44.5 Placebo: 66.4 ± 51.7 p < 0.05, low dose (and high dose? – table unclear) vs. placebo No p-value reported for high dose vs. low dose 4) Nasal reactivity: Not abstracted 5) Skin reactivity: Not abstracted 6) Allergen-specific IgE and IgG antibody levels: Not abstracted	experience or rhinitis experience, but number of subjects in these subgroups is not provided.

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Bousquet, Maasch, Hejjaoui, et al., 1989	Design: RCT, parallel-group Interventions: 1) Standardized and lyophilized orchard-grass pollen (*Dactylis glomerata*) extract (n = 18). Rush protocol used, with rapid increase in allergen dose; maintenance dose (3,000 BU) reached in 3 days. Four maintenance injections then given. Co-seasonal immuno-therapy (dose reduced by half) then given every 2 weeks from April 1 to October 1. Mean cumulative dose: 3678 ± 567 PNU. 2) Mixed-grass pollen unfractionated and lyophilized allergoid, prepared from pollens of 6 grasses (*Dactylis glomerate, Festuca elatior, Holcus lanatus, Lolium perenne, Poa pratensis,* and [sixth species?]) (n = 15). Injections of gradually increasing dose (50 to 2,000 PNU) given over 5 weeks (3 injections during week 1, 2 during week 2, 1 per week thereafter). Four maintenance injections (2,000 PNU) given before April 1st. Co-seasonal immunotherapy (dose reduced by half) given bimonthly from April 1 to October 1. Mean cumulative dose: 9,096 ± 6,304 PNU. 3) High-molecular-weight, formalinized and lyophilized mixed-grass pollen allergoid,	No. of subjects at start: 70 Dropouts/withdrawals: 0 No. of subjects at end: 70 Inclusion criteria: Rhinitis during grass-pollen season; positive prick test (to 1/100 wt/vol standardized extract) and IgE (at RAST class 3 to 4) indicating allergy to orchard grass pollen Exclusion criteria: Previous specific immunotherapy to grass pollens Age: Mean 25.2 ± 12.1 years (range, 12 to 46) Sex: NR Race: NR Other: Asthma 54% Conjunctivitis 67%	1) Adverse reactions 2) Patient-assessed symptom severity: rhinorrhea, sneezing, nasal obstruction, watery eyes, red eyes, pruritus, wheezing, and shortness of breath graded (twice?) daily during allergy season on scale of 0-5 (not described) 3) Use of symptomatic medication: recorded daily during allergy season; method of scoring not described 4) Skin reactivity 5) Specific IgG and IgE levels	1) Adverse reactions: Placebo 0 GOID 67% HMW-GOID 42% Std-ext 72% 2) Patient-assessed symptom severity: Symptom score: Placebo 63.5 ± 54.6 GOID 38.1 ± 27.4 HMW-GOID 20.4 ± 18.1 Std-ext 14.8 ± 22.9 Std-ext < Placebo (p < 0.001) HMW-GOID < Placebo (p < 0.001) HMW-GOID < GOID (p < 0.02) GOID vs Placebo (p = NS) Number of days of rhinitis symptoms: Placebo 26.5 ± 8.6 GOID 20.9 ± 10.0 HMW-GOID 9.15 ± 9.5 Std-ext 9.0 ± 10.7 Std-ext < Placebo (p < 0.001) HMW-GOID < Placebo (p < 0.001) Std-ext < GOID (p < 0.05) HMW-GOID < GOID (p < 0.05) GOID vs Placebo (p = NS) 3) Use of symptomatic medication (medication score): Placebo 53.7 ± 54.1 GOID 33.1 ± 41.0 HMW-GOID 30.5 ± 32.8 Std-ext 22.9 ± 39.1 Std-ext < Placebo (p < 0.01) 4) Skin reactivity: Not abstracted 5) Specific IgG and IgE levels: Not abstracted	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Not described Dropouts described: No Intention-to-treat: Can't determine Note: Group receiving standardized orchard-grass pollen extract not blinded.

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Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	prepared from pollens of the 6 grasses described above (n = 13). Protocol same as 2), above. Mean cumulative dose: 13,735 ± 6,355 PNU. 4) Placebo, with increasing doses of histamine dihydrochloride (n = 14) Duration of study treatment: 7 months Symptomatic medication permitted: For conjunctivitis, ocular cromoglycate, followed by H1 blocker, if necessary; for asthma, inhaled salbutamol (200-600 µg), plus theophylline, if necessary; patients asked to take drugs only if they had symptoms Dates: NR Location: Montpellier, France (Northern Mediterranean area) Setting: Allergy clinic Type(s) of providers: Allergists				

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Bruce, Norman, Rosenthal, et al., 1977	Design: RCT, parallel-group (matched-pairs design) Interventions: 1) Lyophilized aqueous extract of ragweed containing 10 µg AgE/ml or 3570 PNU/ml (n = 14). Weekly injections given from January through August of 1973 and 1974. Mean cumulative doses in terms of antigen E were 11.7 µg (4180 PNU) in 1973 and 31.2 µg (11,140 PNU) in 1974. 2) Placebo containing histamine (n = 18) Duration of study treatment: 2 years; injections given January through August of both years, symptoms monitored through ragweed pollen seasons (August to mid-October) of both years Symptomatic medication permitted: For hay fever, decongestants and chlorpheniramine; for asthma, aminophylline, steroids, ephedrine, and nebulized bronchodilators Dates: 9/72-3/73 Location: Baltimore, MD Setting: Academic allergy practice Type(s) of providers: Specialists	No. of subjects at start: 39 Dropouts/withdrawals: Unclear. Not specified at 1-year time point. No. of subjects at end: 32 patient data points at 1 year shown in Fig 2. 29 patients described as continuing thru second year. Inclusion criteria: Symptomatic asthma during ragweed season; positive skin test to ragweed Exclusion criteria: Perennial asthma; IT in previous 2 years Age: NR Sex: NR Race: NR Other:	1) Investigator-assessed severity of *asthma* symptoms 2) Investigator-assessed severity of *hay fever* symptoms 3) Patient-assessed severity of *asthma* symptoms and use of asthma medications (combined in a single measure): patients recorded following items twice daily during ragweed season (Aug to mid-Oct): duration of difficulty breathing and cough, number and duration of asthma attacks, amount of sputum produced, and asthma medication taken 4) Patient-assessed severity of *hay fever* symptoms and use of hay fever medications (combined in a single measure): patients recorded following items twice daily during ragweed season (Aug to mid-Oct): duration of sneezing, stuffy or runny nose, red itchy eyes, and hay fever medication taken 5) Bronchial reactivity 6) Leukocyte histamine release 7) IgE and IgG antibodies	1) Investigator-assessed severity of *asthma* symptoms: Not abstracted 2) Investigator-assessed severity of *hay fever* symptoms: Not abstracted 3) Patient-assessed severity of *asthma* symptoms and use of asthma medications (combined in a single measure): No significant difference. 4) Patient-assessed severity of *hay fever* symptoms and use of hay fever medications (combined in a single measure): No significant difference. 5) Bronchial reactivity: Not abstracted 6) Leukocyte histamine release: Not abstracted 7) Allergen-specific IgE and IgG blocking antibody: Not abstracted	Quality Scoring: Population similar: Not adequately described Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: No Intention-to-treat: No Notes:

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Brunet, Bédard, Lavoie, et al., 1992	Design: RCT, parallel-group Interventions: 1) Alum-precipitated ragweed extract (n = 13). Weekly injections given over 9 weeks in following doses: 50; 100; 200; 500; 1,000; 2,000; 3,000; 3,000; and 3,000 PNU. 2) Placebo (alum-precipitated human serum albumin, with histamine phosphate and caramelized glucose) (n = 14) Duration of study treatment: Injections given over 9 weeks during allergy preseason (May to July); outcomes assessed during one allergy season (mid-August to mid-September) Symptomatic medication permitted: Chlorpheniramine 4-mg tablets; pseudoephedrine 60-mg tablets; and naphazoline HCl, pheniramine maleate, eyedrops Dates: NR Location: Quebec, Canada Setting: University Type(s) of providers: Specialists	No. of subjects at start: 27 Dropouts/withdrawals: 0 No. of subjects at end: 27 Inclusion criteria: Ragweed allergic rhinitis without asthma; positive prick skin test and IgE antibody to ragweed Exclusion criteria: NR Age: 19-56 Sex: Active 10M/3F; placebo 8M/6F Race: NR Other: None had other serious disease or prior immunotherapy	1) Allergen-specific IgE and IgG antibody levels 2) Patient-assessed symptom severity: sneezing, itchy nose, rhinorrhea, nasal obstruction, lacrimation, and itchy eyes graded twice per day during allergy season on scale of 0 (none, no symptoms evident) to 3 (severe, disabling and/or interfering with daily activities and/or sleep) 3) Investigator-assessed symptom severity 4) Use of symptomatic medication: type and amount used recorded daily by patients in study diaries 5) Nasal reactivity 6) Allergen-induced basophil histamine release 7) Adverse reactions	1) Allergen-specific IgE and IgG antibody levels: Not abstracted 2) Patient-assessed symptom severity: Score: 4.7 ± 0.7 active vs. 7.5 ± 1.2 placebo; $p < 0.05$ 3) Investigator-assessed symptom severity: Not abstracted 4) Use of symptomatic medication: Score: 0.9 ± 0.2 active vs. 0.7 ± 0.2; $p = 0.6$ 5) Nasal reactivity: Not abstracted 6) Allergen-induced basophil histamine release: Not abstracted 7) Adverse reactions: Unspecified number of local reactions; one subject with late phase reaction of 8 cm associated with wheezing – continued in study	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Yes Notes:

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Cockcroft, Cuff, Tarlo, et al., 1977	Design: RCT, parallel-group (matched-pairs design) Interventions: 1) Glutaraldehyde-modified ragweed tyrosine adsorbate (MRTA) (n = 21). Four weekly injections given in doses of 300; 700; 2,000; and 4,000 NU per 0.5 ml. 2) Placebo (tyrosine base) (n = 22) Duration of study treatment: Injections given over 4 weeks in July; outcomes measured through one allergy season (end of September) Symptomatic medication permitted: Chlorpheniramine maleate 4-mg tablets; naphazoline-antazoline eyedrops (0.05 mg/ml and 0.5 mg/ml, respectively); beclomethasone dipropionate nasal aerosol (50 µg/spray); medrysone (1%) eyedrops; and prednisone 5-mg tablets. Used according to pre-defined protocol. Minimum dose required to control symptoms used. Dates: NR Location: Hamilton, Ontario, Canada Setting: University practice Type(s) of providers: Specialists	No. of subjects at start: 43 Dropouts/withdrawals: 1 withdrew from placebo group for reasons unrelated to the trial. 6 patients in active treatment group could not complete IT regimen but continued in trial (see AEs) No. of subjects at end: 42 Inclusion criteria: Moderate to severe allergic rhinitis during August/September; positive prick skin tests to ragweed Exclusion criteria: Positive prick skin test to mold Cladosporium and Alternaria Age: 29.9 active; 33.2 placebo Sex: 7M/14F active; 8M/14F placebo Race: NR Other: 7 active and 5 placebo patients had receive prior immunotherapy 7 active and 6 placebo patients with mild asthma	1) Patient-assessed symptom severity: sneezing, stuffy and/or runny nose, itchy eyes, and cough graded twice per day on scale of 0 (none) to 3 (lasted longer than 3 hours) 2) Use of symptomatic medication: types and doses used recorded daily by patients in study diaries 3) Patient global assessment of efficacy: patients asked at end of trial whether result of injections "very good" (minimal symptoms, minimal medication requirement), "good" (noticeably better than previous years), or "poor" (slight or no improvement) 4) Allergen-specific IgE and IgG antibody levels, eosinophil counts 5) Adverse reactions	1) Patient-assessed symptom severity: Symptom score (active vs. placebo) Sneezing 1.42 vs. 1.32 (ns) Rhinorrhea congestion 2.06 vs. 2.38 (ns) Eye 0.92 vs. 1.49 (ns) Cough 0.52 vs. 0.58 (ns) Total 4.95 vs. 5.75 (ns) 2) Use of symptomatic medication: Number subjects requiring (active vs. placebo): Chlorpheniramine 20 vs. 20 (ns) Beclomethasone 9 vs. 15 (ns) Eye drops 10 vs. 14 (ns) Medrysone eye drops 0 vs. 1 (ns) Prednisone 1 vs. 2 (ns) Mean daily consumption: Chlorpheniramine 0.77 vs. 0.96 (ns) Beclomethasone 1.01 vs. 2.10; $p < 0.05$ Eye drops 0.50 vs. 1.24 (ns) Total 2.29 vs. 4.37; $p < 0.05$ 3) Patient global assessment of efficacy: (active vs. placebo) Very good 5 vs. 3 Good 9 vs. 5 Poor 7 vs. 13 (ns) 4) Allergen-specific IgE and IgG antibody levels, eosinophil counts: Not abstracted 5) Adverse reactions: Late swelling > 10 cm resulted in stopping injections in 3 patients after second injection and after third injection in another 3. These subjects were followed in intention-to-treat manner.	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Yes Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Yes Notes:

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Corrado, Pastorello, Ollier, et al., 1989	Design: RCT, parallel-group Interventions: 1) Standardized extract of *Dermatophagoides pteronyssinus* (house dust mite) conjugated to alginate and containing known amounts of antigen P1 (Conjuvac®) (n = 22). Build-up phase: 11 weekly injections of doses increasing from 56 x 10^1 to 448 x 10^3 IU *D. pteronyssinus*. Maintenance phase: 15 monthly injections, each containing 448 x 10^3 IU *D. pteronyssinus.* 2) Placebo (lyophilized sodium alginate diluent ± 5 µg histamine dihydrochloride) (n = 29). Duration of study treatment: 18 months Symptomatic medication permitted: Beclomethasone dipropionate, xylometazoline, or sodium cromoglycate nasal sprays, and chlorpheniramine; patients "encouraged to reduce their medication as much as possible" Dates: 11/83-3/85 Location: Italy and UK Setting: 3 academic centers Type(s) of providers: Specialists	No. of subjects at start: 66 Dropouts/withdrawals: 15 (11 active, 3 placebo): 6 withdrawn for pregnancy, 4 with severe local reactions, 2 with late or generalized reactions, one for lack of benefit, and 2 lost to followup No. of subjects at end: 51 Inclusion criteria: Not specified, although all were determined to have *D. pter*. as "main cause of symptoms on basis of history and nasal provocation and skin prick testing. Exclusion criteria: Pregnancy; nasal polyps or other nasal deformity; proven sensitivity to animals and pets kept in home; systemic corticosteroid use Age: 17-55 (mean 29.5) Sex: 40 F Race: NR Other: 34/66 also had asthma	1) Nasal reactivity 2) Patient-assessed symptom severity (diary data): nasal blockage, sneezing, and rhinorrhea graded twice daily on a scale of 0-3 (not described) 3) Peak flow rates 4) Patient-assessed symptom severity (clinic visits): nasal blockage, sneezing, and rhinorrhea graded on 10-cm visual analog scale (running from "no symptoms" to "could not be worse") during clinic visits at baseline and after 5, 9, and 15 months of maintenance therapy 5) Use of symptomatic medication: recorded in daily study diaries and monitored via tablet counts and nasal spray canister weights 6) Adverse reactions: Prior to each injection, patients asked, "Did you notice anything unusual after the last injection?" Reported problems classified as local or systemic and early or late (> 30 min after injection)	1) Nasal reactivity: Not abstracted 2) Patient-assessed symptom severity (diary data): Last observation carried forward for dropouts. Questionable compliance with diary card collections. Significant difference (p = 0.028) for final diary recordings for AM score, but not PM score (p = 0.12). Actual data not given. 3) Peak flow rates: Not abstracted 4) Patient-assessed symptom severity (clinic visits): Not significant except for congestion subscore (p < 0.01). Data not given. 5) Use of symptomatic medication: No data given. Both groups used little medication at end of study. 6) Adverse reactions: No immediate systemic reactions. Immediate local reaction of < 5 cm in 29% A v 1% placebo, > 5 cm in 1% A and 0% placebo. Delayed systemic reactions in 3% active and 1% placebo. Local < 5 cm 12% v 2. Local > 5 cm 23% v 1%. No anaphylaxis.	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Yes Notes:

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Creticos, Reed, Norman, et al., 1996	Design: RCT, parallel-group Interventions: 1) Lyophilized extract of short-ragweed pollen, prepared by a professional lab (n = 37). Initial dose of 0.05 ml of a 1:10,000 dilution of extract (0.001 mg of Amb a 1) doubled every week until maximum tolerated dose or 0.5 ml of a 1:10 dilution (10 µg of Amb a 1) reached (19 weeks). Maintenance doses then administered every 2 weeks for 3 months and every 4 weeks thereafter. 2) Placebo (n = 40) Duration of study treatment: 2 years Symptomatic medication permitted: Rhinitis medication not described; asthma medications permitted and adjusted by investigators every 3 weeks during period in which diaries were kept Trial preceded by 4-month observation phase (July 1 through October 31) Dates: NR Location: Baltimore and Rochester, MN Setting: Academic centers Type(s) of providers: Specialists	No. of subjects at start: 90 randomized; 77 began treatment phase Dropouts/withdrawals: 13 dropouts between randomization and treatment. No reason given. 13 dropped out in year 1, 11 in year 2. 8 active group dropouts: 4 moved, 3 withdrew, 1 became pregnant 16 placebo dropouts: 3 moved, 11 withdrew, 1 had worsened asthma, 1 possible adverse reaction No. of subjects at end: 53 Inclusion criteria: Age 16-70; asthma for 1+ year with exacerbation during fall season requiring medication; positive skin test to ragweed with less reactivity to other possible confounding allergens; drop in FEV1 of 20% after methacholine inhalation of less than 25 mg/ml Treatment phase inclusions criteria: Worsened asthma symptom scores during ragweed season, worsening peak flow, and worsening medication scores, return 80% of symptom diaries Exclusion criteria: Asthma requiring 2+ hospitalizations in previous year; inability to wean from long-term oral steroids or cromolyn; sensitivity to animals on regular exposure; current smoking; IT in previous 3 years, or ragweed IT; systemic illness; pregnancy; inability to undergo	1) Peak flow rates 2) Use of asthma medication: recorded daily in study diaries from July 1 through October 31 each year 3) Patient-assessed severity of *asthma* symptoms: unspecified symptoms of asthma recorded twice daily and graded on scale of 0 (none) to 6 (incapacitating) from July 1 through October 31 each year 4) Patient-assessed severity of *rhinitis* symptoms: unspecified symptoms of rhinitis recorded twice daily and graded on scale of 0 (none) to 6 (incapacitating) from July 1 through October 31 each year 5) Bronchial reactivity (antigen and methacholine challenges) 6) Allergen-specific IgE and IgG antibodies 7) Skin reactivity 8) Adverse reactions	1) Peak flow rates: Not abstracted 2) Use of asthma medication: Score 19 active v 43 placebo in year 1 (p = 0.01), and 29 v 33 in year 2 (p = 0.7). 3) Patient-assessed severity of *asthma* symptoms: Not significant in year 1 or 2. Numbers not given. 4) Patient-assessed severity of *rhinitis* symptoms: Baseline: 4.1 A v 4.5 P Year 1: 3.5 A v 4.3 P (p = 0.1) Year 2: 3.1 A v 3.8 P (p = 0.04) 5) Bronchial reactivity: Not abstracted 6) Allergen-specific IgE and IgG antibodies: Not abstracted 7) Skin reactivity: Not abstracted 8) Adverse reactions: Year 1: 7 patients in active group had 14 systemic reactions. 5 were mild, 9 rhinitis, generalized urticaria, angioedema, or combination requiring antihistamine or epinephrine. 2 patients dropped out after several systemic reactions. 4 placebo patients had moderate reactions and received treatment. One patient in placebo group received active treatment by mistake and had severe reaction with bronchospasm and hypotension. Recovered.	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Can't determine Notes:

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Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
		diagnostic tests Age: Mean 36.0 A v 35.1 P Sex: Active 18 F; placebo 20 F Race: NR Other:			
Cvitanovic, Zekan, Capkun, et al., 1994	Design: RCT, parallel-group Interventions: 1) Partially purified, characterized, and standardized pollen extract of *Parietaria officinalis* (alum-absorbed depot preparation) (n = 40). Increasing doses administered weekly until the appearance of a local reaction, then decreased and slowly increased until a new local reaction occurred; "after some time," injections given on biweekly basis. Injections given pre-seasonally, from beginning of November to mid-March. 2) Oral ketotifen 1 mg twice per day from March 15 to end of June (n = 35) Duration of study treatment: 3 years Symptomatic medication permitted, but not described Dates: NR Location: Split, Croatia	No. of subjects at start: 90 Dropouts/withdrawals: 10/50 active: 6 for incomplete evaluation and 4 for anaphylaxis to IT 5/40 study medication: cause not listed No. of subjects at end: 40 active; 35 drug Inclusion criteria: 2-year history of seasonal rhinoconjunctivitis; positive skin test and specific IgE antibody to *P. officinalis* Exclusion criteria: NR Age: Active (after dropouts) 19-45 years Ketotifen (after dropouts) 18-35 years Sex: Active 20M/20F; Ketotifen 17M/18F Race: NR Other: All subjects were non-allergic, but testing regimen not described. No prior corticosteroids or immiunotherapy.	1) Adverse reactions 2) Allergen-specific IgE and IgG antibody levels 3) Histamine serum concentration 4) Skin reactivity 5) Eosinophil levels 6) Patient-assessed symptom severity: nasal secretion, congestion, itching, and sneezing graded daily on scale of 0 (no symptoms) to 3 (severe symptoms) 7) Use of symptomatic medication: graded daily on scale of 0-3 (as above), with 1 point given for each dose of symptomatic medication	1) Adverse reactions: Active: 4 anaphylaxis in active group. 15 patients with reduced IT dose because of local reactions or rhinorrhea. 2) Allergen-specific IgE and IgG antibody levels: Not abstracted 3) Histamine serum concentration: Not abstracted 4) Skin reactivity: Not abstracted 5) Eosinophil levels: Not abstracted 6) Patient-assessed symptom severity: Score (active vs. ketotifen) Year 1 12.2 ± 5.0 vs. 22.2 + 7.6 Year 2 9.3 ± 3.5 vs. 15.8 ± 4.3 Year 3 8.1 ± 1.2 vs. 12.3 ± 3.1 7) Use of symptomatic medication: Score (active vs. ketotifen) Year 1 5.6 ± 2.3 vs. 15.5 ± 2.8 Year 2 5.9 ± 1.2 vs. 11.2 ± 3.0 Year 3 3.8 ± 1.0 vs. 12.1 ± 2.6	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: No Dropouts described: Yes Intention-to-treat: No Notes: 15 of 40 patients failed to achieve maintenance dose because of local reactions. IT dosing not standardized. Presumably not blinded.

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Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Setting: University practice Type(s) of providers: Specialists	Antihistamines stopped 1 month before study.			
Dolz, Martínez-Cócera, Bartolomé, et al., 1996	Design: RCT, parallel-group Interventions: 1) Aluminum hydroxide-adsorbed grass-pollen extract containing allergens PDL *(Phleum, Dactylis, Lolium)* (Alutard® SQ) (n = 18). Rush protocol followed using aqueous extract. Doses ranging from 0.1 ml x 100 USQ/ml to 1.0 ml x 100,000 USQ/ml given over 4 days. Depot extract used after maximum dose of aqueous extract reached; repeated every 4 weeks until end of study. Regime modified if any adverse reaction occurred. 2) Placebo (0.01 mg histamine hydrochloride and 0.4 mg human serum albumin) (n = 10). Duration of study treatment: 3 years Symptomatic medication permitted: Cromoglycate, oral antihistamines, inhaled bronchodilators, and inhaled corticoids Dates: 1990-1992 Location: Madrid, Spain Setting: Allergy clinic	No. of subjects at start: 30 Dropouts/withdrawals: 2 excluded (1 due to initiation of beta-blocker treatment; 1 for personal reasons) No. of subjects at end: 28 Inclusion criteria: Allergy to grass pollen by history, skin test, conjunctival provocation test, and positive specific IgE Exclusion criteria: Previous immunotherapy; sensitization to other pollens or aeroallergens Age: Mean 19.4 (range 15 to 35) Sex: NR Race: NR Other: Asthma: 21%	1) Skin reactivity 2) Conjunctival reactivity 3) Bronchial reactivity 4) Total IgE and allergen-specific IgE, IgG, and IgG4 5) Adverse reactions 6) Patient-assessed symptom severity: nasal symptoms (itching, sneezing, rhinorrhea, and obstruction), ocular symptoms (itching, reddening, photophobia, and sensation of foreign body), and bronchial symptoms (pharyngeal and palatal itching, persistent coughing, dyspnea, and wheezing) graded daily during pollen season an a scale of 0 (no symptoms) to 3 (severe) 7) Use of symptomatic medication: graded daily during pollen season, as follows: Cromoglycate: 1 Oral antihistamines: 2 Inhaled bronchodilators: 3 Inhaled corticoids: 4	1) Skin reactivity: Not abstracted 2) Conjunctival reactivity: Not abstracted 3) Bronchial reactivity: Not abstracted 4) Total IgE and allergen-specific IgE, IgG, and IgG4: Not abstracted 5) Adverse reactions: Local 4 Systemic 7 6) Patient-assessed symptom severity: Results presented in graph only (cannot be interpolated, because daily scores are not aggregated to a single parameter) Nasal symptoms significantly improved compared to placebo in 2nd and 3rd year ($p < 0.001$) 7) Use of symptomatic medication: Results presented in graph only (cannot be interpolated, because daily scores are not aggregated to a single parameter) Medication score significantly improved compared to placebo in 2nd and 3rd year ($p < 0.01$)	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Not described Dropouts described: Yes Intention-to-treat: No Notes: Duration of follow-up longer than most. Absence of statistically significant benefit during first year suggests early benefit of rush IT.

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Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Type(s) of providers: Allergists				
Dorward, Waclawski, and Kerr, 1984	Design: RCT, parallel-group Interventions: 1) Alum-precipitated five-grass extract (Allpyral®) (n = 18). Five grasses: timothy, rye, cocksfoot, Yorkshire for, and meadow grass. Nine weekly injections starting with a dose of 20 PNU and rising to 4,000 PNU. Dose reduced in event of severe local reaction. Injections completed 2-4 weeks before start of pollen season. No maintenance injections given. 2) Two-grass conjugated extract (Conjuvac®) (n = 21). Two grasses: timothy and cocksfoot. Eleven weekly injections rising from 1 AUR (activity units by RAST) to 800 AUR. Dose reduced in event of severe local reaction. Injections completed 2-4 weeks before start of pollen season. No maintenance injections given. Duration of study treatment: Injections given over 9-11 weeks during allergy pre-season; outcomes assessed during single pollen season (mid-May to end of July) Symptomatic medication permitted: oral antihistamines	No. of subjects at start: 39 Dropouts/withdrawals: 1 discontinued due to adverse reaction; 10 failed to completed diary cards; 4 did not have antibody levels for before and after treatment No. of subjects at end: 25 (could be analyzed for both antibody results and diary scores) Inclusion criteria: Seasonal pollen rhinitis for at least 2 years; attending allergy clinic; positive skin-prick tests to pollen extract Exclusion criteria: None stated Age: 23.6 (range 8 to 52) Sex: NR Race: NR Other: 22 patients had had immunotherapy in the past	1) Adverse reactions 2) Patient-assessed symptom severity: itching eyes, swelling of eyes, watery eyes, sneezing, nasal blockage, runny nose, and wheezing graded daily on scale of 1 (mild) to 3 (severe) 3) Total IgE and allergen-specific IgE and IgG antibody levels 4) Patient global evaluation of efficacy: number of patients who thought that treatment had improved their symptoms 5) Patient satisfaction: number of patients who would repeat the same treatment again next year 6) Use of symptomatic medication: Number of patients requiring antihistamine treatment to control symptoms during the pollen season	1) Adverse reactions: Severe local requiring d/c treatment (Conjuvac) n = 1 Local Minor 10 Conjuvac; 9 Allpyral Frequent 0 Conjuvac; 2 Allpyral Severe 9 Conjuvac; 4 Allpyral Systemic Wheeze 1 Conjuvac; 2 Allpyral Rhinitis 1 Conjuvac; 0 Allpyral Requiring d/c treatment 1 conjuvac; 0 Allypyral 2) Patient-assessed symptom severity: Allpyral significantly higher than Conjuvac (1.31 ± 0.29 versus 0.81 ± 0.18; $p < 0.05$) 3) Total IgE and allergen-specific IgE and IgG antibody levels: Not abstracted 4) Patient global evaluation of efficacy: Allypyral 12/18 cases Conjuvac 16/18 cases 5) Patient satisfaction: Allypyral 15/18 Conjuvac 17/18 6) Use of symptomatic medication: Allpyral 4/18 Conjuvac 3/18	Quality Scoring: Population similar: Yes Intervention(s) described: No Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: No (alternate allocation) Double-blind: No Blinding adequate: Not applicable Dropouts described: Yes Intention-to-treat: No Notes:

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Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Dates: Spring/summer 1982 Location: Glasgow, Scotland Setting: Allergy clinic Type(s) of providers: Allergists				
D'Souza, Pepys, Wells, et al., 1973	Design: RCT, parallel-group Interventions: 1) Extract of *Dermatophagoides pteronyssinus* (house dust mite) prepared by professional laboratory (n = 45). A 1-g sample of mites and mite excreta, separated from the culture medium, was extracted in 100 ml of glycerinated extraction fluid to make a 1% extract. Three concentrations of vaccine made (0.005%, 0.04%, and 0.33%). Build-up phase: increasing injections of 0.1, 0.2, 0.4, and 0.8 ml given weekly from each vial in order, starting with the lowest concentration (0.005%). Dose repeated or reduced in event of adverse reactions. Treatment stopped after 12 injections (3 months), regardless of whether top dose reached or not. 2) Placebo (carbol saline solution) (n = 46) Patients in both groups were advised to vacuum their mattresses and pillows, damp-dust their bedrooms, and	No. of subjects at start: 96 Dropouts/withdrawals: 5 (2 placebo, 3 active); 2 failed to return after 12 injections, 2 dropped out without reason given, 1 mild asthmatic reaction and was excluded No. of subjects at end: 91 Inclusion criteria: Positive skin test to *D. pter.;* history of symptoms induced by house dust or positive nasal challenge with *D. pter.* Exclusion criteria: Steroid therapy within previous 3 months; house dust IT within 3 years Age: 10-41+ Sex: 16 F/46 placebo, 21 F/45 active Race: NR Other: 10 subjects in each group previously received house dust IT	1) Adverse reactions: As observed by investigators and recorded by patients in study diaries 2) Patient global assessment of efficacy: following parameters graded as "improved" (very much, moderately, or slightly), "not changed," or "worse" (slightly, moderately, or very much) at 1 and 3 months: Asthma Rhinitis Exercise tolerance Dust tolerance (3 months only) Time off work Drug use (3 months only) Overall assessment 3) Nasal reactivity 4) Skin reactivity 5) Patient-assessed symptom severity: wheeze, rhinitis, and night asthma graded daily on scale of 0-3 6) Use of permitted symptomatic medication:	1) Adverse reactions: Active: Local reaction in 34 patients 18 patients mild asthma and/or rhinitis 4 short term generalized urticaria 3 fainting and dizziness Placebo: 2 discontinued treatment because of mild asthma 2) Patient global assessment of efficacy: At 1 and 3 months, 91 patients assessed. No difference at 1 month in any parameter. Results at 3 mo. (%) (active v plac): Asthma improved: 33 v 62.5 p = 0.02 Rhinitis improved: 29 v 22 NS Exercise tolerance better: 35 v 19 NS Dust tolerance better: 55 v 30 p = 0.05 Time off work less: 25 v 14 NS Drug use less: 43 v 19 p = 0.05 Overall very much better: 35 v 19 NS 3) Nasal reactivity: Not abstracted 4) Skin reactivity: Not abstracted 5) Patient-assessed symptom severity: Adequate data for 70 patients. No difference between groups with both groups improving. 6) Use of permitted symptomatic medication:	Quality Scoring: Population similar: No Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Notes: *(continued on next page)*

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	wash their blankets every 6-8 weeks, and to exclude feathers from their beds. Duration of study treatment: 3 months Symptomatic medication permitted: Antihistamines, Mogadon®, isoprenaline inhaler, Ventolin® inhaler, and Intal® Dates: NR Location: London Setting: Academic unit Type(s) of providers: Specialists		recorded daily in study diaries 7) Total IgE, and allergen-specific IgE and IgG antibody levels 8) Lymphocyte transformation and leucocyte inhibition 9) Histamine release	No difference. 7) Total IgE, and allergen-specific IgE and IgG antibody levels: Not abstracted 8) Lymphocyte transformation and leucocyte inhibition: Not abstracted 9) Histamine release: Not abstracted	
Durham, Walker, Varga, et al., 1999	Design: RCT, parallel-group Interventions: All patients had received 3-4 years of active immuno-therapy as described by Varney, Gaga, Frew, et al., 1991 and Durham, Varney, Gaga, et al., 1991, below. At start of this phase of the trial, all were randomized to one of following: 1) Continued maintenance immunotherapy (n = 16). Monthly injections of a standardized, aluminum hydroxide-adsorbed grass pollen extract (Alutard®), each containing 100,000 SQ units. Dose reduced by 40% during pollen season.	No. of subjects at start: 32 Dropouts/withdrawals: 5 No. of subjec ts at end: 27 Inclusion criteria: Participation in IT group of previous RCT of IT for allergic rhinitis for timothy grass pollen allergy Exclusion criteria: None specified Age: Median 40 Sex: 19 men, 13 women Race: NR Other:	1) Patient-assessed symptom severity (daily diary): breathlessness, coughing, wheezing, chest tightness, sneezing, blocked nose, running nose, itching eyes, red eyes, streaming eyes, swollen eyes, and itching and dryness of mouth and throat graded daily from May through September on visual analog scale of 0 (no symptoms) to 3 (severe symptoms) 2) Use of symptomatic medication: scored daily from April to October as follows: Each eye drop, nasal spray, or albuterol	1) Patient-assessed symptom severity (daily diary): No differences Nose symptoms: Year Difference b/w Maint & d/c 1993 -74 (-325 to 266) 1994 67 (-287 to 490) 1995 -5 (-462 to 462) p = NS 2) Use of symptomatic medication: No differences Year Difference b/w Maint & d/c 1993 54 (-724 to 2009) 1994 4 (-1064 to 2121) 1995 11 (-689 to 1488) p = NS 3) Patient-assessed symptom severity (every 2 weeks): No differences Year Difference b/w Maint & d/c	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Notes: Randomized patient population same as in Varney, Gaga, Frew, *(continued on next page)*

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	2) Placebo maintenance immunotherapy (diluent plus 0.01 mg of histamine per ml) (n = 16) Duration of study treatment: 3 years Symptomatic medication permitted: Cromolyn sodium eye drops and nasal spray, acrivastine, and albuterol; 7-day course of prednisolone could be given, if necessary Dates: 1992-1995 Location: London, UK Setting: Allergy clinic Type(s) of providers: Allergists		inhalation: 1 Each acrivastine or prednisolone: 2 3) Patient-assessed symptom severity (every 2 weeks): During pollen season, patients asked to grade their overall symptoms every 2 weeks on a visual analog scale from 0 (minimal symptoms) to 10 (maximal symptoms) in response to question, "How has your hay fever been during the past week?" 4) Conjunctival reactivity 5) Skin reactivity 6) CD3 and T cells, and interleukin-4 mRNA 7) Adverse reactions	1993 -1 (-2.6 to 0.3) 1994 0 (-3 to 3.1) 1995 0.2 (-1.9 to 1.6) p = NS 4) Conjunctival reactivity: Not abstracted 5) Skin reactivity: Not abstracted 6) CD3 and T cells, and interleukin-4 mRNA: Not abstracted 7) Adverse reactions: No substantial immediate or late systemic reactions were observed Less than 2% of injections resulted in early or delayed local reactions.	et al., 1991 and Durham, Varney, Gaga, et al., 1991, below. Paper also described 15 matched natural-history controls who had never received immunotherapy and were not randomized to treatment in this trial. Only trial examining effect of discontinuing maintenance treatment.

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Eriksson, Ahlstedt, and Lövhagen, 1979	Design: RCT, parallel-group Interventions: 1) Birch, alder, and hazel allergen extract (Allpyral®) (n = 17). Injections given once a week until highest tolerated dose or maximum dose of 4,000 PNU reached; this dose then given as a maintenance dose every 6-8 weeks. 2) Allpyral® (as above) plus other aqueous tree pollen extracts, as identified by nasal provocation tests using other tree pollens (n = 16). Aqueous allergen extracts given twice a week in increasing doses until highest tolerated dose reached; this dose then administered every 4 weeks. 3) No immunotherapy (n = 14) Patients in groups 1) and 2) who were also allergic to grass and/or compositae pollen were given immunotherapy with those allergens as well. Duration of study treatment: 3 years ("as a rule") Symptomatic medication permitted: antihistamine tablets (brompheniramine 40 mg + phenylpropanololamine 167 mg) for mild symptoms and prednisolone 5 mg if symptoms intolerable in spite	No. of subjects at start: 47 Dropouts/withdrawals: Not specified, but analysis based on smaller number of patients than originally treated. No. of subjects at end: Estimated at 46 Inclusion criteria: Adult hay fever patients with positive nasal provocation test to birch pollen Exclusion criteria: NR Age: Group 1 (15-46) Group 2 (15-33) Group 3 (14-45) Sex: Group 1 8M/9F Group 2 8M/8F Group 3 7M/7F Race: NR Other:	1) Nasal reactivity 2) Patient-assessed symptom severity and use of symptomatic medication (combined in a single measure): sneezing, rhinorrhea, and eye symptoms graded daily during pollen season in year 1 on scale of 0 (no symptoms) to 3 (severe symptoms); number of antihistamine and prednisolone tablets taken also scored from 0 to 3 3) Patient global evaluation of treatment efficacy: at end of pollen season in year 1, patients asked to grade their symptoms relative to previous year's symptoms on scale of 0 (no symptoms) to 4 (worse) 4) IgE and non-IgE antibody levels (against birch and beech allergens) 5) Allergen-induced histamine release	1) Nasal reactivity: Not abstracted 2) Patient-assessed symptom severity and use of symptomatic medication (combined in a single measure): Data presented as graph with score vs. time. Values for medication significant $p < 0.01$ and symptoms scores $p < 0.05$. 3) Patient global evaluation of treatment efficacy: Less troublesome symptoms: Group 1 83% Group 2 93% Group 3 64% all ns 4) IgE and non-IgE antibody levels (against birch and beech allergens) : Not abstracted 5) Allergen-induced histamine release: Not abstracted	Quality Scoring: Population similar: Not adequately described Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: No Blinding adequate: Not applicable Dropouts described: No Intention-to-treat: No Note: Not blinded

(continued on next page)

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	of treatment with antihistamine Dates: Treatment preceded 1974 pollen season Location: Sweden Setting: University clinic Type(s) of providers: Specialists				
Ewan, Alexander, Snape, et al., 1988	Design: RCT, parallel-group Interventions: 1) Standardized, partially purified, freeze-dried extract of *Dermatophagoides pteronyssinus* (house dust mite) (Pharmalgen®) (n = 16). Modified "semi-rush" technique used. Injections given at 1- to 2-week intervals, using aqueous extracts in gradually increasing concen-trations. Initial dose was 70 BU (20 + 50); planned top dose was 100,000 BU. Dose increased until a reaction occurred, then reduced and slowly increased again until a second phase of reaction encountered. Dose just below this (maximum tolerated dose) then used for maintenance injections, in depot diluent, which were given monthly for remainder of 3-month period. 2) Placebo extract (contained histamine) (n = 20). Also given in gradually increasing doses.	No. of subjects at start: 38 Dropouts/withdrawals: NR. However, before and after skin test data provided on only 34 patients No. of subjects at end: NR Inclusion criteria: Perennial rhinitis ± asthma; history suggesting allergy to *D. pter*. and no other active perennial allergy Exclusion criteria: IT within last 3 years; systemic corticosteroids within last 1 year Age: 16-55 Sex: 17 F Race: NR Other: Assessment made after 3 months of treatment. All had positive skin test response, positive nasal challenge, and serum IgE antibodies to *D. pter.*	1) Skin reactivity 2) Nasal reactivity 3) Patient-assessed symptom severity: (unspecified) nasal symptoms graded 1 month before treatment and 3 months after start of treatment on visual analog scale (10-cm line, with "no symptoms" at 0 cm, "minimal symptoms" at 1 cm, "slight symptoms" at 4 cm, "moderate symptoms" at 7 cm, and "severe symptoms" at 10 cm) 4) Allergen-specific IgE antibody levels 5) Adverse reactions	1) Skin reactivity: Not abstracted 2) Nasal reactivity: Not abstracted 3) Patient-assessed symptom severity: VAS symptoms: Active: 66.8 to 28.8 Placebo: 50.2 to 39.3 Drop in active group significantly greater than in placebo group ($p < 0.01$). 4) Allergen-specific IgE levels: Not abstracted 5) Adverse reactions: 31 generalized reactions (15% of injections) in active group. 8 were serious or potentially serious and classified as anaphylaxis. Patients responded to epinephrine. Some patients received oxygen, nebulized b-agonists and parenteral steroids. 7 had asthma exacerbation, 5 asthma/uricaria, 3 rhinitis exacerbation, 5 erythema or pruritis, 3 erythema with "other" symptoms. All were early reactions. 13 generalized reactions (5% of injections) in placebo group. All were mild: 10 with generalized pruritis and	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: No Intention-to-treat: No Notes: Article reports interim (3-month) results of trial scheduled to last 1 year. No daily symptom data analyzed. Potentially significant differences in baseline symptom scores may influence result if there was a "floor" effect on reduction of symptoms. *(continued on next page)*

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Duration of study treatment: 3 months (see Notes) Symptomatic medication permitted: Beclomethasone nasal spray or short-acting antihistamines (chlor-pheniramine or terfenadine) Dates: NR Location: London Setting: Hospital-based allergy department Type(s) of providers: Specialists			erythema, 2 with rhinitis, 1 with asthma. Localized reactions in 6% of active group (induration) and mild flare in 3% and 2% of active and placebo group respectively.	
Gabriel, Ng, Allan, et al., 1977	Design: RCT, parallel-group Interventions: 1) Extract of *Dermato-phagoides pteronyssinus* (house dust mite) made up in four concentrations in a solution of 50% aqueous glycerine containing 0.5% phenol (n = 37). Vaccines prepared in concentrations of 0.0004% (for children under 12 only), 0.003%, 0.025% and 0.20%. Build-up phase: weekly injections of gradually increasing doses, with variations according to age; children aged 8-11 could complete course in 22 weeks, older children in 19 weeks, and adults in 18 weeks. Maintenance phase: monthly injections of highest concentration (1 ml of 0.20% vaccine).	No. of subjects at start: 72 Dropouts/withdrawals: 3 excluded because of lack of symptom, and 3 "defaulted" during weekly course leaving 66 patients for initial evaluation (33A, 33P). 16 pts. excluded from maintenance course (10A, 6P). 7 defaulted or left country (3A, 4P), 6 enrolled late did not complete monthly course (5A, 1P), 3 withdrawn (2A, 1P) for moderately severe reactions. No. of subjects at end: 50 (23A, 27P). Inclusion criteria: Chinese; age ≥ 8; history of seasonal or perenial rhinitis for 3+ consecutive years, characterized by sneeze, nasal obstruction and discharge, ± asthma; positive skin test to *D. pter.;* positive nasal challenge to	1) Patient-assessed symptom severity: sneezing, nasal obstruction, nasal discharge, and asthma graded daily on 4-point scale (none, mild, moderate, severe) 2) Investigator-assessed symptom severity 3) Skin reactivity 4) Nasal reactivity 5) Allergen-specific IgE and IgG antibody levels 6) Eosinophil counts 7) Adverse reactions	1) Patient-assessed symptom severity: Symptom Improvement after weekly course-% of pts. improved (Active v Placebo) Sneezing 50 v 32 NS Obstruction 24 v 24 NS Discharge 32 v 31 NS All symptoms 27 v 21 NS Symptom imrovement after 12 month maintenance course-% pts. improved (Active v Placebo) Sneezing 55 v 36 Obstruction 69 v 18 Discharge 75 v 43 All symptoms 55 v 19 (p = 0.02) 2) Investigator-assessed symptom severity: Not abstracted 3) Skin reactivity: Not abstracted 4) Nasal reactivity: Not abstracted 5) Allergen-specific IgE and IgG levels:	Quality Scoring: Population similar: No Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Notes: *(continued on next page)*

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	2) Placebo vaccine (saline only) (n = 35) Duration of study treatment: 1 year No description of symptomatic medication permitted (if any) Dates: 5/73-3/74 Location: Hong Kong Setting: Hospital-based chest clinic Type(s) of providers: Specialists	*D. pter.* Exclusion criteria: Current use of corticosteroids or nasal cromoglycate Age: 11 patients under age 12 Sex: 34 F Race: 100% Asian Other: 22 subjects in each group reported a history of asthma symptoms. Only 6/66 monosensitized to *D. pter.*		Not abstracted 6) Eosinophil counts: Not abstracted 7) Adverse reactions: Weekly course: One or more reactions in 91% of active group and 33% of placebo group. Average 9.2/pt active and 0.9/pt placebo. Breakdown by group % (active v placebo) Cutaneous local 91 v 33 Cutaneous general 6 v 3 Rhinitis 9 v 6 Wheezing/asthma 6 v 6 Anaphylaxis 3 v 0 Other 9 v 9 (not specified) Maintenance course: 95% of active group and 11% of placebo group. 7.2/pt active and 0.1/pt placebo. Breakdown by group % (active v placebo) Cutaneous local 96 v 11 Cutaneous general 0 v 0 Asthma 12 v 0	

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Grammer, Shaughnessy, Bernhard, et al., 1987	Design: RCT, parallel-group (matched-pairs design) Interventions: 1) Polymerized ragweed (PRW) prepared by a professional lab (n = 35). Short and giant ragweed pollens extracted, precipitated, and fractionated, then polymerized with glutaraldehyde. Injections given weekly for 15 weeks. AU and PNU delivered gradually increased from 2.5 to 62.5 and from 30 to 746, respectively, over the course of the first 5 injections. The last 10 injections were of a constant dose (125 AU, 1492 PNU). Cumulative totals were 1359 AU and 16,218 PNU. 2) Placebo (carmelized glucose and histamine phosphate, 20 µg/ml) (n = 35). Identical to active treatment in terms of volume injected. Duration of study treatment: Treatment lasted 15 weeks; outcomes assessed for 6 months Symptomatic medication permitted: Not described Dates: 1985 ragweed season Location: Chicago, IL Setting: University allergy practice	No. of subjects at start: 81 subjects who ultimately formed 35 pairs (no discussion of 11 unpaired subjects) Dropouts/withdrawals: 15 pairs (5 pairs lost to followup) No. of subjects at end: 10 "new" pairs formed under blinded status. Presumably 30 pairs were analyzed at end. Inclusion criteria: History compatible with AR caused by ragweed for previous 2+ years; positive skin test to ragweed; no IT for 3 years prior; healthy by H,x, PE and lab evaluation Exclusion criteria: None specified Age: 21-60 Sex: NR Race: NR Other: 12 patients with mild asthma	1) Adverse reactions: Recorded during clinic visits and by patients on reporting forms at specified intervals up to 48 hours after each injection; also reported to treatment nurse before next injection 2) Laboratory studies (urinalysis, CBC, etc.) 3) Total serum AgE-binding capacity and AgE binding by IgE 4) Patient-assessed symptom severity and medication use (combined in a single measure): nasal congestion, nasal discharge, sneezing, ocular pruritus, cough, and wheeze graded 3 times daily during pollen season on scale of 0-3 (not described); use of symptomatic medication recorded in study diaries daily during pollen season	1) Adverse reactions: 19/37 placebo pt with immediate local reaction (51%). 26 of 36 active group patients with immediate local reaction (72%). No systemic allergic reactions in either group. 2) Laboratory studies: Not abstracted 3) Total serum AgE-binding capacity and AgE binding by IgE: Not abstracted 4) Patient-assessed symptom severity and medication use (combined in a single measure): Absolute values not given, but scores significantly favored active treatment at all time points from week 1 until week 5. Week 1 p = 0.008 Week 2 p = 0.035 Week 3 p = 0.013 Week 4 p = 0.004 Week 5 p = 0.05 Primary season (Week 2-4) p = 0.005 Secondary season (Week 1-5) p = 0.02 Results obtained from 68 patients. No data on other patients.	Quality Scoring: Population similar: Not adequately described Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: No Intention-to-treat: No Notes:

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Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Type(s) of providers: Specialists				
Grammer, Shaughnessy, Shaughnessy, et al., 1987	Design: RCT, parallel-group Interventions: 1) Polymerized ragweed (PRW) (n = 19). 15 weekly injections supplying 50,000 PNU of ragweed, equivalent to 1200 µg antigen E. No further details provided. 2) Placebo (carmelized glucose and histamine) (n = 19) 3) No treatment (n = 19) Duration of study treatment: Treatment lasted 15 weeks; outcomes assessed through ragweed pollen season (1st week in August through 1st week in October) Symptomatic medication permitted: Antihistamines and decongestants; patients with asthma permitted to continue with their regular asthma meds Dates: NR Location: Chicago, IL Setting: Univ allergy practice Type(s) of providers: Specialists	No. of subjects at start: 57 Dropouts/withdrawals: NR No. of subjects at end: NR, but only 50 of 57 patients reported clinical response data Inclusion criteria: Symptoms of allergic rhinitis during ragweed season Exclusion criteria: None specified Age (means): Untreated no asthma 29 Untreated asthma 33 Treated no asthma 32 Untreated asthma 34 Sex: 14 F Race: NR Other: 23 patients had diagnosis of asthma at enrollment.	1) Patient-assessed symptom severity and medication use (combined in a single measure): nasal congestion and sneezing graded 3 times daily during pollen season on scale of 0-3 (not described); number of antihistamine or decongestant tablets taken recorded in study diaries daily during pollen season 2) Total serum AgE-binding capacity and AgE binding by IgE	1) Patient-assessed symptom severity and medication use (combined in a single measure): 50 of 57 patients completed diary. Allocation across groups not given. Primary outcome was a comparison of cumulative symptom score in treated and untreated asthmatics and treated and untreated non asthmatics. Treated asthmatics had significantly lower scores (p = 0.01) and treated non-asthmatics had significantly lower scores (p = 0.04). 3) Total serum AgE-binding capacity and AgE binding by IgE: Not abstracted	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: No Dropouts described: No Intention-to-treat: No Notes: Initially 3 groups were defined: treated, placebo and untreated. Analysis was performed on combination of placebo and untreated group. Not possible to determine if treatment group improved from baseline. All we can determine is that cumulative score was lower.

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Grammer, Shaughnessy, Suszko, et al., 1983	Design: RCT, parallel-group Interventions: 1) Multiple (either five or six) grass-pollen polymer mixtures (n = 10). Treatment started in February. 12 weekly injections given, ranging in dose from 90 PNU (week 1) to 7200 PNU (weeks 8-12). Dose repeated in event of large local reaction (in which case additional injections given to reach target total dose, approximately 48,000 PNU). 2) Placebo (caramelized glucose histamine) (n = 13) Duration of study treatment: Injections given over 12 weeks (Feb-Apr); outcomes assessed through pollen season (early July) Symptomatic medication permitted: Not specified, but implied that antihistamines could be taken Dates: Feb-Jul 1982 Location: Chicago, IL Setting: Allergy clinic Type(s) of providers: Allergists	No. of subjects at start: 26 Dropouts/withdrawals: 3 No. of subjects at end: 23 Inclusion criteria: History typical of grass pollinosis; 4+ prick test to at least 1 grass pollen extract (1/20 wt/vol) of rye, timothy, redtop, June, orchard or Bermuda (ALO, Columbus, OH) Exclusion criteria: Immunotherapy within 5 years; abnormal ESR, CBC, UA Age: Range 21 to 65 years Sex: NR Race: NR Other:	1) Adverse reactions 2) Immunologic studies (total serum antibody against rye grass group I [RGGI], IgE against RGGI) 3) Patient-assessed symptom severity and medication use (combined in a single measure): symptoms (e.g., sneezing, nasal discharge, pruritus, cough) graded 3 times per day during pollen season (May - early July) on scale of 0-3 (not described); names of medication and numbers of pills taken also recorded 4) Patient global evaluation of efficacy of treatment: patients asked whether or not their symptoms were significantly improved (yes/no) 5) Lab tests (CBC with differential leukocyte count, erythrocyte sedimentation rate, urinalysis)	1) Adverse reactions: IT 2/10 pts had at least 1 immediate local reaction (erythema and induration); 1/10 had erythema alone; 1/10 had large late local reaction; no systemic reactions Placebo: 2/13 had at least one immediate local reaction; 3/13 had erythema alone; 1/13 had large local reaction 2) Immunologic studies: Not abstracted 3) Patient-assessed symptom severity and medication use (combined in a single measure): IT significantly lower than placebo (p = 0.02) (Fig. 5 interpolated figures IT 210 ± 75 [mean ± SEM]; placebo 500 ± 115) 4) Patient global evaluation of efficacy of treatment: IT 9/10 improved Placebo 3/13 improved P < 0.01 5) Lab tests: Not abstracted	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Notes:

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Grammer, Zeiss, Suszko, et al., 1982	Design: RCT, parallel-group Interventions: 1) Polymerized ragweed (PRW) (n = 21). 15 weekly injections given. Doses for injections 1-5 were as follows (PNU per injection): 125; 312; 625; 1,250; 3,125. Dose for injections 6-15 was 6,250 PNU. Total dose approximately 50,000 PNU of ragweed, equivalent to 1,200 µg antigen E. Schedule modified in event of large local reaction. 2) Placebo (carmelized glucose and histamine) (n = 19) 3) No treatment (n = 15) Duration of study treatment: Injections given over 15 weeks; outcomes measured during one allergy season (Aug-Oct) Symptomatic medication permitted: Not described Dates: Treatment prior to 1981 ragweed pollen season Location: Chicago, IL Setting: University practice Type(s) of providers: Specialists	No. of subjects at start: 42 study patients + 15 no-treatment controls Dropouts/withdrawals: 2 No. of subjects at end: 40 study patients + 15 no-treatment controls Inclusion criteria: Symptoms of ragweed hay fever; positive prick skin test to ragweed pollen Exclusion criteria: NR Age: 21-65 Sex: NR Race: NR Other: None had received immunotherapy within previous 5 years	1) Adverse reactions 2) Antibody levels (IgE against AgE) 3) Patient-assessed symptom severity: sneezing, nasal discharge, nasal congestion, pruritus, and wheezing graded 3 times per day during allergy season on scale of 0 to 3 (not described)	1) Adverse reactions: 3/21 active treatment with local reaction. 7/21 had large reactions requiring additional dosing. No systemic reactions. 2/19 placebo subjects with local reactions. 1/19 with large local reaction requiring additional dosing. 2) Antibody levels (IgE against AgE): Not abstracted 3) Patient-assessed symptom severity: Average daily symptom scores plotted on graph with score vs. time. All values except final 2 weeks statistically significant. Also, total symptom scores shown on a graph, with significant differences between treatment vs. no-treatment control group (p = 0.0107) and between treatment and placebo (p = 0.0224).	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: No Intention-to-treat: No Notes:

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Hirsch, Kalbfleisch, and Cohen, 1982	Design: RCT, parallel-group (matched-pairs design) (see Notes) Interventions: 1) Standard immunotherapy using glycerinated aqueous ragweed extract (n = 20). Weekly injections given from early March through late April, then twice weekly through mid-August. Maintenance injections (schedule not described) given through 1st week of October. Dose increased to tolerance, limited only by local reactions. Mean cumulative dose 5,391 PNU (20.1 µg of antigen E). 2) Placebo (glycerinated caramelized histamine) (n = 14) Duration of study treatment: 7 months (early March to early October) Symptomatic medication permitted: Not described Dates: 1980 Location: Milwaukee, WI Setting: University-based clinic Type(s) of providers: Specialist	No. of subjects at start: 34 Dropouts/withdrawals: Variable number of subjects at weekly assessment shown in primary data table. No. of subjects at end: 32 Inclusion criteria: History of allergic nasal and ocular symptoms of allergic rhinitis without asthma during August and September for 2+ years; positive skin test Exclusion criteria: Immuno-therapy during last 2 years, except for subjects who participated in a previous trial in 1979; positive mold skin test; positive dust mite skin tests Age: Active 26-64 mean 40.7 Placebo 17-64 mean 38.6 Sex: Active 13M/7F Placebo 9M/5F Race: NR Other: Several patients in the trial participated in an IT trial in the prior year. These subjects were not re-randomized in this trial but received active treatment or placebo according to what was received in the previous trial.	1) Adverse reactions 2) Patient-assessed symptom severity: unidentified symptoms recorded daily "for several weeks before, during, and after" pollen season 3) Use of symptomatic medication: recorded daily "for several weeks before, during, and after" pollen season 4) Physical exam score 5) Allergen-specific IgE antibody levels	1) Adverse reactions: 10% of subjects in each group experienced local reactions. No systemic reactions. Two subjects in placebo group had flushing and palpitations for 10-15 minutes after the injection. 2) Patient-assessed symptom severity: Mean weekly symptom scores for the 6 weeks in which pollen was present were significantly lower in the treatment group during 5 of 6 weeks (active vs. placebo): Week 1) 12.6 ± 16.0 vs. 30.9 ± 23.5; $p < 0.02$ Week 2) 34.9 ± 22.6 vs. 51.6 ± 28.3; ns Week 3) 37.8 ± 21.8 vs. 62.7 ± 23.7; $p < 0.01$ Week 4) 33.0 ± 18.5 vs. 59.4 ± 33.4; $p < 0.02$ Week 5) 18.1 ± 16.1 vs. 39.2 ± 22.3; $p < 0.01$ Week 6) 17.4 ± 18.9 vs. 34.4 ± 19.3; $p < 0.025$ Mean symptoms (6 weeks of exposure): Active 24.8 ± 15.1; placebo 45.9 ± 18.6; $p < 0.005$ 3) Use of symptomatic medication: Medication scores were significantly different during 2 of the 6 exposure weeks. Data presented as mean weekly scores with SD. 4) Physical exam score: Not abstracted 5) Allergen-specific IgE antibody levels: Not abstracted	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: No Double-blind: Yes Blinding adequate: Yes Dropouts described: No Intention-to-treat: No Note: 8/20 patients in the ragweed group and 8/14 in the placebo group had participated in an earlier controlled trial of ragweed vs. placebo (Hirsch, Kalbfleisch, Golbert, et al., 1981 [status?; patients were from Milwaukee 1979 ragweed trial]). These patients continued to receive extracts of same allergen as before (ragweed or placebo), though using a different protocol. Newly recruited patients (n = 18) were randomized to treatment. Results abstracted here for 1980 trial only (SIT [Tr] vs. placebo), and not for SIT vs. RIT comparisons (1980 vs. 1979).

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Hirsch, Kalbfleisch, Golbert, et al., 1981	Design: RCT (?), parallel-group (matched-pairs design) Interventions: 1) Rinkel injection therapy using glycerinated aqueous ragweed, grass, or mountain cedar pollen extracts (n = 81). "Optimal dose" determined for each patient based on s kin test by serial dilution titration and patient's clinical status. Optimal dose usually reached in 6-8 injections given at weekly intervals; maintenance injections then given weekly. Total mean cumulative dose 18.6 PNU. 2) Placebo (glycerinated caramelized histamine) (n = 74) Duration of study treatment: Each treatment seems to have been given "for several weeks before, during, and after" a single pollen season during 1978 and/or 1979 Symptomatic medication permitted: Not described Dates: 1978-79 Location: Multiple centers in US (Milwaukee; Yonkers, NY; Denver; Charleston; Washington, DC; San Antonio) Setting: Private allergy practices	No. of subjects at start: NR Dropouts/withdrawals: NR No. of subjects at end: 155 Inclusion criteria: 15+ years of age; two successive seasons of allergic rhinitis; no immunotherapy in previous 2 years Exclusion criteria: History suggestive of mold, house dust, or food allergies Age: Active 19-70 mean 38.2 Placebo 14-63 mean 35.6 Sex: Active 44M/37F Placebo 44M/30F Race: NR Other:	1) Patient-assessed symptom severity: unidentified symptoms recorded daily "for several weeks before, during, and after" pollen season 2) Use of symptomatic medication: recorded daily "for several weeks before, during, and after" pollen season 3) Physical exam score 4) Allergen-specific IgE antibody levels	Results were reported separately for multiple sites, seasons, and allergens; results summarized below are pooled results for all sites/seasons/allergens. 1) Patient-assessed symptom severity: Dot plots comparing active and placebo treatments are shown with lines designating mean and median symptom scores. Text describes differences as not significant. 2) Use of symptomatic medication: Dot plots comparing active and placebo treatments are shown with lines designating mean and median medication scores. Text describes differences as not significant. 3) Physical exam score: Not abstracted 4) Allergen-specific IgE antibody levels: Not abstracted	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: No Allocation concealed: Yes Double-blind: Yes Blinding adequate: Yes Dropouts described: No Intention-to-treat: Can't determine Notes: Not absolutely clear whether randomized or not.

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Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Type(s) of providers: Specialists				
Horst, Hejjaoui, Horst, et al., 1990	Design: RCT, parallel-group Interventions: 1) Lyophilized and standardized mold (*Alternaria*) extract (n = 13). Two-day rush protocol used to initiate therapy (6 injections increasing from 40 to 2,000 BU and from 1/10,000 to 1/1,000 weight-by-volume). Maintenance injections of 2,000 BU each given every week for first 6 weeks after rush protocol, then every 2 weeks for 1 year. 2) Placebo (0.9% NaCl, 0.4% phenol, and 0.5 to 0.05 mg histamine dihydrochloride) (n = 11) Duration of study treatment: 1 year Symptomatic medication permitted: For asthma: inhaled and oral sympathomimetics, theophylline, bronchial disodium cromoglycate, ketotifen, and inhaled and system corticosteroids. For rhinoconjunctivitis: nasal and ocular disodium cromoglycate, beclomethasone, terfenadine, ketotifen, and oral steroids. Dates: Oct-Dec, 1986 Location: France	No. of subjects at start: 24 Dropouts/withdrawals: 2 placebo patients dropped out after 6 and 8 months. One for social reasons, one for lack of efficacy. No. of subjects at end: 22 Inclusion criteria: Clinical history of rhinitis ± asthma; perennial symptoms with possible seasonal exacerbation in summer and autumn; positive prick skin test to *Alternaria*; positive RAST to *Alternaria*; no other perennial allergy; negative skin tests and RAST to dust mite; exclusive mold sensitivity Exclusion criteria: Prior immunotherapy Age: 5-56 years Sex: Active 9M/4F Placebo 8M/3F Race: NR Other: 38-45% with asthma	1) Adverse reactions 2) Patient global assessment of efficacy: At end of 1st year, patients asked to grade efficacy of treatment on visual analog scale from 0% (complete failure) to 100% (total success) 3) Patient-assessed symptom severity and use of symptomatic medication (combined in a single measure): patients graded asthma and rhinoconjunctivitis symptoms and medication daily on scale of 0-3 4) Skin reactivity 5) Nasal reactivity 6) Allergen-specific IgE and IgG antibody levels	1) Adverse reactions: 2 patients with asthma exacerbation in active group. No systemic reactions in placebo group. 2) Patient global assessment of efficacy: Active 76.5 ± 27.9% Placebo 39.5 ± 30.4% p < .001 3) Patient-assessed symptom severity and use of symptomatic medication (combined in a single measure): 3 patients in active and 1 in placebo group did not complete symptom diary Global symptoms: active 0.84 ± 0.93 vs. placebo 3.55 ± 2.00 (p < 0.005) Rhinitis: active 0.64 ± 0.83 vs. placebo 2.65 ± 1.89 (p < 0.005) 4) Skin reactivity: Not abstracted 5) Nasal reactivity: Not abstracted 6) Allergen-specific IgE and IgG antibody levels: Not abstracted	Quality Scoring: Population similar: Not adequately described Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Note: Because most subjects were sensitized to multiple perennial allergens, the authors note that 6,000 subjects were screened to identify 50 potential subjects. Significant for generalizability.

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Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Setting: Hospital-based pulmonary clinic Type(s) of providers: Specialists				
Iliopoulos, Proud, Adkinson, et al., 1991	Design: RCT, parallel-group (matched-pairs design) Interventions: 1) Short ragweed extract prepared by professional lab (n = 21). Initial dose equivalent to 0.0024 µg Amb a 1 (antigen E). Injections of gradually increasing strength given weekly until maintenance dose (equivalent to 1.92 µg Amb a 1) achieved (3 months). Maintenance injections then administered biweekly through final nasal challenge test (2 months after end of 1986 pollen season). Cumulative dose approximately 24 µg Amb a 1. 2) Placebo (vehicle + histamine) (n = 20). Increasing doses of histamine administered to simulate local reactions in treated group. Duration of study treatment: ~10 months; immunotherapy started Feb 1986 and continued until 2 months after end of pollen season Symptomatic medication permitted: Not described Dates: 1986 ragweed season	No. of subjects at start: 41 Dropouts/withdrawals: NR No. of subjects at end: Presumably 41 Inclusion criteria: Ragweed hay fever history; positive skin test to ragweed Exclusion criteria: None specified Age: NR Sex: NR Race: NR Other:	1) Patient-assessed symptom severity and medication use (combined in single measure): unspecified symptoms and medication use recorded in study diaries during pollen season (mid-Aug to mid-Oct); scoring system used not described 2) Allergen-specific IgE and IgG antibodies 3) Adverse reactions 4) Nasal reactivity 5) Skin reactivity	1) Patient-assessed symptom severity and medication use (combined in single measure): Significantly less symptoms in treated group ($p < 0.04$). Data not given. No baseline differences (data not shown). 2) Allergen-specific IgE and IgG antibodies: Not abstracted 3) Adverse reactions: 6/21 systemic reaction with wheezing, coughing, hives, stuffy/runny nose. 4/6 required epinephrine. One subject had lip swelling. 4) Nasal reactivity: Not abstracted 5) Skin reactivity: Not abstracted	Quality Scoring: Population similar: Not adequately described Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Yes Notes:

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Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Location: Baltimore, MD Setting: Univ allergy practice Type(s) of providers: Specialists				
Juniper, Kline, Ramsdale, et al., 1990	Design: RCT, parallel-group (matched-pairs design) Interventions: 1) Modified ragweed tyrosine adsorbate (Pollinex®-R), an aqueous extract of short ragweed pollen (n = 30). Four 0.5-ml injections of increasing strength (110, 250, 710, and 2100 PNU/0.5 ml) given during the 6 weeks before the start of the ragweed pollen season. 2) Budesonide aqueous nasal spray (n = 30). 100 µg given twice daily into each nostril beginning 1 week before the start of ragweed pollen season and continuing for a total of 7 weeks (encompassing entire pollen season). Duration of study treatment: 12 weeks: 6 weeks of pre-season immunotherapy overlapping at end with 1st week of nasal spray, plus 6 additional weeks of nasal spray Symptomatic medication permitted: Terfenadine 60 mg, up to 240 mg per day;	No. of subjects at start: 60 Dropouts/withdrawals: After randomization, 3 withdrew (one joined military, one with chicken pox, one with severe asthma exacerbation requiring corticosteroids) 1 IT subject withdrew after 1st dose because of systemic reaction, 5 in IT group withdrew after 1st injection, 1 after 2nd injection and 7 after 3rd dose because of large local reactions. Seven patients completed all 4 injections. 1 patient in med group had systemic symptoms after 2nd injection and withdrew. 8 from IT group withdrew during pollen season. All for uncontrolled symptoms. No. of subjects at end: Not clear. 30 med and 27 IT analyzed. Inclusion criteria: Moderate to severe rhinoconjunctivitis during ragweed season for at least 2 years; positive skin test to ragweed; no more mild skin test reactivity to fungal spores Exclusion criteria: Perennial rhinitis; polyps; chronic nasal obstruction; serious illness; inhaled or oral corticosteroids for	1) Patient-assessed symptom severity: severity and duration of sneezing, stuffy nose, runny nose, itchy nose, and eye symptoms graded daily on scale of 0 (none) to 3 (severe/ continuous) 2) Use of symptomatic medication: amount of terfenadine and eye drops used recorded daily 3) Adverse reactions: recorded during clinic visits at 1, 3, and 7 weeks after starting nasal spray	1) Patient-assessed symptom severity: Mean daily symptom scores significantly better in med group vs IT group: Sneezing $p < 0.0001$, stuffy nose $p < 0.0001$, runny nose $p = 0.0004$, itchy nose $p = 0.0008$. Numbers not given. Eye symptoms: no difference 2) Use of symptomatic medication: Terfenadine use higher in IT group: $p < 0.0001$ Eye drop use: no difference 3) Adverse reactions: Number of subjects (IT v Med): Headache 6 v 9 Nasal irritation 4 v 4 Drowsiness/fatigue 1 v 2 Injection reaction leading to withdrawal 13 v 1	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Yes Note: Double-dummy blinding technique employed.

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Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	naphazoline HCl with pheniramine maleate eye drops, one drop in each eye, up to 4 times per day; salbutamol inhaler, 200 µg, up to 800 µg daily Dates: 1988 ragweed season Location: Hamilton, Ontario Setting: Univ hospital clinic Type(s) of providers: Specialists	1 month prior to enrollment; IT in prior 12 months; pregnant or lactating women Age: Mean 43.5 IT, 45.8 med Sex: 14 F/30 IT, 16 F/30 med Race: NR Other:			
Krouse and Krouse, 2000	Design: RCT, parallel-group (matched-pairs design) Interventions: 1) Experimental group: twice weekly immunotherapy injections in an accelerated protocol over 6 months (n = 5). Injections consisted of active serum containing all specific positive antigens identified in pre-study skin end-point titration, including all of the 3 study antigens (oak, short ragweed, and *D. pteronyssinus* [house dust mite]) to which they tested positive. 2) Control group: twice weekly immunotherapy injections in an accelerated protocol over 6 months (n = 5). Injections consisted of active serum containing all specific positive antigens identified in pre-study skin end-point titration, *except for*	No. of subjects at start: 18 Dropouts/withdrawals: 8 failed to complete 6-month study No. of subjects at end: 10 (5 each group) Inclusion criteria: Symptoms of rhinosinusitis; positive skin prick test to short ragweed and oak or *D. pteronyssinus* Exclusion criteria: ?? Age: 42.4 A, 57.8 P Sex: NR Race: NR Other:	1) Patient-assessed disability: assessed using the Rhinosinusitis Disability Index (RSDI) and the Sino-Nasal Outcome Test-16 (SNOT-16), completed before and after treatment 2) Patient-assessed symptom severity: assessed using the Sinus Symptom Questionnaire (SSQ), completed before and after treatment 3) Nasal endoscopy (purulent rhinorrhea, mucosal erythema nasal obstruction, and nasal edema) 4) Nasal reactivity	1) Patient-assessed disability: Significant difference in Emotional Scale Score of RSDI 2) Patient-assessed symptom severity: Not significant. 3) Nasal endoscopy: Not abstracted 4) Nasal reactivity: Not abstracted	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: Yes Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Notes: No outcomes based on daily recording of symptoms. No standardization of experimental intervention. No restrictions on concomitant use of other medications, *(continued on next page)*

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	the 3 study antigens (oak, short ragweed, and *D. pteronyssinus* [house dust mite]). Duration of study treatment: 6 months Symptomatic medication permitted: Patients "able to use whatever adjuvant therapies they chose to assist them with managing their symptoms" Dates: NR Location: Florida Setting: Community ENT practice Type(s) of providers: Specialist-ENT				including steroids, which could have a substantial effect on symptoms.
Leynadier, Banoun, Dollois, et al., 2001	Design: RCT, parallel-group Interventions: 1) Purified, standardized, calcium phosphate-adsorbed allergen extract composed of equal parts of five grass pollens (orchard, meadow, rye, sweet vernal, and timothy) (n = 16). Build-up phase: 16 weekly injections given in increasing doses (0.01 IR to 30 IR). Maintenance phase: injections given once every 2 weeks before the beginning of pollen season, then once a month during pollen season (with a 50% reduction in	No. of subjects at start: 29 Dropouts/withdrawals: 2 No. of subjects at end: 27 Inclusion criteria: Allergy to grass pollen; typical symptoms of rhinoconjunctivitis during the grass pollen season from May to July; positive skin prick test to 5 grass pollen extracts (wheal > 5 mm); serum grass pollen specific IgE antibody levels > class 2, as determined by RAST; positive grass pollen nasal provocation test Exclusion criteria: Specific	1) Patient-assessed symptom severity: sneezing, blocked nose, running nose, itching nose, red eyes, itching eyes, tearing eyes, coughing, wheezing, and breathlessness graded daily during allergy season on scale of 0-3 (not described) 2) Use of symptomatic medication: scored daily during allergy season, as follows: Each levocabastine eye drop or puff of salbutamol or beclomethasone: 1	1) Patient-assessed symptom severity (area under curve): Total symptoms: IT 49.5 Placebo 56 Difference 6.4 (-18.6 to 31.5; p = NS) Nose: IT 33.5 Placebo 38.6 Difference 5.1 (-12.7 to 23.1; p = NS) Eyes: IT 16.0 Placebo 17.3 Difference 1.2 (-8.6 to 11.2; p = NS) 2) Use of symptomatic medication: IT: 11.1	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: Not adequately described Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Not described Dropouts described: Yes Intention-to-treat: No *(continued on next page)*

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	volume of solution injected). Dose/schedule modifications "allowed for medical indications according to the routine specific immunotherapy procedure." 2) Placebo (diluent, no histamine) (n = 13). Duration of study treatment: 1 year Symptomatic medication permitted: Antihistamines (levocabastine eye drops and cetirizine 10 mg tablets) and inhaled ß-agonist (salbutamol) permitted on regular basis; max of 2 short courses of betamethasone (0.5 mg) could be prescribed during pollen season if symptoms not controlled by antihistamines; inhaled beclomethasone (250 µg) permitted in case of severe asthma Dates: Sep 1997 to Sep 1998 Location: France Setting: NR Type(s) of providers: NR, but presumably allergists	immunotherapy during last 5 years; perennial rhinitis; severe seasonal asthma; patients receiving systemic corticosteroids; contraindications to immunotherapy Age: 30 (range 18-44 years) Sex: 15 women; 14 men Race: NR Other:	Each cetirizine tablet: 2 Each betamethasone tablet: 3 3) Nasal reactivity 4) Skin reactivity 5) Specific IgE and IgG4 levels 6) Adverse reactions	Placebo: 40.8 Difference 29.6 (6.5 to 52.7; p = 0.005) 3) Nasal reactivity: Not abstracted 4) Skin reactivity: Not abstracted 5) Specific IgE and IgG4 levels: Not abstracted 6) Adverse reactions: Local reactions (swelling and erythema > 5 cm at injection site): IT 6/16 Placebo 0/13 Systemic reactions (mild exacerbations of rhinoconjunctivitis and urticaria): IT 7/16 Placebo 2/13	Notes:

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Leynadier, Herman, Vervloet, et al., 2000	Design: RCT, parallel-group Interventions: 1) Standardized natural rubber latex extract (n = 9). Treatment started with a 2-day course of rush immunotherapy in hospital (doses progressing from 0.001 IR to 2 IR). First month thereafter, weekly injections of gradually increasing doses given. Maximum tolerated dose achieved within 2 months, with maintenance doses given every month thereafter. 2) Placebo (no histamine) (n = 8) Duration of study treatment: 1 year Symptomatic medication permitted: antihistamines, cromones, short-acting ß$_2$-agonists, or inhaled cortiocosteroids Dates: Enrollment 1995-1997 Location: France Setting: Hospital-based clinics Type(s) of providers: Specialists	No. of subjects at start: 17 Dropouts/withdrawals: 3 in placebo group: 1 underwent surgery, 1 withdrew consent, 1 lost to followup. No. of subjects at end: 14 Inclusion criteria: Rhinitis and cutaneous allergy to latex demonstrated by skin test and specific IgE Exclusion criteria: Clinically significant dust mite allergy; animal allergy if pet lived in home; severe asthma; immunotherapy for another allergen Age: 22-41 years Sex: 1M/16F Race: NR Other:	1) Patient-assessed symptom severity: symptoms of rhinitis (rhinorrhea, nasal itching, nasal blockage, sneezing), conjunctivitis (tearing, itching, edema, erythema), and cutaneous signs (pruritus, urticaria, eczema) graded weekly on scale of 0 (absent) to 3 (intolerable); asthma symptoms also graded weekly on scale of 0 (absent) to 3 (asthma attack making patient unable to perform everyday activities) 2) Use of symptomatic medication: quantities consumed each week recorded ; doses scored as follows: 1 point: local antiallergic treatment or puff of ß$_2$-agonist; 2 points: antihistamine tablet; 2.5 points: inhaled corticosteroid equivalent to 250 µg beclo-methasone; 18 points: corticosteroid tablet equivalent to 20 mg prednisolone 3) Conjunctival reactivity 4) Adverse reactions	1) Patient-assessed symptom severity: Rhinitis scores: Baseline (active vs. placebo) 2.8 ± 2.15 vs. 4.8 ± 1.85 6 months (active vs. placebo) 1.6 ± 2.9 vs. 4.0 ± 2.11 ($p < 0.04$) 12 months (active vs. placebo) 0.9 ± 1.22 vs. 2.9 ± 2.26 2) Use of symptomatic medication: Line graph shown. Calculated area under the curve showed ratio of active to placebo of 21%, indicating 79% improvement. 3) Conjunctival reactivity: Not abstracted 4) Adverse reactions: Half of patients in active group with local reaction. Active vs. placebo (%) Rhinitis: 15.2 vs. 5.6 Conjunctivitis: 10.4 vs. 2.0 Asthma attack: 2.7 vs. 0.8 Pharyngeal edema: 1.2 vs. 0 Giant urticaria: 1.2 vs. 0 Angioedema: 0.6 vs. 0 Hypotension: 0.3 vs. 0.4 Other 14.9 vs. 4.4	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Note: No histamine in placebo injections.

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Lichten-stein, Norman, and Winken-werder, 1968	Design: RCT, parallel-group (matched-pairs design) (see Notes) Interventions: 1) Immunotherapy using ragweed antigen E (n = 24 at start; 22 included in analysis). Injections given weekly for 14 weeks. Dosage "based on the patient's tolerance to the injections;" total dose ranged from 16.9 to 800 µg antigen E (mean: 285.5 µg). 2) Placebo (dilutions of buffer containing 0.5 mg histamine/ml (n = 24 at start; 18 included in analysis). Duration of study treatment: Injections given over 14 weeks; symptoms monitored for one allergy season (early Aug to early Oct) Symptomatic medication permitted: Chlorpheniramine 4 mg or tripellenamine 50 mg; no corticosteroid therapy required Dates: 1965-66 Location: Baltimore, MD Setting: Academic allergy clinic Type(s) of providers: Specialists	No. of subjects at start: 48 Dropouts/withdrawals: 2 dropouts and incomplete clinical data on 6 others No. of subjects at end: 40 Inclusion criteria: Hay fever symptoms during ragweed season Exclusion criteria: NR Age: NR Sex: NR Race: NR Other:	1) Blocking antibody levels 2) Cell sensitivity (amount of antigen E required to evoke a 50% response from leukocytes) 3) Patient-assessed symptom severity and use of symptomatic medication (combined in a single measure): sneezing, stuffy/runny nose, red/itchy eyes, and coughing graded daily during allergy season on scale of 0 to 3 (not described); number of antihistamine tablets taken recorded daily and "added to the symptom score" 4) Investigator-assessed symptom severity 5) Adverse reactions	1) Blocking antibody levels: Not abstracted 2) Cell sensitivity: Not abstracted 3) Patient-assessed symptom severity and use of symptomatic medication (combined in a single measure): Average symptom score 7.2 active vs. 9.8 placebo. Table presents symptom scores for matched pairs. Average peak season symptom in active group 6.5 vs. placebo group 9.8 ($p < 0.01$ Wilcoxon signed rank test) 4) Investigator-assessed symptom severity: Not abstracted 5) Adverse reactions: 11 experienced local reactions in active group; 1 with systemic reaction of hives and wheezing.	Quality Scoring: Population similar: Not adequately described Intervention(s) described: No Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: No Blinding adequate: Not applicable Dropouts described: Yes Intention-to-treat: No Notes: 10/24 patients in the antigen-E group and 10/24 in the placebo group were recruited from a previous trial (Lichtenstein, Norman, Winkenwerder, et al., 1966, below). All continued with the therapy to which they were assigned in the earlier trial, except two patients who had been receiving crude ragweed extract, who were assigned to the antigen-E group. Only newly acquired patients (n = 28) were randomized to treatment.

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Lichtenstein, Norman, and Winkenwerder, 1971	Design: RCT, parallel-group Interventions: 1) Whole or crude ragweed pollen extract, supplied as a lyophilized powder for reconstitution (n = 19). Initial dose 0.012 µg (0.2 PNU). Further dosing schedule described below. Mean cumulative dose 0.55 mg protein (8800 PNU) in 26.7 injections. 2) Antigen E, prepared by professional lab (n = 18). Initial dose 0.02 µg protein. Further dosing schedule described below. Mean cumulative dose 1.0 mg in 23.1 injections. 3) Antigens E + K (in 2:1 ratio), prepared by professional lab (n = 21). Initial dose 0.02 µg protein. Further dosing schedule described below. Mean cumulative dose 1.4 mg in 23.7 injections. 4) Placebo (diluent with histamine) (n = 21). Dilutions prepared from 0.5 mg/ml histamine base, so that graded increase in local reaction was attained as dose was increased. All treatments: Injections given every week beginning Mar 6. Doses doubled each week, unless local or systemic reactions warranted a slower	No. of subjects at start: NR Dropouts/withdrawals: "Few" (actual numbers NR) No. of subjects at end: 88 Inclusion criteria: Questionnaire data suggesting allergic rhinitis Exclusion criteria: NR Age: NR Sex: NR Race: NR Other:	1) Adverse reactions 2) Patient-assessed symptom severity: unspecified symptoms recorded daily in study diaries during ragweed season; method of scoring not described 3) Blocking antibody levels 4) Leukocyte histamine release	1) Adverse reactions: One moderate to severe local reaction per patient. Systemic reactions 1.6 per patient with crude extract vs. 0.4 per patient with purified. 2) Patient-assessed symptom severity: Treatment groups had symptom scores 35-40% lower than placebo. No mean given. Average seasonal symptom scores estimated at 11 for placebo group and 7-7.5 for treatment groups. Scatter-gram given with means. P < 0.01 3) Blocking antibody levels: Not abstracted 4) Leukocyte histamine release: Not abstracted	Quality Scoring: Population similar: Not adequately described Intervention(s) described: No Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: No Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: No Blinding adequate: Not applicable Dropouts described: No Intention-to-treat: No Note: Apparently only single-blinding.

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	increase. Near end of injection period (1st week of Aug), patients who had fallen behind in dosage because of adverse reactions received injections twice per week to increase total dose. Duration of study treatment: Approximately 8 months; injections given Mar 6 - 1st week of Aug; outcomes monitored through ragweed season (mid-Aug through mid-Oct) Symptomatic medication permitted: Not described Dates: 1968 ragweed season Location: Baltimore, MD Setting: Academic hospital allergy practice Type(s) of providers: Specialists				

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Lichtenstein, Norman, Winkenwerder, et al., 1966	Design: RCT, parallel-group (matched-pairs design) (see Notes) Interventions: 1) Crude ragweed pollen extract (n = 15). Given as 15 weekly injections. First injection 0.001 µg protein N; dose doubled every week provided previous dose had produced no reaction. Total dose ranged from 0.39 to 28.8 µg protein N, containing 0.15 to 11 µg antigen E (0.026 to 1.84 µg protein N). 2) Ragweed antigen E (n = 11). Given as 15 weekly injections. First injection 0.0003 µg protein N; dose doubled every week provided previous dose had produced no reaction. Total dose ranged from 4.0 to 61.7 µg antigen E (0.7 to 11.2 µg protein N). 3) Placebo (saline) (n = 15). Duration of study treatment: Injections given over 15 weeks; symptoms monitored for one allergy season (early August to late September) Symptomatic medication permitted: Dexchlorpheniramine maleate 2 mg Dates: 1964 Location: Baltimore, MD	No. of subjects at start: 41 Dropouts/withdrawals: 7 Crude antigen group: 3 Antigen E group: 1 Control (placebo): 3 Only reason given was "various technical reasons". No. of subjects at end: 34 Inclusion criteria: Hay fever symptoms restricted generally to ragweed pollen season; "adequate" in vitro histamine release to ragweed antigen Exclusion criteria: Asthma Age: NR Sex: NR Race: NR Other:	1) Cell sensitivity (amount of antigen E required to evoke a 50% response from leukocytes) 2) Patient-assessed symptom severity and use of symptomatic medication (combined in a single measure): sneezing, stuffy/runny nose, red/itchy eyes, and coughing graded twice daily during allergy season on scale of 0 (no symptoms) to 3 (symptoms lasting more than 2 hours); number of antihistamine tablets taken recorded daily and added to the symptom score 3) Investigator-assessed symptom severity 4) Adverse reactions	1) Cell sensitivity: Not abstracted 2) Patient-assessed symptom severity and use of symptomatic medication (combined in a single measure): Graph showing symptom score vs. time given for each treatment group. Table with average daily symptom scores given. Differences not significant Control 3.7 (0.3-11.8) Crude antigen 3.0 (0.9-6.5) Antigen E 3.4 (1.1-7.3) 3) Investigator-assessed symptom severity: Not abstracted 4) Adverse reactions: 2/15 patients completed the full dose escalation for crude ragweed allergen. Doses limited by local injection site reactions. 4 subjects had systemic reactions (hives). 5/10 patients receiving antigen E achieved the highest dose level. 4 patients had local reactions and 1 patient had a systemic reaction. No data are given for AEs in the control group.	Quality Scoring: Population similar: Not adequately described Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Yes Double-blind: No Blinding adequate: Not applicable Dropouts described: Yes Intention-to-treat: No Notes: Patients were drawn from a larger trial (no publication cited). 11/41 had been receiving antigen E and continued with this therapy. Remaining 30 patients were randomly divided between crude ragweed and placebo groups.

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Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Setting: Academic allergy practice Type(s) of providers: Specialists				
Lowell and Franklin, 1965	Design: RCT, parallel-group (matched-pairs design) Interventions: Recruited patients had all been receiving injections of "ragweed and other pollen extracts" for an unspecified period of time before the study started. Were then randomized to: 1) Continued treatment with same mixture of extracts (n = ?); or 2) Continued treatment with previous mixture of extracts *minus* ragweed-pollen extract (n = ?). Duration of study treatment: 8 months (early March to end of October) Symptomatic medication permitted: Not described Dates: 1963 Location: Boston, MA Setting: Hospital Allergy Clinic Type(s) of providers: Specialists	No. of subjects at start: 27 Dropouts/withdrawals: 3 No. of subjects at end: 24 Inclusion criteria: Symptoms of allergic rhinitis coinciding with 1962 ragweed pollen season ± prior or ongoing immunotherapy; absence of symptoms of AR at other times of the year Exclusion criteria: Pregnancy Age: NR Sex: NR Race: NR Other:	1) Patient- and investigator-assessed symptom severity: symptoms recorded daily by patients; these records reviewed and discussed with patient at each clinic visit, and consensus scores for duration and severity of symptoms reached by patient and investigator; sev erity of symptoms graded on numerical scale from 0 (none) to 100 (incapacitating) 2) Use of symptomatic medication: recorded daily by patients in study diaries 3) Total symptom-medication scores: combines above two measures	1) Patient- and investigator-assessed symptom severity: This is a joint score negotiated based upon discussion between patient and physician. Data presented as graph of symptoms over time. Data also presented as a Table with symptom scores compared between treated and untreated subjects each week. All values for symptom scores favored the treated group. Values were significant during the weeks corresponding to ragweed pollen exposure. 2) Use of symptomatic medication: Data presented as graph of medication scor e over time. Data also presented as a Table with medication scores compared between treated and untreated subjects each week. All values for medication scores favored the treated group. Values were significant during the weeks corresponding to ragweed pollen exposure. 3) Total symptom-medication scores: Data from symptom and medication scores merged. Week-by-week analysis shows statistical significance during weeks of presumed ragweed pollen exposure.	Quality Scoring: Population similar: Not adequately described Intervention(s) described: No Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: No Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Yes Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Notes: This is actually a withdrawal of therapy study. Pollen counts not performed during experimental period. Of a clinic population of 500 patients, only 27 met entry criteria.

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
McAllen, 1969	Design: RCT, parallel-group Interventions: 1) Alum-precipitated extract of pollens of 5 grasses (Allpyral G®) (n = 47). Given in nine weekly injections, with dose gradually increasing from 50 to 10,000 PNU. 2) Depot emulsion extract of pollens of 12 grasses (D-Vac®) (n = 40). Three injections of 750; 3,500; and 7,500 Noon units given at 4-week intervals. 3) Placebo (normal saline) (n = 23). Given in three injections at 4-week intervals. Duration of study treatment: Injections given over 9 or 12 weeks; outcomes measured during single pollen season Symptomatic medication permitted: "Tablets" and nasal decongestants Dates: Nov 1966 - Feb 1967 Location: London, UK Setting: Allergy clinic Type(s) of providers: Allergists	No. of subjects at start: 110 Dropouts/withdrawals: 19 No. of subjects at end: 91 Inclusion criteria: Symptoms of hay fever for at least 2 previous years; positive skin prick test to grass pollen extract Exclusion criteria: Age < 12 or > 60; symptoms outside months of May-July; perennial rhinitis; systemic corticosteroids; previous satisfactory response to antihistamine drugs Age: 26 years Sex: 60 women; 50 men Race: NR Other:	1) Patient global evaluation of efficacy: at end of pollen season, patients graded treatment as "satisfactory" or "unsatisfactory" 2) Patient-assessed symptom severity: unspecified symptoms graded daily during pollen season on scale of 0 (clear of symptoms all day) to 3 (severe symptoms which were not controlled by tablets or nasal decongestants) 3) Adverse reactions	1) Patient global evaluation of efficacy: ITT / Completers alum extract: 30/47 30/41 depot emul: 21/40 21/30 placebo: 7/23 7/20 alum vs. placebo; p = 0.01 depot vs. placebo; p = 0.046 (chi-square test) 2) Patient-assessed symptom severity: Symptom-free days Alum: 35 Depot: 38.5 Placebo: 28.5 Alum vs. placebo: p = 0.087 Depot vs placebo: p = 0.038 Mean points count Alum: 54 Depot: 49 Placebo: 72 Alum vs. placebo: p = 0.074 Depot vs. placebo: p = 0.054 3) Adverse reactions: Generalized urticaria within 1 hour Alum 1 pt; depot 2 pts Asthma and rhinitis after 12 hours Alum 8 pt; depot 1 pt Small persistent nodules at injection site Depot 10 pts	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: No Dropouts described: Yes Intention-to-treat: Yes Notes: Placebo was normal saline rather than weak histamine solution; local reactions not reported, but this could have unblinded placebo patients.

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
McHugh and Ewan, 1992	Design: RCT, parallel-group Interventions: 1) House dust mite (*Dermatophagoides pteronyssinus*) extract (Pharmalgen®) (n = 30). Administered according to protocol described in Ewan, Alexander, Snape, et al., 1988 (above), and McHugh, Lavelle, Kemeny, et al., 1990 2) House dust mite extract (Allpyral®) (n = 20). Administered according to protocol described in McHugh, Lavelle, Kemeny, et al., 1990 3) Placebo (histamine dihydrochloride) (n = 30) Duration of study treatment: 12 months Symptomatic medication permitted: beclomethasone nasal spray, terfenadine, chlorpheniramine Dates: NR Location: Cambridge, UK Setting: Academic allergy unit Type(s) of providers: Specialists	No. of subjects at start: 80 (20 of 80 enrolled in single blind trial of an alternate agent) Dropouts/withdrawals: 2 in Pharmalgen group 1 in placebo 3 in Allpyral group Reasons not given No. of subjects at end: 74 Inclusion criteria: Described in prior publication. Patients had known allergy to dust mite with positive prick skin tests and nasal challenge studies. Exclusion criteria: NR Age: 15-72 Sex: 44M/36F Race: NR Other:	1) "Clinical index": composite measure derived from: a) visual analog symptom score; b) diary card symptom score; c) nasal challenge results; d) skin prick test results; e) medication score 2) Patient-assessed symptom severity: rhinitis symptoms (sneezing, discharge, and obstruction) graded a) daily (?) on visual analog score where 0% = asymptomatic and 100% = very severe; and b) twice daily on categorical scale of 0-3 (not described) 3) Nasal reactivity 4) Skin reactivity 5) Use of symptomatic medication: recorded daily on study diary cards	1) "Clinical index": Scores are baseline, 3 mo, 12 mo. Pharmalgen: 27.0, 42.5, 49.5 Placebo: 27.0, 32.5, 32.0 Allpyral: 27.0, 36.5, 38.0 Pharmalgen vs. placebo ($p < 0.002$ and $p < 0.001$ at 3 and 12 months) Allpyral vs. placebo ($p = 0.15$) Pharmalgen vs. Allpyral ($p < 0.006$) favoring Pharmalgen 2) Patient-assessed symptom severity: Comparison of baseline vs. 12 mo. SE shown Pharmalgen: 30.9 ± 4.0, 16.0 ± 2.7 Allpyral: 14.7 ± 4.1, 14.5 ± 3.2 Placebo: 28.8 ± 3.5, 22.4 ± 2.4 3) Nasal reactivity: Not abstracted 4) Skin reactivity: Not abstracted 5) Use of symptomatic medication: Comparison is 0 and 12 months. SE shown Pharmalgen: 1.42 ± 0.42, 0.19 ± 0.12 Allpyral: 0.94 ± 0.29, 1.05 ± 0.57 Placebo: 1.28 ± 0.55, 0.96 ± 0.37	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: No Allocation concealed: Not described Double-blind: No Blinding adequate: Not applicable Dropouts described: Yes Intention-to-treat: No Notes: Interim results for some patients (n = 38) in this trial reported in Ewan, Alexander, Snape, et al., 1988 (above).

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Mischler, O'Brien, Rugloski, et al., 1981	Design: RCT, parallel-group Interventions: 1) Gluteraldehyde-modified ragweed pollen tyrosine adsorbate (MRTA) (n = 177). Four weekly injections given in doses of 300; 700; 2,000; and 6,000 NU/0.5 ml. 2) Placebo (tyrosine suspension) (n = 189). Duration of study treatment: Injections given over 4 weeks; outcomes assessed for one allergy season. Symptomatic medication permitted: Chlorpheniramine maleate 4 mg supplied; however, "many patients also took medication on their own, without consent of their physician" Dates: 1976 Location: Eastern Canada Setting: Multicenter (presumably) allergy practices Type(s) of providers: Specialists (presumed)	No. of subjects at start: 366 (177 active, 189 placebo) Dropouts/withdrawals: 119 active 103 placebo No. of subjects at end: Completing injections and diary data: 58 active 86 placebo Inclusion criteria: Seasonal AR for 2+ years; positive skin test to ragweed Exclusion criteria: Pregnancy; chronic asthma or other respiratory disease; immunotherapy within 12 months Age: 266 adults (15-73, mean 32.8) 100 children (5-16, mean 11.2) Sex: 195M/171F Race: NR Other:	1) Patient-assessed symptom severity: sneezing, stuffy and/or runny nose, itchy eyes, and cough graded twice daily on scale of 0 (none) to 3 (lasted more than 2 hours) 2) Use of symptomatic medication: use of investigator-supplied antihistamine and (separately) other symptomatic meds recorded by patients in study diaries 3) Total symptom-and-medication score (combination of above measures, called "combined efficacy score" by investigators) 4) Allergen-specific IgE and IgG antibody levels 5) Adverse reactions	1) Patient-assessed symptom severity: Active vs. placebo Sneeze: 27.8 vs. 38.6 (ns) Nose: 40.7 vs. 56.9 (ns) Eye: 21.1 vs. 39.4 (p = 0.0183) Cough 4.3 vs. 8.1 (ns) 2) Use of symptomatic medication: Antihistamine: Active 9.9 vs. placebo 22.0 (p = 0.0352) Other medications: Active 71.3 vs. placebo 151.2 (p = 0.0646) 3) Total symptom-and-medication score (combination of above measures, called "combined efficacy score" by investigators): Active 181.1 vs. placebo 318.3 (p = 0.0154) 4) Allergen-specific IgE and IgG antibody levels: Not abstracted 5) Adverse reactions: 13% overall discontinued therapy because of late local reactions or sneezing and wheezing (n = 1).	Quality Scoring: Population similar: No Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Notes: Patients who participated in RCT phase (1st year) given opportunity to receive MRTA (in open fashion) during 2nd year. Symptom data reported for only 5/8 centers in 1976 phase of study. Data abstracted from from RCT phase (1976) only. High dropout rate.

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Movérare, Vesterinen, Metso, et al., 2001	Design: RCT, parallel-group Interventions: 1) Immunotherapy using extracts of birch (n = 26) or timothy (n = 4) pollen. Initial rush phase with standardized aqueous extracts (Aquagen®). Three injections given daily using gradually increasing doses up to highest tolerated dose at end of 1st week (target dose: 10,000 SQ). Treatment then continued with standardized depot preparations (Alutard®), given every 3 weeks in increasing doses until individual maintenance dose reached (target: 60,000 to 100,000 SQ). Maintenance dose continued every 3 weeks for 3 years. 2) No immunotherapy (n = 16). Duration of study treatment: 3 years (active treatment; see Notes) Symptomatic medication permitted: Not specified Dates: NR Location: Helsinki, Finland Setting: Allergology clinic Type(s) of providers:	No. of subjects at start: 46 Dropouts/withdrawals: 7 No. of subjects at end: 39 Inclusion criteria: History of birch- or timothy-pollen allergy; rhinitis or conjunctivitis during at least 3 pollen seasons; positive skin prick test to birch- or timothy pollen; specific serum IgE to birch or timothy pollen Exclusion criteria: NR Age: 20 years Sex: 21 women; 25 men Race: NR Other: 41 birch pollen 5 timothy grass pollen	1) Total IgE and allergen-specific IgE, IgG, and IgG4 antibody levels 2) Patient-assessed symptom severity: symptoms graded once per allergy season (pretreatment, 1st year, and 3rd year) on visual analog scale from 0 to 100 (not described) 3) Use of symptomatic medication: assessed two ways: a) graded once per allergy season (pretreatment, 1st year, and 3rd year) on visual analog scale from 0 to 100 (not described); and b) graded once every month from March to October of 1st year on scale of 0 (no use of medication) to 2 (regular use of medication) ("monthly medication index") 4) Adverse reactions	1) Total IgE and allergen-specific IgE, IgG, and IgG4 antibody levels: Not abstracted 2) Patient-assessed symptom severity: RIT 21.2 ± 19.5; n = 24 Control 39.0 ± 15.1; n = 11 P = 0.002 3) Use of symptomatic medication: a) Medication scores Year 1 RIT 20.4 ± 19.9; n = 24 Control 45.4 ± 23.3; n = 11 P = 0.0077 b) Average monthly med index RIT 1.59 ± 1.82 control 3.29 ± 1.77 p < 0.05 4) Adverse reactions: RIT – systemic reaction (fever after injection) 1 case; generalized urticaria 3 cases; mild asthmatic symptoms 1 case (all pts continued RIT at decreased dose)	Quality Scoring: Population similar: Not adequately described Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: No Blinding adequate: Not applicable Dropouts described: Yes Intention-to-treat: Can't determine Notes: No attempt at blinding. No outcomes based on daily recording of symptoms or medication use. Control patients offered active treatment after 1 year; those who accepted left the study. Five control patients followed up for 3 years. Imbalance in conjunctivitis symptoms at baseline. Year 3 data compromised by > 50% dropout rate in control group.

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Naclerio, Proud, Moylan, et al., 1997	Design: RCT, parallel-group Interventions: All included patients had been receiving maintenance immunotherapy with aqueous ragweed extract at a dose of approximately 12 µg of Amb a 1 (5000 AU) every 2 weeks for a minimum of 3 years when they entered trial. Then randomized to receive either: 1) Continued maintenance therapy (as above) (n = 10); or 2) Placebo maintenance therapy (saline mixed with histamine) (n = 10). Duration of study treatment: 1 year Baseline measurements taken during ragweed season before randomization (symptoms and antibody levels) and in December or early January immediately before randomization (nasal reactivity) Symptomatic medication permitted: Not described Dates: Year not given. Included one ragweed season. Location: Baltimore, MD Setting: Academic hospital clinic Type(s) of providers:	No. of subjects at start: 20 Dropouts/withdrawals: 0 No. of subjects at end: 20 Inclusion criteria: Receiving ragweed IT for 3+ years Exclusion criteria: Significant nasal abnormalities or pathology Age: NR Sex: NR Race: NR Other:	1) Nasal reactivity 2) Patient-assessed symptom severity and medication use (combined in a single measure): unspecified rhinitis symptoms and medication use recorded in daily diaries during ragweed season; scoring system not described 3) Allergen-specific IgE and IgG antibodies	1) Nasal reactivity: Not abstracted 2) Patient-assessed symptom severity and medication use (combined in a single measure): Data available for 16/20 (8 per group). No significant difference. Data could be interpreted from graph. Determined that study power would have allowed 90% chance to miss significant difference. 3) Allergen-specific IgE and IgG antibodies: Not abstracted	Quality Scoring: Population similar: Not adequately described Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate Yes Dropouts described: Yes Intention-to-treat: Yes Note: Does not provide efficacy data, since this was a withdrawal of therapy study with pre-determined laboratory endpoints.

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Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Specialists				
Norman, Lichten-stein, Kagey-Sobotka, et al., 1982	Design: RCT, parallel-group (matched triplets) Interventions: Patients in all 3 treatment groups divided into "average" and higher-than-average" sensitivity groups. 1) Ragweed allergoid administered in a clustered regimen (n = 22 at start; 16 completed). "Average" sensitivity patients: 5 clinic visits totaling 11 injections. 1st visit, three injections at 30-min intervals in doses of 5, 10, and 20 allergoid units. Two injections given at each subsequent visit for cumulative projected dose of 1,925 units (168,000 PNU). Approximately 3 weeks between 1st and 2nd visit; 2-3 weeks between subsequent visits. "Higher-than-average" sensitivity patients: 6 clinic visits totaling 13 injections. 1st visit, three injections at 30-min intervals in doses of 0.5, 2, and 3 allergoid units. Two injections given at each subsequent visit for cumulative projected dose of 1,175.5 units (103,000 PNU). Approximately 3 weeks between 1st and 2nd visit; 2-3 weeks between subsequent visits. Mean cumulative dose actually administered 727 units (364µg AgE; 63,600 PNU).	No. of subjects at start: 66 Dropouts/withdrawals: 2 dropouts before completion of screening; then: 2 dropouts allergen group 6 dropouts allergoid group 5 dropouts placebo group No. of subjects at end: 53 completed first year Inclusion criteria: 3+ years of seasonal rhinitis; positive intradermal skin test to ragweed antigen Exclusion criteria: NR Age: NR Sex: NR Race: NR Other:	1) Adverse reactions 2) Patient-assessed symptom severity and use of symptomatic medication (combined in a single measure): duration of sneezing, rhinitis, conjunctivitis, and cough, and use of symptomatic medication recorded twice daily during allergy season 3) Cell sensitivity (amount of antigen E required to evoke a 50% response from leukocytes) 4) Total and allergen-specific IgE, and IgG-against-AgE antibody levels	1) Adverse reactions: Allergen group: All patients had at least one local reaction and "most" had multiple reactions. Large local reactions in 5 patients. Nine systemic reactions occurred in 8 patients who completed the injection series. Allergoid group: 11 systemic reactions in 5 patients. Similar incidence of large local reactions compared to allergen group. 2) Patient-assessed symptom severity and use of symptomatic medication (combined in a single measure): Analyzable data reported on 16 allergen, 16 allergoid and 20 placebo patients Mean score: Allergen 5.3 Allergoid 5.1 Placebo 8.8 Active vs. placebo ($p < 0.01$) 3) Cell sensitivity (amount of antigen E required to evoke a 50% response from leukocytes): Not abstracted 4) Total and allergen-specific IgE, and IgG-against-AgE antibody levels: Not abstracted	Quality Scoring: Population similar: Not adequately described Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: No Allocation concealed: Not described Double-blind: No Blinding adequate: Not applicable Dropouts described: Yes Intention-to-treat: No Notes: Assignment not described; may not have been random. Also, blinding not described. At end of initial trial, patients in allergoid and extract groups invited to continue with booster injections of same materials; results reported for this open follow-up.

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Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	2) Unaltered ragweed extract (glycerinated extract of short ragweed pollen) administered in a weekly regimen (n = 22 at start; 20 completed). "Average" sensitivity patients: 17 weekly injections, starting at 1.0 allergen unit and progressing to 500 units (1,200 PNU, for a projected cumulative dose of 2,083 units (5,000 PNU). "Higher-than-average" sensitivity patients: 20 weekly injections, starting at 0.1 allergen unit and progressing to 500 units, for a projected cumulative dose of 2,084 units. Mean cumulative dose actually administered 856 units (8.56 µg AgE; 2,000 PNU). 3) Placebo administered in a clustered regimen (n = 22 at start; 17 completed). Duration of study treatment: Varied, depending on treatment (see above); outcomes assessed during a single allergy season Symptomatic medication permitted: Antihistamine "and other medication" Dates: 1978 Location: Baltimore, MD Setting: University allergy clinic Type(s) of providers: Specialists				

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Ortolani, Pastorello, Incorvaia, et al., 1994	Design: RCT, parallel-group Interventions: 1) Alginate-conjugated extract of *Parietaria judaica* (wall pellitory) pollen (Conjuvac®-*Parietaria*) (n = 18). Extract used was biologically standardized and partially purified; 1 U of preparation represented 61.2 µg of pollen. Build-up phase: 12 weekly injections of increasing dose (1, 2, 4, 8, 10, 20, 40, 80, 100, 200, 400, and 800 U). Maintenance phase: top dose or maximum tolerated dose given at monthly intervals. 2) Placebo (lyophilized sodium alginate ± 5 µg histamine dihydrochloride) (n = 17) Duration of study treatment: 1 year Symptomatic medication permitted: Terfenadine tablets and salbutamol spray Dates: NR Location: Milan, Italy Setting: Academic internal medicine department Type(s) of providers: NR	No. of subjects at start: 35 (18 active, 17 placebo) Dropouts/withdrawals: 4 No. of subjects at end: 31 Inclusion criteria: Severe rhinoconjunctivitis ± asthma during *Parietaria* season for 2+ years; positive prick skin test to *Parietaria*; negative skin tests to grass, tree, weed, mite, mold, and pet allergens; positive RAST to *Parietaria* Exclusion criteria: Prior IT for *Parietaria;* other active respiratory diseases; nasal polyps; systemic corticosteroid use; pregnancy Age: Range, 14-59; mean, 41 Sex: 20 F Race: NR Other:	1) Patient-assessed symptom severity and medication use (combined in a single measure): eye (itching, redness, or weeping), nasal (sneezing, rhinorrhea, or blockage), and lung (cough, dyspnea, or asthma) symptoms graded daily on scale of 0-3 (not described); use of symptomatic medication recorded daily in study diaries 2) Nasal, conjunctival, and skin reactivity 3) Adverse reactions: recorded and described as local vs. systemic and immediate (within 30 minutes) vs. late 4) Allergen-specific IgE, IgG, IgG1, and IgG4 antibody levels	1) Patient-assessed symptom severity and medication use (combined in a single measure): Complete assessment on 17 active and 14 placebo patients who submitted diaries. Significantly lower S-M scores in active vs. treatment group ($p < 0.05$). Sub-symptom analysis showed significance for runny nose ($p = 0.0087$), sneezing ($p = 0.0488$), but not nasal blockage. No means or SDs given. 2) Nasal, conjunctival, and skin reactivity: Not abstracted 3) Adverse reactions: 16/18 active and 1/17 placebo patients had local reactions. 5/18 active and 2/17 placebo had systemic reactions. 5 rhinitis and 1 urticaria in active group. 2 rhinitis in placebo group. All but one reaction immediate. 4) Allergen-specific IgE, IgG, IgG1, and IgG4 levels: Not abstracted	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: No Intention-to-treat: No Notes:

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Parker, Whisman, Apaliski, et al., 1989	Design: RCT, parallel-group (matched-pairs design) Interventions: 1) Extract of *Juniperus ashei* (mountain cedar) pollen (n = 26). Extract prepared in a single lot by lab in Spokane, WA. "Conventional high-dose" protocol used, beginning with 0.1 ml of 1:50,000 wt/vol dilution and progressing by 0.05- to 0.1-ml increments until 0.5 ml was reached. A 10-fold higher concentration then administered in the same dosing increments until the highest tolerated dose or 0.5 ml of 1:50 wt/vol was reached. 1-3 injections per week given during build-up phase; weekly injections given during maintenance phase. 2) Placebo (carmelized glucose, HSA, and histamine phosphate) (n = 25) Duration of study treatment: NR No description of symptomatic medication permitted (if any) Dates: Jan-July 1987 Location: Lackland AFB, Tx Setting: Military hospital allergy clinic Type(s) of providers: Specialists	No. of subjects at start: NR Dropouts/withdrawals: NR No. of subjects at end: 51 Inclusion criteria: History consistent with *Juniperis* rhinoconjunctivitis; positive skin prick test to *Juniperis* Exclusion criteria: Age < 18; pregnancy; use of ß-blocker; IT within prior 5 years Age: 22-75 (mean 43.4 active, 47.1 placebo) Sex: 26 F Race: NR Other:	1) Patient-assessed symptom severity and medication use (combined in a single measure): itchy nose, nasal congestion, sneezing, nose blowing, itchy eyes or throat, wheezing, shortness of breath, chest tightness, and cough graded daily during the pollen season on scale of 1 to 5 (not described); use of symptomatic medication recorded daily in study diaries (scored as 1 point per standard dose) 2) Skin reactivity 3) Allergen-specific IgE, IgG1, and IgG4 antibody levels	1) Patient-assessed symptom severity and medication use (combined in a single measure): Mean score 57.0 active, 129.9 placebo (p = 0.0001). Individual data provided. 2) Skin reactivity: Not abstracted 3) Allergen-specific IgE, IgG1, and IgG4 levels: Not abstracted	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: No Blinding adequate: Not applicable Dropouts described: No Intention-to-treat: No Notes:

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Pastorello, Pravettoni, Incorvaia, et al., 1992	Design: RCT, parallel-group Interventions: 1) Alum-absorbed grass allergoid obtained by mild formalinization of a mixed grass-pollen extract (six grasses: *Dactylis glomerata, Festuca elatior, Holcus lanatus, Phleum pratense, Lolium perenne, Poa pratensis*) (n = 10). Treatment started in January. Weekly injections of increasing doses given to a top dose of 20,000 PNU or maximum tolerated dose. Weekly doses administered until mid-April, after which a 50% equivalent dose was given every 3 weeks as maintenance. Mean pre-seasonal cumulative dose 46,050 PNU (range, 20,700 to 54,500). Mean maximum dose administered in a single injection 16,250 PNU (range, 4500 to 20,000). 2) Placebo (caramel NF acid solution ± histamine hydrochloride [randomly added to approximately 50% of vials]) (n = 9) Duration of study treatment: 1 year Symptomatic medication permitted: Xylometazolin, terfenadine, and salbutamol Dates: Jan 1986 – Jun 1986 Location: Milan, Italy	No. of subjects at start: 19 Dropouts/withdrawals: NR No. of subjects at end: NR Inclusion criteria: Seasonal rhinoconjunctivitis for at least 3 years; positive skin prick test for a mix of grass pollen extracts with wheal at least twice area of wheal induced by 1 mg/ml histamine; negative SPT for other pollens (birch, hazel, alder, mugwort, and wall pellitory; positive RAST for grass pollen (at least class 3) Exclusion criteria: Previous specific IT with grass pollen extracts Age: 27.4 years (range 18-56) Sex: 12 women; 5 men Race: NR Other:	1) Adverse reactions 2) Patient-assessed symptom severity and medication use (combined in a single measure): unspecified nasal, conjunctival, and bronchial symptoms graded daily during pollen season on scale of 0-3 (not described); use of symptomatic medication scored daily during pollen season as follows: Nasal vasoconstrictor: 1 per drop Antihistamine: 1 per tablet ß-2-agonist: 1 per puff 3) Skin reactivity 4) Nasal reactivity 5) Allergen-specific IgE and IgG	1) Adverse reactions: IT group: Late local reactions 3/10 pts Late systemic reactions 1/10 pt Placebo group: No adverse reactions 2) Patient-assessed symptom severity and medication use (combined in a single measure): IT patient had significantly lower symptom and medication scores ($p < 0.01$). Data shown in figure of scores over time. 3) Skin reactivity: Not abstracted 4) Nasal reactivity: Not abstracted 5) Allergen-specific IgE and IgG: Not abstracted	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Not described Dropouts described: No Intention-to-treat: Can't determine Notes:

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Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Setting: Allergy clinic Type(s) of providers: Allergists				
Pence, Mitchell, Greely, et al., 1976	Design: RCT, parallel-group Interventions: 1) Aqueous extract of *Juniperus sabinoides* (mountain cedar) pollen (n = 17). Extract prepared in a single lot by lab in Lenoir, NC. Build-up phase: gradually increasing doses given twice weekly, beginning with thousand-fold dilution of the full-strength concentration, until maintenance dose was reached. Maintenance phase: maintenance dose (6 mg of extracted pollen) given weekly. Total dose given ranged from 1 mg to 157 mg of extracted pollen, with mean dose of 58 mg. 2) Placebo (caramelized glucose with histamine added) (n = 15) Duration of study treatment: 1 year Symptomatic medication permitted: Antihistamines or antihistamine-decongestant combinations Dates: 1974-75 mountain cedar pollen season Location: Texas	No. of subjects at start: 40 Dropouts/withdrawals: 8 No. of subjects at end: 32 Inclusion criteria: History of seasonal hay fever or asthma during Nov-March; strongly positive intradermal skin test to mountain cedar pollen; not currently on IT Exclusion criteria: None specified Age: Active group 15-78, mean 37; placebo group 27-62, mean 44 Sex: Active 10 F/17 M, placebo 9 F/15 M Race: NR Other: 8 patients with prior IT. None to mountain cedar.	1) Patient-assessed symptom severity and medication use (combined in a single measure): presence and duration of stuffy/runny nose, sneezing, itchy/watery eyes, cough, and shortness of breath/wheezing recorded twice daily (persisted for ½ hour, ½ to 2 hours, or > 2 hours); use of symptomatic medication recorded daily in study diaries 2) Skin sensitivity 3) Allergen-specific IgE antibody levels	1) Patient-assessed symptom severity and medication use (combined in a single measure): Mean daily symptom-medication scores (± SD) were lower for treated patients (5.46 ± 3.22) than for control patients (8.83 ± 3.15) ($p < 0.01$) 2) Skin sensitivity: Not abstracted 3) Allergen-specific IgE levels: Not abstracted	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Note: SDs calculated from raw data presented in paper.

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Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Setting: Military hospital allergy clinic Type(s) of providers: Specialists				
Pichler, Marquardsen, Sparholt, et al., 1997	Design: RCT, parallel-group Interventions: 1) Standardized extract of *Dermatophagoides pteronyssinus* and *D. farinae* (house dust mite) adsorbed to aluminum hydroxide (Alutard®) (n = 16). "Clustered rush protocol" used: 2-3 injections given at 30-min intervals during weekly visits until maintenance dose (100,00 SQ Units) reached; maintenance dose given every 8 weeks thereafter. 2) Placebo extract (n = 14) Duration of study treatment: 1 year (RCT phase); trial followed by 1-year period during which some (but not all) patients in the placebo group elected to receive active treatment Symptomatic medication permitted: Antihistamine-containing eye drops or nasal spray (levocabastine) and topical steroids (budesonide) for nasal or bronchial use were allowed freely Dates: Not given	No. of subjects at start: 33 Dropouts/withdrawals: 3 (non-compliance or pregnancy) No. of subjects at end: 30 Inclusion criteria: Typical history of perennial rhinopathy and/or asthma; positive prick ST to *D. pteronyssinus* and/or *D. farinae;* positive test for specific IgE to *D. pteronyssinus* and/or *D. farinae;* positive conjunctival or nasal provocation test with mixture of *D. pteronyssinus* and/or *D. farinae;* FEV1 >80% predicted Exclusion criteria: Immunologic or cardiovascular diseases; pregnancy; poor compliance; severe asthma (defined as requiring emergency treatment in last 3 years, nocturnal symptoms despite treatment in past 3 months, need for oral corticosteroids, asthma associated with aspirin or bisulfites); allergy to animal dander if exposed to animals Age: Active, 20-46 (mean 28.8); placebo, 20-42 (mean 31.7) Sex: Active, 5 F/10 M; placebo, 4 F/10 M	1) Adverse reactions 2) Skin reactivity 3) Conjunctival reactivity 4) Patient-assessed symptom severity: rhinitis and bronchial asthma "complaints" recorded daily during two 4-week periods and quantified on a visual analog scale, of which the length was measured 5) Bronchial hyperreactivity to methacholine 6) Use of symptomatic medication: recorded daily during two 4-week periods	1) Adverse reactions: 2 patients with local swelling > 8 cm. 3 patients with mild systemic reaction (rhinorrhea, broncho-spasm), 1 with late exacerbation of rhinoconjunctivitis, 2 with late increase in asthma symptoms. 1 with systemic symptoms requiring epinephrine. 2) Skin reactivity: Not abstracted 3) Conjunctival reactivity: Not abstracted 4) Patient-assessed symptom severity: Values based upon analysis of data from 30 patients because of missing data points. Rhinitis symptoms: Active: 22 before and 9 after (p = 0.0064) Placebo: 39.5 before and 28 after (p = 0.5762) Active vs. placebo before p = 0.1972 Active vs. placebo after p = 0.0383 Asthma symptoms: Active: 5.5 before and 3.5 after (p = 0.0140) Placebo: 13 before and 7 after (p = 0.8467) Active vs. placebo before p = 0.4551 Active vs. placebo after p = 0.0903 5) Bronchial hyperreactivity to methacholine: Not abstracted	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: No Intention-to-treat: No Notes:

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Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Location: Switzerland Setting: Hospital allergy practice Type(s) of providers: Specialists	Race: NR Other: 10 asthmatics in active group and 8 in placebo group		6) Use of symptomatic medication: Use of b-agonists/inhaled corticosteroids (baseline v 1 year): Active: 8/11 v 4/8 Placebo: 4/9 v 2/6 Use of nasal corticosteroids (baseline v 1 year): Active: 5 v 2 Placebo: 2 v 2	
Radcliffe, Lampe, and Brostoff, 1996	Design: RCT, crossover Interventions: 1) Allergen-specific, low-dose immunotherapy using the maximum intradermally tolerated dose (MITD). MITD determined individually for each allergen and defined as 0.05 ml of the strongest concentration in a 1:5 dilution series that did not produce a positive intradermal wheal (positive = mean diameter ≥ 3 mm or more than 2 mm larger than wheal occurring with negative control). Skin-prick testing done to establish MITD for following allergens: house dust, house dust mite, mixed mold spores, cat dander, dog dander, mixed feathers, mixed grass pollen, histamine (positive control), and phenol + glycerin (negative control). Multiple-dose, multiple-allergen MITD injection solution prepared for each patient. Treatment consisted of daily self-administered subcutaneous injection of 0.2 ml of the solution.	No. of subjects at start: 39 Dropouts/withdrawals: 3 No. of subjects at end: 36 Inclusion criteria: Symptoms of perennial allergic rhinitis Exclusion criteria: Positive response to the negative control skin test; well controlled on drug therapy; lack of positive skin test to relevant allergen; nasal polyps Age: 16-66 mean 38.78 Sex: 16M/20F Race: NR Other:	1) Patient preference: patients asked at end of trial whether they had a preference for one treatment over another based on overall symptom improvement 2) Patient-assessed rhinitis symptom severity: nasal blockage, nasal discharge, postnasal drip, sneezing, and anosmia graded daily on scale of 0 (none) to 4 (severe) 3) Patient-assessed *non*-rhinitis symptom severity: assortment of CNS, respiratory, gut, musculo-skeletal, and skin symptoms also graded daily on scale of 0 (none) to 4 (severe) 4) Use of symptomatic medication: recorded daily in study diaries	1) Patient preference: 78% preferred active treatment (p = 0.006) 2) Patient-assessed rhinitis symptom severity: Total (active period vs. placebo period) Total symptoms: -6.81 vs. 1.03 p = 0.006 Nasal blockage -2.31 vs. 0.19 p = 0.02 Nasal discharge -1.86 vs. 0.47 p = 0.006 Postnasal drip -1.42 vs. 0.75 p = 0.02 Sneezing: -0.28 vs. -0.28 p = 1.00 Anosmia -0.94 vs. -0.11 p = 0.02 3) Patient-assessed *non*-rhinitis symptom severity: No data given 4) Use of symptomatic medication: No data given, as concurrent medication use minimal.	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Yes Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Note: This is a crossover study with intervention periods of 2 weeks. Carry-over effect very likely. Also, adequacy of blinding is an issue, with no histamine in the placebo vaccine.

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Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	2) Placebo (diluent [benzyl alcohol + saline] alone) Duration of study treatment: 2 weeks per treatment period (2-week run-in / 2 weeks treatment A / 2-week wash-out / 2 weeks treatment B) Symptomatic medication permitted: "mainly" oral antihistamines and nasal steroids; patients instructed to keep doses to minimum compatible with reasonable comfort Dates: NR Location: England Setting: University Clinic Type(s) of providers: NR				

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Rak, Heinrich, Jacobsen, et al., 2001	Design: RCT, parallel-group Interventions: 1) Standardized depot preparation of birch pollen allergen extract (Alutard® SQ) (n = 21). Treatment given before start of pollen season. Dosage schedule described in Nielsen et al. All patients reached the maintenance dose of 1 ml of 100,000 SQ and received a total of 120-150 µg of allergen before the start of the pollen season. 2) Budesonide nasal spray 200 µg in each nostril once daily in the morning (n = 20). Treatment started 2 weeks before the predicted start of birch pollen season and continued throughout the entire season (mid-April to end of May = 6 weeks). Duration of study treatment: Unclear for immunotherapy (1 pre-season); 6 weeks for nasal steroid; outcomes assessed just before and during one birch pollen season Symptomatic medication permitted: decongestant drops, local antihistamine drops (levocabastine), antihistamine tablets (acrivastine), and for asthmatics, salbutamol Dates: 1992-93	No. of subjects at start: 41 Dropouts/withdrawals: 0 No. of subjects at end: 41 Inclusion criteria: Rhino-conjunctivitis symptoms during birch pollen season; positive prick skin test to birch allergen; specific IgE antibody to birch pollen; if designated asthmatic, positive methacholine challenge test Exclusion criteria: Daily contact with animals in animal allergic subjects; patients with perennial rhinitis symptoms and/or positive skin test response to mites and molds Age: 19-42 mean 29 Sex: 22M/19F Race: NR Other:	1) Patient-assessed symptom severity: eye and nose symptoms graded on scale of 0 (no symptoms) to 3 (severe); recorded daily during three 1-week periods (winter [baseline], just before start of pollen season, and during pollen season) 2) Spirometry (morning and evening peak flow rates) 3) Use of symptomatic medication: recorded daily during three 1-week periods (winter [baseline], just before start of pollen season, and during pollen season); anti-rhinitis drugs scored as follows: decongestant drops, 0.5; acrivastine, 1; and levoca-bastine, 1.5; use of salbutamol assessed separately 4) Bronchial reactivity 5) Eosinophil measures (count, cationic protein, chemotactic activity)	1) Patient-assessed symptom severity: Mean daily symptom scores for combined eyes and nose shown on graph for each of the 6 weeks of pollen season. Numeric values not given. Values were significantly different favoring nasal steroids during weeks 5 and 6 ($p < 0.03$ and $p < 0.04$, respectively). 2) Spirometry: Not abstracted 3) Use of symptomatic medication: Composite medication scores shown on a graph. No significant differences between groups at any time point. 4) Bronchial reactivity: Not abstracted 5) Eosinophil measures: Not abstracted	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Yes Note: Double-dummy blinding technique employed.

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Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Location: Sweden Setting: ENT clinic in county hospital Type(s) of providers: Specialists				
Tari, Mancino, Ghezzi, et al., 1997	Design: RCT, parallel-group Interventions: 1) Alum-adsorbed *Parietaria judaica* (wall pellitory) pollen allergoid (Allergovit®) (n = 20). Pollen extracts standardized against a well-characterized, biologically standardized reference extract. Build-up phase: weekly injections of 0.1, 0.2, 0.4, and 0.8 ml of strength A preparation (1,000 TU/ml) (with slight variations for individual patients), followed by weekly injections of increasing concentrations of strength B preparation (10,000 TU/ml), to a maximum of 1.0 ml (mean cumulative dose of 24,500 TU). Maintenance phase: injections of half the maximum dose administered every 3-4 weeks. 2) Placebo (alum suspension colored with caramel NF acid) (n = 20) Duration of study treatment: 1 year (RCT phase); trial followed by 1-year open study during which all patients received active treatment No description of symptomatic	No. of subjects at start: 40 Dropouts/withdrawals: 1 placebo subject (noncompliance) No. of subjects at end: 39 Inclusion criteria: Clinical history of rhinitis to *Parietaria* ± asthma for 3+ consecutive years; positive prick ST to *Parietaria;* positive nasal provocation with *Parietaria;* positive *Parietaria*-specific IgE test Exclusion criteria: IT in previous 3 years; acute or chronic respiratory infections; active immunologic or systemic disease Age: Active, 20-46 (mean 33.65); placebo, 13-50 (mean 31.65) Sex: Active, 10 F/10 M; placebo, 10 F/10 M Race: NR Other: Asthma present in 14 active and 10 placebo patients	1) Patient-assessed symptom severity and medication use (combined in a single measure): nasal, conjunctival, and bronchial symptoms graded daily on 4-point severity scale (not described); "corresponding scores" compiled for medication use 2) Peak flow rates 3) Adverse reactions: all possible adverse reactions (immediate and late reactions, and systemic responses) were recorded by investigators and graded as mild, moderate, or severe 4) Nasal reactivity 5) Skin reactivity 6) Total IgE and allergen-specific IgE, IgG, IgG1, and IgG4 antibody levels 7) Lymphocyte populations	1) Patient-assessed symptom severity and medication use (combined in a single measure): Described as significant ($p \leq 0.05$) improvement in symptom score for active treatment group. No means or statistics given. 2) Peak flow rates: Not abstracted 3) Adverse reactions: Active: 9 immediate local reactions in 6 patients, and 9 late local reactions in 5 patients. 3 late systemic reactions in 2 patients. No anaphylaxis. Placebo: No local, systemic or anaphylactic reactions 4) Specific nasal reactivity: Not abstracted 5) Skin prick test: Not abstracted 6) Total IgE and allergen-specific IgE, IgG, IgG1, and IgG4: Not abstracted 7) Lymphocyte populations: Not abstracted	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Notes:

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Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	medication permitted (if any) Dates: 1989-90 Location: Italy Setting: Academic hospital allergy practice Type(s) of providers: Specialists				
Van Metre, Adkinson, Amodio, et al., 1980	Design: RCT, parallel-group Interventions: 1) Ragweed pollen extract, administered according to standard immunotherapy schedule (n = 15). 24 weekly injections given in gradually increasing doses (from 0.15 ml of a 1:312,500 concentration to 0.5 ml of a 1:20 concentration), as tolerated. Maintenance dose then given (?) through pollen season. 2) Ragweed pollen extract, administered by the Rinkel method (n = 23). "Optimal dose" determined for each patient based on skin test by serial dilution titration and patient's clinical status. This dose (normally 0.5 ml of the end-point dilution) achieved via a series of weekly injections of gradually increasing strength given from February 27 to August 31; maintenance injections then given weekly during ragweed season. Median cumulative	No. of subjects at start: 52 Dropouts/withdrawals: Text states that 15 patients randomized to placebo group which would have totaled 53 patients. However all data discuss 14 patients in placebo group. Possible typographic error in methods section? No. of subjects at end: 52 Inclusion criteria: History of seasonal rhinitis in Aug/Sept for 2 preceding years; positive skin test response to ragweed pollen extract and ragweed antigen E; positive in vitro leukocyte histamine release to ragweed pollen extract Exclusion criteria: Major rhinitis symptoms during mold season of July and Oct/Nov Age: 18-50 Sex: 39M/13F Race: NR	1) Patient-assessed symptom severity and medication use (combined in a single measure): calculated based on daily diary recordings, but symptoms recorded and method of scoring not described 2) Total IgE and allergen-specific IgE and IgG antibody levels 3) Patient global evaluation of efficacy of treatment: at end of trial, symptoms graded in comparison with those of previous year as "less severe," "same," or "more severe" 4) Adverse reactions	1) Patient-assessed symptom severity and medication use (combined in a single measure): Graph of symptom-medication score vs. time given. Mean daily scores reported as significantly lower in the standard treatment group compared to placebo or Rinkel method ($p < 0.01$). No significant difference in comparing Rinkel vs. placebo groups ($p = 0.3$). Data also presented as dot plot with median values given. No numeric data given. 2) Total IgE and allergen-specific IgE and IgG antibody levels: Not abstracted 3) Patient global evaluation of efficacy of treatment: Patients reporting "hay fever symptoms less severe in 1979" Less severe, same, more severe: Standard: 15, 0, 0 Placebo: 9, 2, 1 Rinkel 1979: 11, 2, 1 Rinkel 1978/79: 9, 0, 0 4) Adverse reactions:	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: No Intention-to-treat: No Note: 9/23 pts in the Rinkel-method group were continuing treatment started in the course of an earlier RCT. Results were reported separately for this group.

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Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	dose approx. 0.0285 µg AgE; range, 0.005 to 0.827. 3) Placebo (histamine caramelized glucose), administered according to Rinkel schedule (n = 14). Duration of study treatment: February 27-October 8 Symptomatic medication permitted: Chlorpheniramine maleate 4 mg or carbinoxamine maleate 4 mg + pseudoephedrine 60 mg, every 4 hours, as needed Dates: 1979 Location: Baltimore, MD Setting: University allergy practice Type(s) of providers: Specialist	Other:		One local and no systemic reactions in Rinkel groups or placebo group. 7/15 patients in standard group had 1+ systemic reactions: 6 moderate treated with epinephrine, 3 mild treated with antihistamine, and 10 very mild requiring no medication. 5 local reactions occurred in 4 subjects in standard therapy group.	

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Van Metre, Adkinson, Amodio, et al., 1982	Design: RCT, parallel-group (matched-pairs design) Interventions: 1) Short ragweed pollen extract concentrate (187 µg AgE/ml), weekly injections (n = 15). Initial dose 0.1 ml of 1:10,000 dilution. Dose increased every week over 21 weeks to maximum tolerated or maintenance dose (0.1 ml of concentrate). Maintenance injections given every 1-3 weeks thereafter. Median cumulative dose 70 µg of AgE (range, 16.4 to 252). 2) Short ragweed pollen extract concentrate (187 µg AgE/ml), clustered injections (n = 18). Injections (3, 2, or 1) given every 3 weeks. Initial treatment 3 doses (0.1, 0.5, and 0.9 ml) of 1:10,000 dilution. Doses increased every 3 weeks over 19 weeks to maximum tolerated or maintenance dose (0.1 ml of concentrate). Maintenance injections given approximately every 3 weeks thereafter. Median cumulative dose 17.5 µg of AgE (range, 2.2 to 147). 3) Placebo extract with histamine, weekly injections, gradually escalating to include 0.014 mg of histamine phosphate (n = 5). 4) Placebo extract with histamine, clustered injections, gradually escalating	No. of subjects at start: 44 Dropouts/withdrawals: 0 No. of subjects at end: 44 Inclusion criteria: History of seasonal rhinitis in late Aug and Sep for 2+ preceding years; positive prick ST to ragweed Exclusion criteria: Major rhinitis symptoms in mold-dominated seasons Age: 27 pts age 18-35 and 17 patients age 36-50 Sex: 14 F Race: NR Other: 11 patients had prior ragweed IT but none in last 6 years. Preferentially recruited patients with negative mold ST responses.	1) Adverse reactions 2) Patient-assessed symptom severity and medication use (combined in single measure): unspecified symptoms and medication use recorded in study diaries from June 16 to Oct 6; scoring system used not described 3) Total IgE and allergen-specific IgE and IgG antibody levels 4) Skin reactivity 5) Patient global evaluation of efficacy: At end of study, patients compared symptoms experienced during study pollen season with those experienced during previous year's pollen season ("less severe," "same," "more severe")	1) Adverse reactions: No large local or systemic reactions in placebo group. Active group: Large local: 33 reactions in 13 subjects (weekly); 15 reactions in 9 subjects (cluster) Systemic: 13 reactions in 7 subjects (weekly); 19 reactions in 10 subjects (cluster) 2) Patient-assessed symptom severity and medication use (combined in single measure): Mean daily symptom-medication scores in both treatment groups significantly lower than placebo ($p < 0.01$). Score: weekly 3.79, cluster 2.21, placebo 11.14 3) Total IgE and allergen-specific IgE and IgG antibody levels: Not abstracted 4) Skin reactivity: Not abstracted 5) Patient global evaluation of efficacy: Less severe, same, more severe: Active weekly: 14, 1, 0 Active cluster: 16, 1, 1 Placebo weekly: 4, 1, 0 Placebo cluster: 4, 1, 1	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: No Randomized: Yes Allocation concealed: No Double-blind: No Blinding adequate: Not applicable Dropouts described: Yes Intention-to-treat: Yes Note: Two placebo groups combined for purposes of analysis.

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Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	to include 0.014 mg of histamine phosphate (n = 6). Duration of study treatment: 7+ months (injections given between Feb 25 and Oct 6) Symptomatic medication permitted: Chlorpheniramine maleate 4 mg or carbinoxamine maleate 4 mg + pseudo-ephedrine 60 mg every 4 hours as needed Dates: 1980 ragweed season Location: Baltimore, MD Setting: Academic hospital based allergy practice Type(s) of providers: Specialists				
Varney, Gaga, Frew, et al., 1991 **and** **Durham, Varney, Gaga, et al., 1991**	Design: RCT, parallel-group Interventions: 1) Partially purified, standardized, alum-adsorbed grass pollen (*Phleum pratense*) extract (Alutard® SQ) (n = 21). Treatment started in April. Build-up phase: Twice weekly injections of gradually increasing doses, from 0.1 ml x 100 SQ/ml (injection 1) to 1.0 ml x 100,000 SQ/ml (injection 15). Adjustments in schedule made on an individual basis, with no further increases after May 28. Maintenance doses (volume reduced by 40%) given	No. of subjects at start: 40 Dropouts/withdrawals: 3 No. of subjects at end: 37 Inclusion criteria: History of severe summer hay fever; poor symptom control despite symptomatic treatment; positive skin prick test (wheal > 5 mm) to timothy grass pollen extract Exclusion criteria: Appreciable clinical history of other allergies; previous IT in 5 years; chronic asthma Age: 35 years (range 19 to 52)	1) Patient-assessed symptom severity (daily diary): breathlessness, coughing, wheezing, chest tightness, sneezing, blocked nose, running nose, itching eyes, red eyes, streaming eyes, swollen eyes, and itching and dryness of mouth and throat graded daily from April to October on visual analog scale of 0-3 (not described) 2) Use of symptomatic medication: scored daily from April to October as follows: Each eye drop, nasal	1) Patient-assessed symptom severity (daily diary): IT 360 Placebo 928 Difference 522 (238 to 825) P = 0.001 2) Use of symptomatic medication: IT 129 Placebo 627 Difference 335 (178 to 574) P = 0.002 3) Patient-assessed symptom severity (every 2 weeks): 19 June analysis: IT 2.2 Placebo 5.5 Difference -3 (-4.8 to -0.5)	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: Not adequately described Level of evidence: 2b Randomized: Yes Allocation concealed: yes Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Can't determine Notes: *(continued on next page)*

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	monthly. 2) Placebo ± histamine ("intermittently 'spiked' with histamine") (n = 16) Duration of study treatment: 8 months (April-November) Symptomatic medication permitted: Sodium cromoglycate eye drops and nasal spray, acrivastine, and salbutamol permitted as required; 7-day course of oral prednisolone could be prescribed if these failed to control symptoms Dates: Location: London, UK Setting: Allergy clinic Type(s) of providers: Allergists	Sex: 18 women; 22 men Race: NR Other:	spray, or salbutamol inhalation: 1 Each acrivastine or prednisolone: 2 3) Patient-assessed symptom severity (every 2 weeks): During pollen season, patients asked to grade their overall symptoms every 2 weeks on a visual analog scale from 0-10 4) Conjunctival reactivity 5) Skin reactivity 6) Patient global assessment of efficacy of treatment: At end of pollen season, patients asked to assess the severity of their hay fever in comparison to previous years on scale of +3 (much better) to -3 (a lot worse) 7) Investigator global assessment of efficacy of treatment 8) Adverse reactions	3 July analysis: IT 1.7 Placebo 4.0 Difference -2.3 (-5 to -1) Symptom-free days: IT 29 days Placebo 8 days Diff 21 d (-26 to -1) p = 0.04 4) Conjunctival reactivity: Not abstracted 5) Skin reactivity: Not abstracted 6) Patient global assessment of efficacy of treatment: IT +3 median Placebo +1 P < 0.001 (Mann-Whitney U test) 7) Investigator global assessment of efficacy of treatment: Not abstracted 8) Adverse reactions: 22 delayed local reactions (swelling < 8 cm diameter) 2 systemic reactions (chest tightness and flushing at 10 min; 1 case of delayed urticaria)	

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Walker, Pajno, Lima, et al., 2001 **and** **Wilson, Nouri-Aria, Walker, et al., 2001**	Design: RCT, parallel-group Interventions: 1) Partially purified, standardized, alum-adsorbed grass pollen (*Phleum pratense*) extract (Alutard® SQ) (n = 22). Treatment started in October. Modified "cluster" regimen used: twice-weekly injections given of gradually increasing doses (from 0.1 ml x 100 SQ/ml to 1.0 ml x 100,000 SQ/ml) over 4 weeks. Adjustments in doses made on an individual basis, "according to published guidelines." Maintenance injections given monthly for further 2 years (dose reduced up to 40% during pollen season). 2) Placebo containing 0.01 mg/ml histamine acid phosphate in diluent (n = 22) Duration of study treatment: Approximately 26-27 months (October 1996-December 1998); patients kept pre-trial symptom and medication diaries from May to August 1996 Symptomatic medication permitted: Sodium cromoglycate eye drops and nasal spray, acrivastine, and salbutamol permitted as required; 7-day course of oral prednisolone could be prescribed if these failed to control symptoms	No. of subjects at start: 44 Dropouts/withdrawals: 7 No. of subjects at end: 37 Inclusion criteria: History of severe hay fever uncontrolled by conventional symptomatic treatment; positive skin prick test (wheal > 5 mm) to grass pollen Exclusion criteria: History of multiple allergies; IT in past 5 years; methacholine PC_{20} (concentration of inhaled methacholine that caused a 20% decrease in FEV_1) < 2 mg/mL (normal range > 16 mg/mL) Age: 32 years (range 22 to 64) Sex: 21 women; 23 men Race: NR Other:	1) Patient-assessed symptom severity: breathlessness, cough, wheezing, chest tightness, sneezing, nasal blockage, running nose, itching eyes, red eyes, streaming eyes, swollen eyes, and itching and dryness of mouth and throat graded daily from May to August on visual analog scale of 0-3 (not described) 2) Use of symptomatic medication: scored daily from May to August as follows: Each eye drop, nasal spray, or salbutamol inhalation: 1 Each acrivastine or prednisolone tablet: 2 3) Bronchial reactivity 4) Skin reactivity 5) Eosinophils, T cells, and IL-5 6) Quality of life: assessed using the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ); completed at baseline and during allergy season 7) Adverse reactions	1) Patient-assessed symptom severity: Difference IT vs. placebo 1186.5 (241.5 to 1928.6; p = 0.01) 2) Use of symptomatic medication: Difference IT vs. placebo 1043.0 (332.0 to 2667.1; p = 0.007) 3) Bronchial reactivity: Not abstracted 4) Skin reactivity: Not abstracted 5) Eosinophils, T cells, and IL-5: Not abstracted 6) Quality of life (overall): Difference IT vs. placebo 0.8 (0.18 to 1.5; p = 0.02) 7) Adverse reactions: No immediate (within 1 hr) systemic reactions or large local reactions observed during induction or maintenance. 9 delayed mild systemic reactions during induction period 4 IT group 5 placebo group 3 delayed mild systemic reactions during maintenance period 3 IT group 0 placebo group	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: Yes Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Notes:

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Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Dates: 1996 to 1998 Location: London, UK Setting: Allergy clinic Type(s) of providers: Allergists				
Weyer, Donat, L'Heritier, et al., 1981	Design: RCT, parallel-group Interventions: 1) Crude extract of the pollen of four grasses (*Dactylis glomerata, Lolium perenne, Secale cereale,* and *Phelum pratense*) (n = 17). Five weekly injections of diluted aqueous extract given in increasing doses (from 0.0025 to 0.05 µg protein contained in 0.2 ml). Then 12 (weekly?) injections of $Al(OH)_3$-adsorbed extract given in gradually increasing doses (1-6.25 µg protein in 0.2 ml of solution). Previous dose repeated in event of strong local or general reaction. Mean dose administered 19.3 ± 3.4 µg protein. 2) Placebo (saline-phenol diluent) (n = 16) Duration of study treatment: 5 months (Nov 1978-Apr 1979); outcomes recorded in study diaries from May 15 to June 30, 1979 Symptomatic medication permitted: Antihistamine	No. of subjects at start: 33 Dropouts/withdrawals: 1 No. of subjects at end: 32 Inclusion criteria: Symptoms of seasonal allergic rhinitis with worsening or symptoms from April to July in previous 2 years; positive skin prick test (wheal at least 8 mm) to four-grass pollen extract; Exclusion criteria: Previous IT treatment with grass pollen extracts; history of corticosteroid treatment during grass pollen season; very severe symptoms Age: 26 years (range 9 to 46) Sex: 17 women; 16 men Race: NR Other: Patients with "very severe symptoms" were excluded "for ethical reasons"	1) Patient-assessed symptom severity: sneezing, stuffy nose, running nose, itchy eyes, watery eyes, red eyes, chest tightness, and asthma graded daily during the pollen season on scale of 0 (no symptoms) to 2 (strong symptoms) 2) Use of symptomatic medication: Meds taken recorded daily (with dose) during the pollen season in study diaries; scored by investigators as follows: No meds taken: 0 Mean of 2 tabs of antihistamine per day: 10 Mean of 3 doses of sodium cromoglycate per day: 20 Mean of 2 inhalations of salbutamol per day: 20 1-week prednisone course: 25 3) Patient-assessed symptom severity and medication use (combined in a single measure)	1) Patient-assessed symptom severity: IT 16 ± 10 Placebo 24 ± 8 P < 0.09 2) Use of symptomatic medication: IT 3 ± 5 Placebo 11± 13 P < 0.07 3) Patient-assessed symptom severity and medication use (combined in a single measure): IT 10 ± 7 Placebo 18 ± 15 P < 0.03 4) Adverse reactions: No quantitative data given "Very few reactions were observed" "A few patients had symptoms, both in the treated and in the placebo group."	Quality Scoring: Population similar: Not adequately described Intervention(s) described: No Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: No Dropouts described: No Intention-to-treat: Can't determine Notes:

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Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	(Mequitazine®), up to 2 tablets per day, at first sign of symptoms; if not sufficient, then sodium cromoglycate nasal spray, up to 4 nebulized doses per day; if still not sufficient and pulmonary symptoms present, then salbutamol, 2 inhalations per day; if still not sufficient, then 6-day course of prednisone given Dates: Nov 1978 – Apr 1979 Location: Paris, France Setting: Allergy clinics Type(s) of providers: Allergists		4) Adverse reactions		
Winther, Malling, Moseholm, et al., 2000	Design: RCT (see Note), parallel-group Interventions: 1) Aluminum-adsorbed birch pollen (*Betula verrucosa*) extract (Alutard® SQ) (n = 26). Clustered regimen given, with gradually increasing doses (from 10 to 100,000 SQ-U) given weekly for 6 weeks. Dose/schedule adjusted in event of adverse reactions. Interval between maintenance injections gradually increased to 2 months. Median cumulative dose 613,110 SQ-U (range, 266,210-645,110). 2) Aluminum-adsorbed grass pollen (*Phleum pratense*) extract (Alutard® SQ) (n = 26).	No. of subjects at start: 52 Dropouts/withdrawals: 3/7/2 in years 1/2/3 No. of subjects at end: 40 Inclusion criteria: History of severe allergy to birch and grass pollen with symptoms in Apr-Jul; positive skin prick (wheal area > 7 mm2) to birch and grass pollen; positive RAST for specific IgE (class 2 or greater) to birch and grass pollen Exclusion criteria: Perennial rhinitis; clinical allergy to animal dander with contact at least weekly; IT within previous 5 years Age: 26 years (range 18 to 52)	1) Patient-assessed symptom severity: sneezing, rhinorrhea, nasal congestion, itchy nose and/or throat, and itchy eyes graded once daily from April to August on scale of 0 (no symptoms) to 3 (severe symptoms) 2) Use of rescue medication: intake recorded daily from April to August	1) Patient-assessed symptom severity: Year 1 Birch group had fewer symptoms than untreated group (p = 0.015) Grass group had similar symptoms as untreated group (p = 0.355) 2) Use of rescue medication: Year 1 Birch group had less medication use than untreated group (antihistamine tablets p = 0.015; eye-drops, p = 0.001; mg prednisolone, p = 0.002) Grass group had less use of antihistamine, but similar use of other medications as untreated group (antihistamine tablets, p = 0.001; eye-drops, p = 0.345; mg prednisolone, p-0.873)	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Unclear (see Note) Allocation concealed: Not described Double-blind: Yes Blinding adequate: Not described Dropouts described: Yes Intention-to-treat: Can't determine

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Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Protocol as above. Median cumulative dose 724,110 SQ-U (range, 68,110-6948,110). Duration of study treatment: 1 year (RCT phase); trial preceded by 1-year observation (no treatment) period and followed by a 1-year period during which all patients received treatment with *both* grass and birch pollen extracts Symptomatic medication permitted: Acrivastine and antazoline-naphazoline eye drops; if symptoms inadequately controlled, course of prednisolone could be prescribed Dates: 1992-1994 Location: Copenhagen, Denmark Setting: Allergy clinic Type(s) of providers: Allergist	Sex: 24 women; 28 men Race: NR Other:			Notes: Though study not explicitly described as “randomized,” likely to be RCT.

Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Zenner, Baumgarten, Rasp, et al., 1997	Design: RCT, parallel-group Interventions: 1) Short-term immunotherapy using a partially purified, standardized, and aluminum hydroxide adsorbed extract containing equal parts of six grasses (*Dactylis glomerata, Lolium perenne, Avena elatior, Phleum pratense, Poa pratensis, and Festuca pratensis*) and rye (*Secale cereale*) (n = 45). Seven weekly injections given in increasing doses (from 3 to 1,000 SE [1,000 SE contains between 1.0 and 2.0 µg of individual grasses]). Dose/schedule modifications made "for medical indications according to the routine procedure of specific immunotherapy." 2) Placebo containing increasing doses of histamine dihydrochloride (n = 41) Duration of study treatment: 7 weeks before start of allergy season Symptomatic medication permitted: Disodium cromoglycate eyedrops and nasal spray, local and systemic antihistamines, sympatho-mimetics and local glucocorticosteroids all permitted Dates: NR	No. of subjects at start: 87 Dropouts/withdrawals: 6 No. of subjects at end: 81 Inclusion criteria: Allergic rhinitis history; positive skin prick (wheal at least 5 mm diameter) to grass and/or rye pollen Exclusion criteria: need for treatment for allergic asthma, perennial rhinitis, or acute infected nasal mucosa; current use of systemic corticosteroids; IT in past 3 years Age: 28.5 (range 16 to 53) Sex: 27 women; 59 men Race: NR Other:	1) Patient-assessed symptom severity: nasal, conjunctival, and bronchial symptoms scored daily during allergy season on scale of 0 (no symptoms) to 3 (severe symptoms) 2) Use of symptomatic medication: graded daily during the allergy season as follows: No drugs: 0 Disodium cromoglycate: 1 Topical corticosteroids or antihistamines: 2 Nasal decongestants: 3 3) Skin reactivity 4) Specific IgE and IgG4 5) Adverse reactions	1) Patient-assessed symptom severity: Overall: STI 82.2 ± 10.1 (mean ± SD) 54 (39-96) median, CI Placebo 116.0 ± 13.2 97.5 (81-117) P = 0.02 (one-tailed Mann-Whitney U test) 2) Use of symptomatic medication: STI 26% of 70 days Placebo 33% P = 0.296 3) Skin reactivity: Not abstracted 4) Specific IgE and IgG4: Not abstracted 5) Adverse reactions: Local reactions (swelling, erythema > 5 cm diameter at injection site): STI 30/309 injections Placebo 6/284 injections Systemic reactions (moderate exacerbations of rhinoconjunctivitis, urticaria, edema of eyelid): STI 9 pts (12 injections) Placebo 5 pts (7 injections) No severe systemic reactions	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: No Intention-to-treat: No Notes:

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Evidence Table 3: Immunotherapy (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Location: Germany Setting: NR Type(s) of providers: Allergists				

[†] Quality scoring criteria were as follows:
Population similar: Was the study population described and reasonably similar to an adult working US population? (Yes [described and similar], No [described, but not similar], Not adequately described)
Intervention(s) described: Were the intervention protocols referenced or described in sufficient detail to replicate? (Yes, No)
Comorbidities described: Was the presence of comorbid asthma (or other upper respiratory conditions) described in the study population? (Yes, No)
Diagnosis by MD: Was the diagnosis of allergic rhinitis based on physician diagnosis? (Yes, No, Not applicable [asthma patients only])
Objectively confirmed: If physician-diagnosed, was the diagnosis supported by objective evidence of allergy (e.g., skin prick or serum IgE antibody testing)? (Yes, No, Not applicable)
Outcome measures valid: Were the main outcomes of interest to us measured in a way that has been demonstrated empirically to be valid and reliable (e.g., using a standardized scale such the RQLQ or SF-36)? (Yes, No, Not adequately described)
Level of evidence: Based on Oxford Center for Evidence-Based Medicine Levels of Evidence (1a, 1b, 1c, 2a, 2b, 2c, 3a, 3b, 4, 5)
Randomized: Was the study described as "randomized"? (Yes, No)
Allocation concealed: If the method for concealing allocation from the investigators was described, was it *adequate* (table of random numbers, computer-generated, coin tossing, etc.) or *inadequate* (alternating, date of birth, hospital number, etc.)? (Not described, Yes [described and adequate], No [described, but inadequate])
Double-blind: Was the study described as "double-blind"? (Yes, No)
Blinding adequate: If the method of double-blinding was described, was it *adequate* (e.g., identical placebo, active placebo, injection vs. tablet with double dummy) or *inadequate* (e.g., tablet vs. injection with no double dummy)? (Not described, Yes [described and adequate], No [described, but inadequate])
Dropouts described: Did the study describe dropouts and withdrawals so that all patients entering the trial could be accounted for? (Yes, No)
Intention-to-treat: Was the analysis performed according to the intention-to-treat principle? (Yes, No, Can't determine)

Evidence Table 4: Combined Treatments

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Andri, Senna, Betteli, et al., 1992	Design: RCT, parallel-group Interventions: 1) Terfenadine 60 mg bid + nimesulide (NSAID) 100 mg bid (n = 15) 2) Terfenadine 60 mg bid + placebo (n = 15) Duration of study treatment: 30 days No other drugs "likely to affect hay fever" permitted No pre-trial washout period described Dates: 5/2/89 - 5/30/89 Location: Italy Setting: Outpatient allergy clinic Type(s) of providers: Allergist	No. of subjects at start: 30 Dropouts/withdrawals: 2 (left area during pollen season) No. of subjects at end: 28 Inclusion criteria: History of parietaria pollen AR; positive skin test; RAST positivity; positive nasal provocation Exclusion criteria: "Other major disease;" ASA sensitivity Age: 18-48 (mean 32.1, SD 8.9) Sex: 18 M, 12 F Race: NR Other:	1) Investigator-assessed symptom severity 2) Patient-assessed symptom severity: nasal itching, nasal obstruction, sneezing, running nose, eye irritation, and eye watering graded daily by patients scale of 0 (none) to 3 (severe) 3) Patient global assessment of efficacy: recorded once at end of trial – categorical scale keyed to perceived degree of improvement in symptoms (< 50%, 50-80%, > 80%) 4) Adverse events: Not clear how reported/ recorded	1) Investigator-assessed symptom severity: Not abstracted 2) Patient-assessed symptom severity: Mean symptom score shown Figure 2, $P \leq 0.005$ terfenadine + nimesulide vs. terfenadine + placebo Table 2: Average symptom score (no SD reported): Terfenadine + nimesulide: Day 1, 8.4; day 15, 2.9; day 30, 1.1 Terfenadine + placebo: Day 1, 7.4; day 15, 3.6; day 30, 2.6 $P \leq 0.001$ at days 15 and 30 3) Patient global assessment of efficacy: Terfenadine + nimesulide: Recovering n = 10, good improvement 2, no or slight improvement 2 Terfenadine + placebo: Recovering 5, good improvement 2, no to slight improvement 7 $0.1 < P \leq 0.12$, by Chi-square 4) Adverse events: 3 terfenadine + nimesulide, 2 terfenadine + placebo reported occasional sleepiness and sedation (5 total, with no withdrawal)	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: No Blinding adequate: Not applicable Dropouts described: Yes Intention-to-treat: Can't determine Notes: Local pollen counts conducted daily during trial. No sample size or power calculation.

Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Backhouse, Finnamore, and Gosden, 1986	Design: RCT, parallel-group Interventions: 1) Terfenadine 60 mg bid + flunisolide (two 25-mcg spray to each nostril bid) (T+F) (n = 49) 2) Terfenadine 60 mg bid (T) (n = 50) Duration of study treatment: 11 weeks No mention of rescue med No pre-trial washout period described; patients who had received systemic steroid therapy within previous 3 months or anti-allergic treatment within previous 2 weeks were excluded Dates: May and Aug (1985?) Location: England Setting: Outpatient Type(s) of providers: Specialist	No. of subjects at start: 99 Dropouts/withdrawals: 22 total 17 from T group (10 poor symptom control, 1 headache, 1 pregnancy, 1 glandular fever, 2 lack of symptoms, 1 personal reasons, 1 lost to follow-up) 5 from T+F group (2 poor symptoms control, 2 personal reasons, 1 left country) P < 0.005 No. of subjects at end: 75 Inclusion criteria: 2-year history of moderate-severe seasonal allergic rhinitis Exclusion criteria: Pregnant, lactating, URI, nasal obstruction abnormalities, systemic steroids within 3 months, allergy treatment within 2 weeks Age: 13-65, mean age Sex: 51 M, 48 F Race: NR Other:	1) Investigator-assessed symptom severity 2) Patient-assessed symptom severity: sneezing, runny nose, blocked nose, and eye symptoms assessed on scale of 1-4 by patients in daily diary recordings and at clinic visits at 3,7, and 11 weeks 3) Investigator-and-patient global assessment: overall effect of treatment rated ("by both the doctor and the patient") as excellent, good, poor, none, or symptoms worse at clinic visits at 3, 7, and 11 weeks 4) Adverse events: Not clear how reported/ recorded	1) Investigator-assessed symptom severity: Not abstracted 2) Patient-assessed symptom severity: (see Table 2 for week 3 and 7 results) Week 11 mean scores (SD): Sneezing: T group 1.3 (0.6), T+F group 1.0 (0.2), P = 0.12 Nose blowing: T group 1.3 (0.8), T+F group 1.0 (0.2), P = 0.15 Runny nose: T group 1.4 (0.8), T+F group 1.2 (0.5), P = 0.03 Stuffy nose: T group 1.3 (0.7), T+F group 1.2 (0.5), P = 0.28 Eye symptoms: T group 1.4 (0.8), T+F group 1.1 (0.3), P = 0.18 Note: significant p-values mostly at week 7, when pollen count was high 3) Investigator-and-patient global assessment: Week 7, good or excellent response 96% T&F group, 62% T group, P = 0.001 Not reported for Week 11 4) Adverse events: 29 pts T group (9 drowsiness, 5 nausea/vomiting, 3 headache, 2 loss of concentration, 1 loss of balance, 1 depression, 8 other), only 12 felt to be due to study drug 35 pts T+F group (10 nasal/throat irritation, 7 drowsiness, 2 headache, 2 hangover, 1 irritation, 1 husky voice, 3 dry throat, 9 other), only 21 felt to be due to study drug	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: No Objectively confirmed: No Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: No Blinding adequate: No Dropouts described: Yes Intention-to-treat: Can't determine Notes: Single-blind trial. Local pollen counts recorded during weeks 3-9 of study.

Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Benincasa and Lloyd, 1994	Design: RCT, parallel-group Interventions: 1) Fluticasone propionate nasal spray 200 µg (2 actuations per nostril) + oral cetirizine 10 mg, once per day (n = 227) (Combo group) 2) Fluticasone propionate nasal spray 200 µg once per day (n = 227) (FPANS group) Duration of study treatment: 8 weeks Patients provided with eye drops containing a mixture of antazoline and xylometazoline (Otrivine-Antistin®) to be used "if eye symptoms became troublesome" No pre-trial washout period described; patients who had taken following drugs, in time frames indicated, were excluded: intranasal or oral corticosteroids, ketotifen, or sodium cromoglycate (4 weeks); astemizole (6 weeks); depot corticosteroids (8 weeks); immunotherapy injections (grass pollen) (6 months) Dates: Start date 5/14/90, end date 8 weeks later Location: UK Setting: 64 general practice clinics	No. of subjects at start: 455 screened, 454 randomized (227 per group) Dropouts/withdrawals: 68 (1 withdrew prior to randomization, 37 from FPANS group, 30 from Combo group). No. of subjects at end: 387 Inclusion criteria: Required treatment for hay fever symptoms during June in previous 2 years; at least 2 of following symptoms (1 nasal symptom): sneezing, nasal itching, runny nose, or nasal congestion, eye watering/irritation, or headache. Patients with asthma included if unlikely to require change in medication over 8-week study period. Exclusion criteria: Prescription med for respiratory infection in past 2 weeks; treatment for allergic rhinitis in past week; intranasal or oral corticosteroids, ketotifen or sodium cromoglycate in past 4 weeks; astemizole in past 6 weeks, depot steroids in past 8 weeks, or immunotherapy to grass pollen in past 6 months; nasal surgery past 2 months, nasal pathology (polyp, turbinate hypertrophy, septal deviation), chronic sinusitis; recurrent conjunctivitis, or soft contact lens use; pregnant or lactating Age: FPANS group: mean 31 (range 12-80); Combo group: mean 30 (12-66)	1) Patient-assessed symptom severity: nasal symptoms, eye symptoms, and headache graded daily on scale of 0 (no symptoms) to 7-9 (severe symptoms). Diaries used weeks 3-8. 2) Use of rescue med (eye drops): recorded daily in study diaries 3) Patient global evaluation of efficacy of treatment: patients asked at end of study whether treatment had adequately controlled their nasal, eye, and headache symptoms (yes/no) 4) Investigator global evaluation of efficacy 5) Adverse events: not clear how reported/ recorded; all AEs recorded regardless of possible relationship to study drugs	1) Patient-assessed symptom severity: no significant differences in any symptoms or symptom-free days Symptom scores (mean [SD]): Nasal: 1.5 (1.4) FPANS, 1.5 (1.6) Combo Eye: 1.3 (1.3) FPANS, 1.1 (1.3) Combo Headache: 0.4 (0.9) FPANS, 0.4 (0.7) Combo Proportion symptom-free days (mean [SD]): Nasal: 0.45 (0.38) FPANS, 0.46 (0.4) Combo Eye: 0.56 (0.36) FPANS, 0.57 (0.36) Combo Headache: 0.86 (0.22) FPANS, 0.85 (0.25) Combo 2) Use of rescue medication: No significant difference Proportion of dayswithout rescue medication, mean (SD): FPANS: 0.81 (0.29) Combo: 0.82 (0.26) 3) Patient global evaluation of efficacy of treatment: Percentage reporting adequate control: Nasal: 88% FPANS, 89% Combo Eye: 75% FPANS, 82% Combo Headache: 83% FPANS, 86% Combo 4) Investigator global evaluation of efficacy: Not abstracted 5) Adverse events: Serious AEs: 12 pts (5%) FPANS group, 10 pts (4%) Combo group Highest reported serious AE was drowsiness: 2 FPANS, 3 Combo. Only 1 SAE in FPANS group and 4 serious	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: No Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Yes Note: No sample size calculation reported.

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Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Type(s) of providers: Primary care	Sex: 194 M (95 FPANS, 99 Combo); 260 F (132 FPANS, 128 Combo) Race: NR Other:		AEs in Combo group were judged to be related to study medication. Minor AEs: 295 events from 124 pts (55%) FPANS group; 286 events from 133 pts (59%) Combo group. Most AEs were symptoms of seasonal allergic rhinitis (highest reported AE was headache, 28% of FPANS group, 22% of Combo group). Only 14 (5%) of reports in FPANS group and 17 (6%) in Combo group were considered by MD to be related to study treatment.	
Berger, Fineman, Lieberman, et al., 1999	Design: RCT, parallel-group Interventions: 1) Azelastine nasal spray, 2 sprays per nostril bid (1.1 mg/day) + placebo capsule once per day (AZ) (n = 538) 2) Intranasal beclomethasone dipropionate monohydrate, 2 sprays per nostril bid (336 µg/day) + loratadine 10 mg once per day (BEC+LOR) (n = 532) Duration of study treatment: 7 days Rescue med: chlorphenir-amine maleate 4 mg prn during washout, but not 48 hrs prior to randomization Trial preceded by 1- to 2-week washout period (1 week for pts on oral antihistamine, 2 weeks for pts on nasal steroid) Dates: 1998 spring allergy season	No. of subjects at start: 1070 from 3 separate studies Dropouts/withdrawals: 15 total 10 pts in AZ group: 1 intercurrent illness, 4 protocol violation, 1 withdrew consent, 1 treatment failure, and 3 pts discontinued due to AEs (1 sinusitis, 1 sneezing, 1 upper respiratory infection) 5 pts in BEC+LOR group: 2 intercurrent illness, 1 protocol violation, 2 discontinued due to AEs (1 vertigo/N/CP, 1 nasal burning) No. of subjects at end: 1055 Inclusion criteria: Age ≥ 12; documented seasonal allergic rhinitis; on monotherapy with either oral antihistamine or nasal steroid; MD-determined candidate for combination therapy due to lack of adequate symptom control; symptoms rating score ≥ 18 (range 0-50), with at least 3 symptoms of moderate or greater intensity	1) Investigator global assessment 2) Patient global assessment: Patients asked to compare how they felt on last day of treatment (day 7) with how they felt prior to treatment on scale ranging from +2 (much better, near complete or complete symptom relief) to -2 (much worse, marked deterioration of symptoms), assessment of +1 or +2 considered improvements 3) Adverse events: Not clear how reported/ recorded	1) Investigator global assessment: Not abstracted 2) Patient global assessment: Improved Study 1: AZ 80%, BEC+LOR 90% Improved Study 2: AZ 77%, BEC+LOR 86% Improved Study 3: AZ 84%, BEC+LOR 85% 3) Adverse events: AZ group: 8% aftertaste, 5% headache, 3% rhinitis, 2% somnolence BEC+LOR group: 1% aftertaste, 6% headache, 1% rhinitis, 1% somnolence	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: No Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Yes Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Yes Notes: Bottles of nasal steroid looked different. Reports results of 3 separate RCTs. Treatment lasted only 7 days.

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Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Location: US Setting: 71 outpatient allergy/ENT centers Type(s) of providers: Specialist	Exclusion criteria: Unable to use/tolerate nasal spray; asthma; investigational drug w/in 30 days; use of antidepressants; upper respiratory infection within 30 days; any clinically significant acute/chronic illness Age: Mean 35 (range 12-80) Sex: 57-63% F, 37-43% M Race: 81-90% white				
Bertrand, Jamart, Marchal, et al., 1996	Design: RCT, parallel-group Interventions: 1) Pseudoephedrine 120 mg (extended-release) bid + cetirizine 5 mg bid (n = 70) (COM group) 2) Pseudoephedrine 120 mg (extended-released) bid (n = 70) (PER group) 3) Cetirizine 5 mg bid (n = 70) (CTZ group) Duration of study treatment: 3 weeks No mention of rescue med Pre-trial washout period ranged from 2 days to 6 weeks, depending on pre-trial medication Dates: NR Location: 8 centers in Belgium and Luxembourg	No. of subjects at start: 210 Dropouts/withdrawals: 39 total 7 CTZ group (1 inefficacy, 2 AEs, 4 protocol violation/personal reasons); 19 PER group (2 inefficacy, 9 AEs, 8 protocol violation/personal reasons); 13 COM group (4 AEs, 9 protocol violation/personal reasons) No. of subjects at end: 210 included in analysis Inclusion criteria: Perennial allergic rhinitis of at least 1 year duration; positive skin or RAST allergy test; presence of nasal obstruction, sneezing, and rhinorrhea Exclusion criteria: Pollen-sensitive patients excluded during pollen season; infectious rhinitis; nasal polyposis; nasal septal deviation; dermatitis; infections requiring antibiotic treatment; pregnancy; childbearing potential; breastfeeding	1) Investigator-assessed symptom severity 2) Patient-assessed symptom severity: blocked nose, sneezing, runny nose, itchy nose, and itchy eyes graded on scale of 0 (no symptoms) to 4 (severe symptom interfering with daily activities and/or sleep) at end of every day throughout trial 3) Investigator global assessment 4) Adverse events: Not clear how reported/ recorded	1) Investigator-assessed symptom severity: Not abstracted 2) Patient-assessed symptom severity: Figures 1-5, daily symptom scores per group: Nasal obstruction: P < 0.0001, COM vs. CTZ; P = 0.004, COM vs. PER; P = 0.128, CTZ vs. PER Rhinorrhea: P = 0.174, COM vs. CTZ; P = 0.001, COM vs. PER; P = 0.072, CTZ vs. PER Sneezing: P = 0.790, COM vs. CTZ; P = 0.021, COM vs. PER; P = 0.012, CTZ vs. PER Nasal itching: P = 0.384, COM vs. CTZ; P = 0.158, COM vs. PER; P = 0.018, CTZ vs. PER Eye itching: P = 0.204, COM vs. CTZ; P = 0.080, COM vs. PER; P = 0.006, CTZ vs. PER 3) Investigator global assessment: Not abstracted 4) Adverse events: 31 CTZ (6 somnolence, 4 bronchitis, 3 headache, 2 asthenia, 1 each insomnia and nervousness) 38 PER (7 insomnia, 6 dry mouth, 6	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Yes Note: Double-dummy blinding technique employed. *(continued on next page)*

Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Setting: Outpatient Type(s) of providers: Otolaryngologist	Age: 12-65 Sex: 97 M, 113 F Race: NR Other:		nausea, 5 headache, 4 asthenia, 3 somnolence, 1 nervousness) 35 COM (9 somnolence, 8 headache, 4 each asthenia, dry mouth, nervousness, and insomnia)	
Bronsky, Boggs, Findlay, et al., 1995	Design: RCT, parallel-group Interventions: 1) Loratadine 10 mg + pseudoephedrine 240 mg (extended-release) once per day (Combo group) (n = 212) 2) Loratadine 10 mg once per day (LOR group) (n = 212) 3) Pseudoephedrine 120 mg (extended-release) bid (PSE group) (n = 211) 4) Placebo (n = 212) Duration of study treatment: 2 weeks No mention of rescue med Trial preceded by washout period ranging from 1 day to 1 month (depending on pre-trial medication) and a 4- to 7-day placebo run-in phase (baseline) Dates: Fall allergy season, 1989 Location: US Setting: 14 outpatient allergy centers	No. of subjects at start: 879 Dropouts/withdrawals: 5 dropouts prior to treatment 54 total discontinuations 11 Combo group (5 treatment failure, 4 AEs, 1 noncompliance, 1 lost to follow-up) 17 LOR group (12 treatment failure, 1 AEs, 4 noncompliance) 13 PSE group (4 treatment failure, 9 AEs) 13 placebo group (11 treatment failure, 2 AEs) No. of subjects at end: 874 included in safety analysis, 847 in efficacy analysis (27 protocol violations) Inclusion criteria: Seasonal allergic rhinitis for at least 1 year, confirmed by skin test to ragweed or other prevalent seasonal allergens; total symptom score ≥ 11 on 50% of days during placebo phase; ≥ 80% compliance with placebo phase drug Exclusion criteria: Immuno-therapy within 6 months; asthma requiring steroids; multiple drug allergies; nonresponders or previous reaction to anti-histamines; upper respiratory infection, investigational drug	1) Investigator-assessed symptom severity: rhinor-rhea, nasal stuffiness, nasal itching, sneezing, burning or itching eyes, watering eyes, red eyes, and itching of the ears or palate graded on scale of 0 (none) to 3 (severe) during clinic visits on days 4, 8, and 15 of the treatment period. 2) Patient-assessed symptom severity: Patients kept daily diary of symptom severity (presumably using same scale as above, though this is not stated). 3) Investigator global assessment of response to treatment 4) Patient global assessment of response to treatment: graded on scale of 1 (excellent) to 5 (treatment failure) during clinic visits on days 4, 8, and 15 of the treatment period. 5) Adverse events: Not clear how reported/	1) Investigator-assessed symptom severity: Not abstracted 2) Patient-assessed symptom severity: No quantitative data reported. Results described as "similar" to those of investigator assessment of symptom severity. Total symptom score reduction significantly greater ($P \leq 0.05$) in Combo group than in other three treatment groups. Total symptom score reduction also greater in LOR group than in placebo group ($P = 0.04$). Repeated measures analysis $P \leq 0.01$ in Combo and LOR groups compared to placebo (plus Combo vs. PSE group). Similar results for nasal and nonnasal symptom scores. 3) Investigator global assessment of response to treatment: Not abstracted 4) Patient global assessment of response to treatment: Excellent or good response 125 (61%) Combo, 106 (52%) PSE, 95 (47%) LOR, 73 (35%) placebo 5) Adverse events: 124 Combo (55 headache, 17 dry mouth, 14 pharyngitis, 13 somnolence, 12 insomnia, 11 nervousness) 102 LOR group (50 headache, 18	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Notes: Double-dummy blinding technique employed. Pollen counts determined twice weekly during trial at all study sites.

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Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Type(s) of providers: Allergists	within 1 month; pregnancy/ lactation; significant medical condition Age: Range 12-82, median 28-30 Sex: Of 847 pts, 395 (47%) male, 452 (53%) female Race: Of 847 pts, 747 (88%) white, 43 (5%) black, 57 (7%) other Other:	recorded	pharyngitis, 9 somnolence, 7 dry mouth, 1 each insomnia and nervousness) 133 PSE group (57 headache, 19 insomnia, 16 dry mouth, 11 pharyngitis, 10 somnolence, 8 nervousness) 100 placebo group (60 headache, 15, pharyngitis, 8 somnolence, 6 dry mouth, 1 nervousness) More AEs in Combo and PSE groups than in placebo group, $P \leq 0.05$ Hyperkinesia higher in PSE group compared to placebo or loratadine.	
Brooks, Francom, Peel, et al., 1996	Design: RCT, parallel-group Interventions: 1) Loratadine 10 mg once per day + beclomethasone nasal spray, 2 sprays (about 84 µg) in each nostril twice a day (LOR+BEC) (n = 20) 2) Loratadine 10 mg once per day (LOR) (n = 20) 3) Beclomethasone nasal spray, 2 sprays (about 84 µg) in each nostril twice a day (BEC) (n = 20) Duration of study treatment: 9 days (2-week study period included 5-day no-treatment run-in period) Patients instructed not to take any other drugs that might affect their hay fever during study period Trial preceded by 5-day no-	No. of subjects at start: 60 Dropouts/withdrawals: NR No. of subjects at end: 60 Inclusion criteria: History of ragweed seasonal allergic rhinitis with strongly positive skin tests Exclusion criteria: Evidence of significant complicating disease on history, physical, or laboratory testing; pregnancy Age: Reported as "roughly comparable" Sex: 10M/10F LOR 7M/13F BEC 7M/13F LOR+BEC group Race: NR Other:	1) Patient-assessed symptom severity: congestion, running/ blowing, sneezing, itching, and eye symptoms graded twice daily on scale of 1 (no symptoms) to 5 (maximum symptoms) 2) Patient global evaluation of efficacy of treatment: on last day of study, patients asked to grade overall effectiveness of treatment as "excellent," "good," "fair," or "poor'	1) Patient-assessed symptom severity: Mean changes shown in Figures 1-5 for 3 segments (days 2-3, days 5-7, days 8-10). Overall similar improvement with BEC and LOR+BEC for congestion, eye symptoms, and runny nose. LOR+BEC better than BEC alone for itching ($p = 0.13$) and sneezing ($p = 0.589$), but was not statistically significant. LOR+BEC was significantly better than LOR alone ($p < 0.001$) for all symptoms. 2) Patient global evaluation of efficacy of treatment: LOR+BEC superior to BEC alone ($p = 0.042$), and to LOR alone ($p = 0.001$). No difference between BEC and LOR alone ($p = 0.122$). Excellent: 6 BEC, 4 LOR, 11 LOR+BEC Good: 9 BEC, 5 LOR, 8 LOR+BEC Fair: 4 BEC, 9 LOR, 1 LOR+BEC Poor: 1 BEC, 2 LOR, 0 LOR+BEC	Quality Scoring: Population similar: Not adequately described Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: No Blinding adequate: Not applicable Dropouts described: Yes Intention-to-treat: Can't determine Notes: Double-dummy blinding technique employed. No sample size estimate or adverse events reported.

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Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	treatment run-in period Dates: Aug 18 - Sept 1 (year unknown) Location: US (Kalamazoo, MI) Setting: Pharmaceutical (Upjohn) research clinic Type(s) of providers: NR				
Brooks and Karl, 1988	Design: RCT, parallel-group Interventions: 1) Terfenadine 60 mg bid + flurbiprofen 100 mg tid (n = 14) 2) Terfenadine 60 mg bid (n = 14) Duration of study treatment: 1 week No mention of rescue med Trial preceded by 1-week run-in period, during which patients first took the symptomatic treatment of their choice (first ½ of run-in week), then terfenadine 60 mg bid (second ½ of run-in week) Dates: NR Location: Bronson Clinical Research Unit, Kalamazoo MI Setting: Outpatient **Type(s) of providers: NR**	No. of subjects at start: 28 Dropouts/withdrawals: 1 No. of subjects at end: 27 Inclusion criteria: "Credible" history of seasonal rhinitis and positive skin test Exclusion criteria: Significant complicating disease; aspirin sensitivity Age: Terfenadine + flurbiprofen: mean 36.8 (SD 10.3) Terfenadine alone: 37.9 (SD 9.7) Sex: Terfenadine + flurbiprofen: 5M/9F Terfenadine alone: 9M/5F Race: NR	1) Patient-assessed symptom severity: discrete symptoms graded 4 times per day on different scales, with 0 always indicating no symptoms and highest number always indicating maximum symptoms; symptoms graded were: congestion (0-8); drainage/postnasal drip (0-3); running nose/ blowing (0-4); sneezing in last ½ hour (0-4); hay fever-related itching (0-4); hay fever-related eye symptoms (0-4) 2) Adverse events: not clear how reported/ recorded	1) Patient-assessed symptom severity: Mean daily symptoms scores show in Figures 1-4. No values reported. P-values are based on comparison of mean daily totals. P-values significant (< 0.05) on day 3 (congestion, P = 0.043; sneeze score, P = 0.026) and day 4 (running/blowing nose, P = 0.006) 2) Adverse events: Several volunteers reported side effects, mostly moderate gastrointestinal symptoms. Not quantified further. One dropout after day 1 after experiencing cramps & nausea (received terfenadine + flurbiprofen).	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: No Blinding adequate: Not applicable Dropouts described: Yes Intention-to-treat: Yes Notes: Patients assigned to 1 of 4 strata based on total symptom score, then randomized. P-values are based on comparison of mean daily totals. No overall assessment of treatment (e.g., pre- and post-treatment summary scores). Analysis is incorrect. Time period of treatment may be too short.

Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Bukstein, Biondi, Blumenthal, et al., 1996	Design: RCT, parallel-group Interventions: 1) Nedocromil sodium 1% nasal spray (1 spray per nostril, 4 times per day) + astemizole (one 30-mg dose on Day 1, one 20-mg dose on Day 2, and one 10-mg dose per day thereafter) (n = 147) 2) Astemizole (as above) + placebo nasal spray (n = 150) 3) Double-dummy placebo (n = 74) Duration of study treatment: 4 weeks Pseudoephedrine and artificial tears permitted "for relief of intolerable symptoms" Trial preceded by washout period ranging from 16 hours to 4 weeks (depending on pre-trial medication) and 1-week baseline period timed to coincide with start of local ragweed pollen season Dates: Local ragweed season Location: US Setting: 13 outpatient sites Type(s) of providers: Allergists	No. of subjects at start: 371 Dropouts/withdrawals: 20 dropouts from treatment failure (12), protocol violation/ noncompliance (6), other (2) 6 not included in analysis (4 withdrawn from poor use of treatment, 1 upper respiratory infection, 1 travel out of pollen area) No. of subjects at end: 365 Inclusion criteria: Seasonal allergic rhinitis to ragweed for 2 years requiring continuous treatment; positive skin test Exclusion criteria: Women of childbearing potential; sinusitis; polyposis; immunotherapy; recent astemizole, corticosteroids, cromolyn sodium, short-acting antihistamines, decongestants, vasoconstrictors, or theophylline Age: 12-64; means 33.9 (nedocromil + astemizole), 35.1 (astemizole), and 31.8 (placebo) Sex: 279 (76%) male; 86 (44%) female Race: NR Other:	1) Patient-assessed symptom severity: stuffy nose, runny nose, itchy nose, sneezing, and overall nasal symptoms graded daily on scale of 0 (none) to 4 (very severe) 2) Patient-assessed sleep disturbance due to rhinitis: graded daily on scale of 0 to 2 (not described) 3) Use of rescue med (recorded by patients in daily diaries) 4) Investigator assessment of clinical signs of rhinitis 5) Investigator global assessment of treatment efficacy 6) Patient global assessment of treatment efficacy: graded as "good" (symptoms fully or mostly controlled), "fair" (symptoms fairly well controlled), or "poor" (symptoms controlled poorly or not at all) during clinic visits at 1 and 4 weeks 7) Adverse events: Not clear how reported/ recorded	1) Patient-assessed symptom severity: Symptom summary mean (SD): Nedocromil + astemizole: 1.02 (0.78), $p < 0.001$ vs. placebo, $p < 0.01$ vs. astemizole Astemizole: 1.21 (0.84), $p < 0.001$ vs. placebo Placebo: 1.49 (0.90) Mean change from baseline (SD): Nedocromil + astemizole: -0.39 (0.76), $p < 0.001$ vs. placebo, $p < 0.01$ vs. astemizole Astemizole: -0.22 (0.68), $p < 0.001$ vs. placebo Placebo: +0.21 (0.77) 2) Patient-assessed sleep disturbance due to rhinitis: Nedocromil + astemizole 0.58 (0.63), $p = 0.11$ vs. placebo Astemizole 0.69 (0.62), $p < 0.18$ vs. placebo Placebo 0.73 (0.61) 3) Use of rescue med (pseudo-ephedrine) (tabs/day): Nedocromil + astemizole 0.34 (0.86), $p = 0.02$ vs. astemizole Astemizole 0.55 (1.03) Placebo 0.68 (1.15) 4) Investigator assessment of clinical signs of rhinitis: Not abstracted 5) Investigator global assessment of treatment efficacy: Not abstracted 6) Patient global assessment of treatment efficacy: Symptoms controlled fully/mostly: Nedocromil + astemizole: 64%, $p < 0.001$ vs. placebo, $p < 0.01$ vs. astemizole alone	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Yes Note: Pollen counts measured daily at each site.

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Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
				Astemizole: 47%, p < 0.01 vs. placebo Placebo: 28% 7) Adverse events: 63 (43%) Nedocromil + astemizole 52 (35%) Astemizole 20 (27%) Placebo Trend towards more headache in combo group (p = 0.058)	
Busse, Janssens, and Eisen, 1996	Design: RCT, parallel-group Interventions: 1) Nasal spray containing levocabastine (0.5 mg/ml) and oxymetazoline (0.5 mg/ml), 2 sprays per nostril twice per day (n = 251) 2) Levocabastine nasal spray, 2 sprays per nostril twice per day (n = 255) 3) Oxymetazoline nasal spray, 2 sprays per nostril twice per day (n = 252) 4) Placebo nasal spray (n = 257) Duration of study treatment: 1 week No mention of rescue med No pre-trial washout period described; patients who had taken following drugs, in time frames indicated, were excluded: systemic cortico-steroids (1 month); topical corticosteroids or sodium cromoglycate (2 weeks);	No. of subjects at start: 1015 Dropouts/withdrawals: 38 (7 levocabastine, 5 levocabastine-D, 12 oxymetazoline, 14 placebo No. of subjects at end: 977 Inclusion criteria: Age 18-60 with 1-year history of seasonal allergic rhinitis; positive skin test to ragweed allergen (= 3 mm); moderate-severe nasal congestion and at least one other moderate-severe nasal symptom Exclusion criteria: Other forms of rhinitis or sinusitis; moderate-severe asthma; serious comorbid disease; systemic steroids within 1 month; topical steroids or sodium cromoglycate within 2 weeks; decongestants or antihistamines within 3 days; astemizole within 6 weeks; any use of tricyclic antidepressants, MAOI, other CNS depressants; antihypertensive drugs; change in immunotherapy in past 6 months; pregnant or lactating; investigational drug within 30 days; hypersensitivity to antihistamines; travel outside of	1) Patient-assessed symptom severity: nasal congestion, rhinorrhea, nasal itching, sneezing, itching eyes, lacrimation, and redness of eyes graded daily using scale of 0 (absent) to 3 (severe) 2) Investigator-assessed symptom severity 3) Patient global evaluation of efficacy: effect of treatment on overall severity of rhinitis graded at end of trial as "excellent," "good," "fair," "poor," or "worse" 4) Investigator global evaluation of efficacy 5) Adverse events: spontaneously reported during clinic visits (after 3 days of treatment and at end of week)	1) Patient-assessed symptom severity: Reported mean change in Area Under Curve (AUC) from baseline. Statistical significance calculated versus placebo. Total all symptoms (mean change AUC): -1.7 placebo -3.3 levocabastine-D *** -3.5 levocabastine *** -1.8 oxymetazoline *** P = 0.001 compared to placebo 2) Investigator-assessed symptom severity: Not abstracted 3) Patient global evaluation of efficacy: Report of excellent or good: 26% placebo 52% levocabastine-D 44% levocabastine 39% oxymetazoline 4) Investigator global evaluation of efficacy: Not abstracted 5) Adverse events: 32% placebo 40% levocabastine-D 30% levocabastine 40% oxymetazoline Headache and application site	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Yes Note: Data pooled from 3 RCTs sharing a common protocol.

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Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	astemizole (6 weeks); other decongestants or anti-histamines (3 days) Dates: 1990 fall ragweed pollen season Location: US and Canada Setting: Outpatient Type(s) of providers: specialists	pollen area for longer than 1 day Age: Eligible 18-60; mean (yrs) reported per group 36.5 placebo 35.8 levocabastine-D 36.5 levocabastine 35.7 oxymetazoline Sex: 167M/90F placebo 173M/78F levocabastine-D 168M/87F levocabastine 161M/91F oxymetazoline Race: NR Other:		reactions most frequently reported A Es Headache: 31 placebo 26 levocabastine-D 15 levocabastine 31 oxymetazoline Application site reactions: 15 placebo 23 levocabastine-D 17 levocabastine 34 oxymetazoline	
Diamond, Gerson, Cato, et al., 1981	Design: RCT, parallel-group Interventions: (34-40 pts per group) 1) Triprolidine 2.5 mg + pseudoephedrine 60 mg, given in a single tablet 3 times per day (n = NR) 2) Triprolidine 2.5 mg, 3 times per day (n = NR) 3) Pseudoephedrine 60 mg, 3 times per day (n = NR) 4) Placebo, 3 times per day (n = NR) Duration of study treatment: 1 day, from 10:00 AM to 6:00 PM (drugs administered and outcomes measured on-site) No mention of rescue med	No. of subjects at start: NR Dropouts/withdrawals: NR No. of subjects at end: 151 Inclusion criteria: Allergic rhinitis by symptoms, scratch test, and nasal airway resistance Exclusion criteria: Nasal defect or pathology Age: 18 or older Sex: 100 M, 51 F Race: NR Other:	1) Nasal airway resistance: measured every hour using two Validyne MP45 transducers and an oscilloscope 2) Patient-assessed symptom severity: nasal congestion, sneezing, rhinorrhea, lacrimation, and itching of the eyes, nose, and throat graded on scale of 1-6 (with higher numbers indicating increasing severity) every hour, at time of NAR assessment 3) Adverse events: Patients queried every hour about the occurrence of adverse events in general and specifically about whether or not they	1) Nasal airway resistance: Not abstracted 2) Patient-assessed symptom severity: Nasal congestion: changes in mean scores shown in Figure 2; combination caused greater reduction than placebo at 6, 7, and 8 hours ($P \leq 0.025$), and greater reduction than tripolidine alone at 6 and 8 hours ($P \leq 0.025$) Symptom complex score: changes shown in Figure 3; combination ($P \leq 0.025$) and triprolidine had greatest reduction in mean scores 3) Adverse events: Drowsiness most frequently reported AE due to antihistamine; few reports of jitteriness due to decongestant	Quality Scoring: Population similar: Not adequately described Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: No Intention-to-treat: Can't determine Notes: Patients assessed for a total of 8 hours over the course of a single day.

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Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Patients instructed to refrain from antihistamines for 48 hours and nasal decongestants for 16 hours before reporting for treatment Dates: Grass and ragweed season (Apr-Jun and Aug-Oct) Location: US, Kentucky Setting: Outpatient (academic medical center) Type(s) of providers: NR		had experienced dizziness, drowsiness, nervousness, or nausea		Number of patients in each treatment group not reported; stated only that there were 34-40 per group.
Dockhorn, Aaronson, Bronsky, et al., 1999	Design: RCT, parallel-group, nonallergic and allergic patients stratified separately Interventions: 1) Ipratropium bromide nasal spray 0.03% (42 µg per nostril tid) + beclomethasone dipropionate nasal spray (84 µg per nostril bid) (n = 207) 2) Ipratropium bromide nasal spray 0.03% (42 µg per nostril tid) (n = 103) 3) Beclomethasone dipropionate nasal spray (84 µg per nostril bid) (n = 109) 4) Placebo nasal sprays (n = 106) Duration of study treatment: 2 weeks (Phase III of trial, see Notes) No mention of rescue med	No. of subjects at start: 553 (279 allergic, 274 nonallergic) Dropouts/withdrawals: 43 total 525 completed Part II 510 completed Part III 17 (3%) dropouts due to AEs 18 (3%) dropouts due to administrative reasons 3 protocol violations 5 lack of efficacy No. of subjects at end: 510 Inclusion criteria: Allergic rhinitis (positive skin test and history) or nonallergic rhinitis (negative skin test) Exclusion criteria: Complete nasal obstruction; abnormal sinus film; upper respiratory infection; rhinitis medicamentosa; glaucoma; BPH Age: 8-75 (mean 36.7, SD 16.7, 18% age 8-18)	1) Patient-assessed symptom severity: rhinorrhea, congestion, and sneezing graded daily on scale of 1 (none) to 5 (unbearable); duration of rhinorrhea assessed by having patient record each day the number of hours nose ran between 8 AM and 8 PM 2) Investigator global assessment of efficacy 3) Patient global assessment of efficacy: graded on weekly basis using scale of 1 (no symptom control) to 4 (excellent symptom control); separate assessments for rhinorrhea, nasal congestion, and sneezing 4) Quality of life: Assessed using the SF-36	1) Patient-assessed symptom severity: Mean rhinorrhea severity and duration reduced in all three treatment groups compared to placebo (values shown in figures, $P < 0.05$). Combination therapy caused 45% reduction in rhinorrhea severity and 47% reduction in duration from baseline. Subgroup analysis of patients with substantial reduction: Rhinorrhea severity reduction: 74% combination, 57% ipratropium, 64% beclomethasone, 47% placebo. Rhinorrhea duration reduction: 66% combination, 50% ipratropium, 54% beclomethasone, and 38% placebo. Combination more effective than ipratropium or placebo in reducing severity of nasal congestion or sneezing, $P < 0.05$. Nasal congestion reduction: 31% combination, 23% ipratropium, and 23% placebo. Sneezing reduction: 37% combination,	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: Yes Level of evidence: 1b Randomized: Yes Allocation concealed: Yes Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Can't determine Notes: Trial had 4 phases: Phase I: 1-week run-in period during which patients took no medication (baseline values from this period); Phase II: 2-week RCT comparing monotherapies (ipratropium vs. beclomethasone vs. placebo);

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Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Multiple-phase trial – see Notes Dates: NR Location: US Setting: 10 outpatient clinics Type(s) of providers: Allergy specialists and general practitioners	Sex: 63% F, 37% Race: 90% white, 2% black, 8% other Other:	Health Survey and the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), administered at baseline and at end of treatment (2 weeks) 5) Adverse events: Patients queried about adverse events at each clinic visit; AEs recorded regardless of possible relation to treatment	26% ipratropium, and 26% placebo. 2) Investigator global assessment of efficacy: Not abstracted 3) Patient global assessment of efficacy: Good or excellent control of rhinorrhea: 73% combination, 65% ipratropium, 68% beclomethasone, 51% placebo All three active treatments rated as more effective than placebo for nasal congestion, P < 0.05. Combination more effective than placebo for control of sneezing, P < 0.05. 4) Quality of life: RQLQ scores improved for all 4 treatments compared to baseline, P < 0.05, combined > ipratropium or placebo. SF-36 less able to discriminate between treatment groups, although combination treatment superior to ipratropium for 3 domains (role functioning, vitality, health transition) 5) Adverse events: 56 (27%) combined (33 possibly drug-related) 31 (30%) ipratropium (10 possibly drug-related) 27 (25%) beclomethasone (10 possibly drug-related) 32 (30%) placebo (9 possibly drug-related) Most common AEs were pain, headache, nasal dryness, and epistaxis	Phase III: 2-week RCT comparing combination therapy vs. monotherapies vs. placebo (described here); Phase IV: 1-week washout period, during which patients were monitored for signs of rebound of nasal symptoms. Double-dummy blinding technique employed.

Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Dockhorn, Williams, and Sanders, 1996	Design: RCT, parallel-group Interventions: 1) Acrivastine 8 mg + pseudoephedrine 60 mg, given in one capsule, 4 times per day (n = 176) 2) Acrivastine 8 mg, 4 times per day (n = 175) 3) Pseudoephedrine 60 mg, 4 times per day (n = 177) 4) Placebo (n = 174) Duration of study treatment: 2 weeks No mention of rescue med No pre-trial washout period described (1-day baseline phase); individuals taking antihistamines, nasal decongestants, MAOIs, cromolyn sodium, or corticosteroids within specified times prior to study (based on half-lives of respective drugs) were excluded Dates: NR (during ragweed season) Location: US Setting: 13 outpatient clinics Type(s) of providers: NR	No. of subjects at start: 702 Dropouts/withdrawals: 56 total 5% combination, 10% placebo 20 due to AEs 19 due to worsening allergy symptoms (9 placebo, 5 acrivastine, 4 pseudoephedrine, 1 combination) 7 protocol violations 6 lost to follow-up 4 withdrew consent No. of subjects at end: 646 Inclusion criteria: Seasonal allergic rhinitis (2-year history), positive skin test to ragweed, Exclusion criteria: Anatomic nasal obstruction; vasomotor rhinitis; women of childbearing potential not on birth control; use of antihistamines/nasal decongestants/MAOIs, cromolyn sodium, or steroids Age: 11-73, mean age 32 Sex: 53-60% female Race: 86-90% white Other:	1) Patient-assessed symptom severity: runny nose; sneezing; itchy nose/throat; tearing, itching, or redness of eyes; nasal congestion; and mouth breathing graded 3 times per day on scale of 0 (absent) to 5 (very severe) 2) Investigator global assessment of efficacy 3) Adverse events: Evaluated by spontaneous reports of AEs and changes in vital signs	1) Patient-assessed symptom severity: Mean diary symptom score (no SD): 10.3 combination, 12.3 acrivastine, 11.8 pseudoephedrine, 13.4 placebo P < 0.001 combo vs. acrivastine P = 0.002 combo vs. pseudoephedrine P < 0.001 combo vs. placebo Mean nasal congestion score (no SD): 3.8 combination, 4.7 acrivastine, 4.1 pseudoephedrine, 4.9 placebo P < 0.001 combo vs. acrivastine Mean allergy symptoms score (no SD): 6.5 combination, 7.6 acrivastine, 7.6 pseudoephedrine, 8.6 placebo P < 0.001 combo vs. pseudoephedrine 2) Investigator global assessment of efficacy: Not abstracted 3) Adverse events: Combination therapy: 9% dry mouth, 7% somnolence, 4% nervousness, 4% insomnia 20 dropouts due to AEs (6 combination, 5 acrivastine, 6 pseudoephedrine, 3 placebo)	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Notes:

Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Drouin, Yang, Horak, et al., 1995	Design: RCT, parallel-group Interventions: 1) Beclomethasone dipropionate nasal spray (100 µg in each nostril twice daily) + loratadine 10 mg once per day (Combo) (n = 76) 2) Beclomethasone dipropionate nasal spray (100 µg in each nostril twice daily) (BEC) (n = 78) Duration of study treatment: 1 week No mention of rescue med Trial preceded by washout period ranging from 24 hours to 1 month, as follows: topical or oral decongestants (24 hours); oral antihistamines (48 hours, except astemizole [1 month]); intranasal steroids (72 hours); cromolyn sodium (1 week); systemic or orally inhaled steroids (1 month) Dates: NR Location: Austria, Belgium, Canada, Germany, England Setting: 5 medical centers Type(s) of providers: specialists (2 allergy, 1 ENT, 1 unknown)	No. of subjects at start: 156 Dropouts/withdrawals: 2 (1 per group) failed to return for follow-up visit. No. of subjects at end: 154 Inclusion criteria: Moderately severe seasonal allergic rhinitis with positive skin test; patient on immunotherapy must be on stable dose for at least 1 month prior to study Exclusion criteria: Severe asthma or COPD; nasal polyps or other structural abnormality; pregnant, lactating or not on medically accepted birth control; significant comorbid disease that might interfere with treatment evaluation Age: 18-65 Mean 31 yrs Loratadine + Beclomethasone Mean 32 yrs Beclomethasone Sex: 48 M/33 F Loratadine + Beclomethasone 38 M/40 F Beclomethasone Note: Sex had significant treatment-by-center interaction (P = 0.03) but was determined to have no impact on overall efficacy comparison. Race: Noted to be comparable, actual % not reported Other:	1) Patient-/investigator-assessed symptom severity: nasal discharge, nasal stuffiness, nasal itching, sneezing, itching eyes, tearing, redness of eyes, and ear/palate itching graded daily (by patients) and on days 3 and 7 (by investigator) on scale of 0 (none) to 3 (severe, very disturbing most of the time) 2) Patient global evaluation of efficacy: graded on last day of treatment on scale of 1 (excellent) to 5 (treatment failure) 3) Investigator global evaluation of efficacy 4) Adverse events: recorded by patients in study diaries and elicited by investigators during clinic visits on days 3 and 7	1) Patient-/investigator-assessed symptom severity: Improvement in total symptom score ("improvement" not defined; mean scores not reported): Day 3: 54% Combo, 46% BEC alone (P = 0.08) Day 7: 68% Combo, 58% BEC alone (P < 0.05) 2) Patient global evaluation of efficacy: Combo: Excellent 39% Good 51% Fair 3% Poor or Failure 7% BEC alone: Excellent 19% Good 54% Fair 18% Poor or Failure 9% Good to excellent response, 90% Combo vs. 73% BEC, P < 0.05. 3) Investigator global evaluation of efficacy: Not abstracted 4) Adverse events: 23 pts (30%) Combo 20 pts (26%) BEC Most common AE was somnolence 5% in Combo group, 6% in BEC only group.	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Yes Note: Not clear whether symptom data reported was assessed by patients or investigators.

Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Falliers and Redding, 1980 **Study 1 (seasonal allergic rhinitis)**	Design: RCT, parallel-group Interventions: 1) Azatadine maleate 1 mg + pseudoephedrine 120 mg, combined in one repeat-action tablet; 3 doses over 2 days (n = 30) 2) Azatadine maleate 1 mg, 3 doses over 2 days (n = 30) 3) Pseudoephedrine 120 mg, in a repeat-action tablet (60 mg in coating and 60 mg in core), 3 doses over 2 days (n = 30) 4) Placebo, 3 doses over 2 days (n = 30) Duration of study treatment: 2 days (treatment given and patients assessed on-site) No mention of rescue med Patients abstained from antihistamines and decongestants for 12 hours and systemic steroids for at least 4 weeks before reporting for treatment Dates: Single pollen season, 1978 Location: Denver, CO Setting: Outpatient Type(s) of providers: NR	No. of subjects at start: 120 Dropouts/withdrawals: 3 No. of subjects at end: 117 Inclusion criteria: Seasonal allergic rhinitis based on history and positive skin test Exclusion criteria: Pregnant women; hypersensitivity to study drugs; illnesses that contraindicate antihistamine or sympathomimetic amine use Age: 18 or older Sex: No difference among groups, values not reported Race: NR Other:	1) Patient-assessed symptom severity: frequency of nose blowing and sneezing graded on scale of 1 (1) to 8 (more than 15); severity of runny nose, nasal stuffiness, watery eyes, and itching of eyes, nose, and throat graded on scale of 0 (none) to 3 (severe); scores recorded hourly from 8:00 AM to 4:00 PM (both days), then again from 6:00 to 10:00 PM (first day only) 2) Adverse events: Symptom scoring cards given to patients included questions about drowsiness, dizziness, jitteriness, nausea, and headache	1) Patient-assessed symptom severity: Active treatments superior to placebo, P < 0.10; combination treatment superior (P < 0.05) to both azatadine and placebo. Reductions in mean total symptom score: 70% combination 52% azatadine 43% pseudoephedrine 11% placebo Reductions in mean nasal congestion symptom score: 68% combination 35% azatadine 62% pseudoephedrine 11% placebo 2) Adverse events: Most common = drowsiness (mild-moderate severity) in 30 of 111 (27%), higher in azatadine (50%) and combination groups (30%), P < 0.10. Jitteriness higher in pseudoephedrine group (P < 0.10). Other reactions insomnia, dizziness, nervousness, dry nose, nausea, and headache. No withdrawals due to AEs.	Quality Scoring: Population similar: Not adequately described Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Yes Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Notes:

Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Falliers and Redding, 1980 **Study 2 (perennial allergic rhinitis)**	Design: RCT, parallel-group Interventions: 1) Azatadine maleate 1 mg + pseudoephedrine 120 mg, combined in one repeat-action tablet, 2 times per day (n = 10) 2) Azatadine maleate 1 mg, 2 times per day (n = 10) 3) Pseudoephedrine 120 mg, in a repeat-action tablet (60 mg in coating and 60 mg in core), 2 times per day (n = 11) 4) Placebo, 2 times per day (n = 10) Duration of study treatment: 6 weeks No mention of rescue med No pre-trial washout period described Dates: Single pollen season 1978 Location: Denver, CO Setting: Outpatient Type(s) of providers: NR	No. of subjects at start: 41 Dropouts/withdrawals: 2 No. of subjects at end: 39 Inclusion criteria: Perennial allergic rhinitis (based on history) Exclusion criteria: Pregnant women; hypersensitivity to study drugs; illnesses that contraindicate antihistamine or sympathomimetic amine use Age: 18 or older Sex: No difference among groups, values not reported Race: NR Other:	1) Patient-assessed symptom severity: rhinorrhea, sneezing, itchy nose, itchy eyes, tearing, conjunctivitis, and nasal congestion graded by patients on scale of 0 (none) to 3 (severe) during clinic visits at baseline and weeks 2, 4, and 6 2) Investigator global assessment of efficacy 3) Patient global assessment of efficacy: Assessed at last clinic visit (6 weeks); method of assessment not described 4) Adverse events: Patients asked about AEs at each clinic visit (2, 4, and 6 weeks); physicians specifically asked to note presence/absence of drowsiness	1) Patient-assessed symptom severity: Active treatments superior to placebo, P < 0.10; combination treatment superior (P < 0.05) to both azatadine and placebo. Reductions in mean total symptom score: 82% combination 58% azatadine 55% pseudoephedrine 9% placebo Reductions in mean nasal congestion symptom score: 73% combination 27% azatadine 63% pseudoephedrine 10% placebo 2) Investigator global assessment of efficacy: Not abstracted 3) Patient global assessment of efficacy: Overall response, all active preparations superior to placebo, P < 0.01, in decreasing order of preference: combination therapy, azatadine, pseudoephedrine, placebo 4) Adverse events: Most common = drowsiness (mild-moderate severity) in 8 of 41 (20%), higher in azatadine (50%) and combination groups (30%), P < 0.10	Quality Scoring: Population similar: Not adequately described Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Yes Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Notes:

Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Finn, Aaronson, Korenblat, et al., 1998	Design: RCT, crossover, allergic and nonallergic patients randomized separately Interventions: 1) Terfenadine (60 mg bid) + ipratropium bromide nasal spray 0.03% (42 µg per nostril tid) 2) Terfenadine (60 mg bid) + placebo nasal spray tid Duration of study treatment: 2 weeks for each treatment, with a 1-week washout period between periods 1-week run-in/baseline period; no anticholinergic agents, antihistamines, sympatho-mimetic decongestants, nasal/ocular cromolyn, prostaglandin inhibitors, tranquilizers with anti-cholinergic effects, or gluco-corticosteroids permitted before or during study. Dates: NR Location: US Setting: 7 outpatient centers Type(s) of providers: Specialists	No. of subjects at start: 205 (114 allergic, 91 nonallergic) Dropouts/withdrawals: 16 excluded from efficacy analysis: 3 with seasonal allergic rhinitis 13 completed only 1st treatment period 15 noncompleters: 8 patients due to AEs 5 administrative reasons 2 protocol violations No. of subjects at end: 190 completed; 189 used in efficacy and safety evaluations Inclusion criteria: Perennial rhinitis (allergic or nonallergic) with clinically significant rhinorrhea; allergic rhinitis defined by positive skin tests; rhinorrhea severity score ≥ 2 for 2 hours per day Exclusion criteria: Complete nasal obstruction; sinusitis; abnormal radiograph; upper or lower respiratory infection; rhinitis medicamentosa; glaucoma; BPH; hypersensitivity to study meds Age: Range 18-75, mean 40.1 Sex: 59% F, 41% M Race: 90% white Other:	1) Patient-assessed symptom severity: rhinorrhea graded for severity once daily on a scale of 0 (none) to 5 (very severe) and for duration by the number of hours daily between 8 AM and 8 PM; severity of sneezing and congestion graded once daily on scale of 0-5 (as above) 2) Investigator global assessment of efficacy 3) Patient global assessment of efficacy: overall control of nasal symptoms graded at biweekly clinic visits on scale of 0 (none) to 3 (excellent) 4) Adverse events: Patients queried about AEs at each biweekly clinic visit; investigators instructed to record all AEs regardless of possible relationship to study drugs	1) Patient-assessed symptom severity: Rhinorrhea severity decreased from 2.85 at baseline to 1.78 (38% reduction) with combined therapy (P = 0.0001); 10% additional reduction over terfenadine + placebo. Rhinorrhea duration decreased from 6.04 at baseline to 1.78 (46% reduction) with combined therapy (P = 0.0001); 16% additional reduction over terfenadine + placebo. No statistical differences between treatment groups for congestion and sneezing. 2) Investigator global assessment of efficacy: Not abstracted 3) Patient global assessment of efficacy: Good to excellent control of rhinorrhea: 69% in combined therapy vs. 53% in terfenadine + placebo (P = 0.0008). Good to excellent control of sneezing: higher in combined therapy group, P = 0.0452. No difference in control of congestion. 4) Adverse events: N = 63 (32%) combined therapy (31 [16%] possibly drug-related) N = 31 (16%) terfenadine + placebo (14 [7%] possibly drug-related). Higher % of blood-tinged nasal mucus 6.6% vs. 0.5% (combined vs. terfenadine alone), epistaxis (5.1% vs. 1.5%), and nasal dryness (2.5% vs. 1.5%).	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Notes:

Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Grosclaude, Mees, Pinelli, et al., 1997	Design: RCT, parallel-group Interventions: 1) Pseudoephedrine 120 mg (extended-release) bid + cetirizine 5 mg bid (n = 230) 2) Pseudoephedrine 120 mg (extended-released) bid (n = 226) 3) Cetirizine 5 mg bid (n = 231) Duration of study treatment: 2 weeks No rescue med permitted No pre-trial washout period described; patients who had taken following drugs, in time frame indicated, were excluded: astemizole (6 weeks); systemic cortico-steroids, ketotifen, or MAOIs (2 weeks); topical cortico-steroids or sedative (1 week); nasal decongestants, anti-histamines, or nasal or ocular cromoglycate (2 days) Dates: Mar-Sept 1992 Location: France and Germany Setting: 43 centers (30 France, 13 Germany) Type(s) of providers: NR	No. of subjects at start: 687 Dropouts/withdrawals: 71 total n = 30 lack of efficacy n = 22 adverse events n = 19 unrelated to drug, mostly protocol violations No. of subjects at end: 616 completers Inclusion criteria: Pollen-associated allergic rhinitis of 1 year or more; positive skin or RAST tests to seasonal allergens Exclusion criteria: Asthma requiring change in treatment or systemic/inhaled steroids; atopic dermatitis requiring antihistamines or systemic/topic steroids; upper respiratory infection; nasal polyposis; septal deviation; infection requiring antibiotics; many comorbid illnesses; escalating doses of desensitization therapy; drug trial in previous 3 months Age: Range 9-66, mean 32 Sex: 48-53% M, 47-52% F Race: NR Other:	1) Patient-assessed symptom severity: nasal obstruction, sneezing, rhinorrhea, nasal pruritus, and ocular pruritus graded once per day on scale of 0 (absent) to 3 (severe/ hampering daily activities or sleep) 2) Investigator-assessed symptom severity 3) Investigator global assessment of efficacy 4) Adverse events: Not clear how reported/ recorded; all AEs recorded regardless of possible relationship to study drugs	1) Patient-assessed symptom severity: Median proportion of "comfortable" days (symptoms absent or mild): 53.3% combination, 30.8% cetirizine, 33.3% pseudoephedrine, P < 0.001 5-symptom mean score over total treatment: 0.85 combination, 1.03 cetirizine, and 1.14 pseudoephedrine, P < 0.001 for combo vs. cetirizine, P < 0.001 for combo vs. pseudoephedrine Results of 4-symptom score, excluding blocked nose, showed similar difference between combination vs. cetirizine or pseudoephedrine, P < 0.001. Individual symptom scores showed significant difference for combination vs. cetirizine (P ≤ 0.01) for all symptoms except itchy eyes, and vs. pseudoephedrine for all symptoms except nasal congestion. 2) Investigator-assessed symptom severity: Not abstracted 3) Investigator global assessment of efficacy: Not abstracted 4) Adverse events: 68 (29.6%) combination 68 (30.1%) pseudoephedrine 54 (23.4%) cetirizine Severe AEs: 17 (7.4%) combination 15 (6.6%) pseudoephedrine 7 (3%) cetirizine Withdrawals due to AEs: 9 (3.9%) combination 7 (3.1%) pseudoephedrine	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Notes:

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Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
				6 (2.6%) cetirizine Common AEs: Combination: Headache, insomnia Cetirizine: Somnolence, headache, asthenia Pseudoephedrine: Insomnia, headache, dry mouth	
Henauer, Seppey, Huguenot, et al., 1991	Design: RCT, parallel-group Interventions: 1) Terfenadine 60 mg (rapid-release) + pseudoephedrine 120 mg (extended-release), combined in one tablet, taken twice per day (n = 25) 2) Terfenadine 60 mg (rapid-release) bid (n = 25) Duration of study treatment: 2 weeks No mention of rescue med No pre-trial washout period described Dates: NR Location: Switzerland Setting: Outpatient Type(s) of providers: Allergy specialist	No. of subjects at start: 50 Dropouts/withdrawals: 3 withdrew due to AEs (2 combo, 1 terfenadine) No. of subjects at end: Results reported on 50 patients Inclusion criteria: Perennial rhinitis Exclusion criteria: Allergy to animals; other relevant concomitant diseases and therapies Age: 35 (SD, 9) M; 27 (8) F Sex: 21 M, 29 F Race: NR Other:	1) Investigator global assessment of improvement 2) Investigator-assessed symptom severity 3) Patient-assessed symptom severity: nasal congestion, sneezing, rhinorrhea, itchy nose and/or throat, itchy eyes, watery eyes, and red eyes graded once daily on a scale of 0 (no symptom) to 3 (symptom very troublesome) 4) Adverse events: Assessed at clinic visits at 1 and 2 weeks using check list of potential AEs (drowsiness, nervousness, headache, insomnia, dry mouth, nausea, palpitation) 5) Rhinoscopy assessments (swelling and hyperemia of nasal mucosa, nasal secretion, and nasal obstruction) 6) Acceptability of treatment: Patients asked	1) Investigator global assessment of improvement: Not abstracted 2) Investigator-assessed symptom severity: Not abstracted 3) Patient-assessed symptom severity: All 7 symptoms improved according to patient ratings, appeared to favor combination, but differences between groups were not statistically significant (actual data not shown). 4) Adverse events: 20/25 patients in combination group 9/25 patients in terfenadine group P = 0.004 Frequent AEs: Insomnia (13 vs. 3), dry mouth (11 vs. 2), headache (8 vs. 4) 5) Rhinoscopy assessments: Not abstracted 6) Acceptability of treatment: 15 (65%) combination 18 (78%) terfenadine	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: No Objectively confirmed: No Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Yes Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Yes Notes:

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Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
			at final visit (2 weeks) if they would take the medication again		
Juniper, Kline, Hargreave, et al., 1989	Design: RCT, parallel-group; randomization stratified according to degree of sensitivity to ragweed Interventions: 1) Beclomethasone dipropionate aqueous nasal spray, 50 µg per nostril four times per day + astemizole 10 mg once per day (n = 30) 2) Beclomethasone dipropionate aqueous nasal spray, 50 µg per nostril four times per day (n = 30) 3) Astemizole 10 mg once per day (n = 30) Duration of study treatment: 6 weeks Patients instructed to take rescue med as follows if symptoms inadequately controlled by study med: for nasal symptoms, freon-propelled beclomethasone dipropionate nasal spray, one puff (50 µg) in each nostril, up to 4 times per day; for eye symptoms, naphazoline HCl and anatazoline ophthalmic drops, one drop in each eye, up to 4 times per day; sodium cromoglycate eye drops, up to 4 times per day, permitted if this treatment insufficient	No. of subjects at start: 90 Dropouts/withdrawals: 1 due to med noncompliance No. of subjects at end: 89 Inclusion criteria: Rhino-conjunctivitis requiring treatment during 2 previous ragweed-pollen seasons; positive skin test to ragweed-pollen Exclusion criteria: Pregnant; lactating; astemizole, steroid nasal spray, or oral steroid within 6 weeks Age: Mean 39.8-42.2 (SD 11.8-13.8) Sex: 46 M, 44 F Race: NR Other:	1) Patient-assessed symptom severity: severity and duration of sneezing, stuffy nose, runny nose, eye symptoms, and asthma graded twice per day on scale of 0 (absent) to 3 (severe/continuous) 2) Use of rescue med: recorded by patients at end of each day in study diaries 3) Adverse events: Patients asked at regular clinic visits (weeks 1, 3, and 6) to report all non-rhinoconjunctivitis symptoms experienced since the previous visit, regardless ofwhether they perceived them to be related to study treatment 4) Treatment compliance: assessed by weighing nasal spray bottles and counting unused tablets (at end of study or at each clinic visit?)	1) Patient-assessed symptom severity (mean daily scores): Sneezing: Astemizole 0.395 Beclomethasone 0.193 Combination 0.155 p < 0.05, BEC vs. astemizole p < 0.05, combination vs. astemizole p = ns, combination vs. BEC Stuffy nose: Astemizole 0.594 Beclomethasone 0.319 Combination 0.322 p < 0.05, BEC vs. astemizole p < 0.05, combination vs. astemizole p = ns, combination vs. BEC Runny nose: Astemizole 0.406 Beclomethasone 0.152 Combination 0.192 p < 0.05, BEC vs. astemizole p < 0.05, combination vs. astemizole p = ns, combination vs. BEC Eye symptoms: Astemizole 0.424 Beclomethasone 0.563 Combination 0.335 Asthma: Astemizole 0.030 Beclomethasone 0.015 Combination 0.048 2) Use of rescue med: Beclomethasone use: Astemizole 0.871 Beclomethasone 0.206	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Yes Notes: Double-dummy blinding technique employed. Intermittent pollen counts made throughout the study.

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Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	No astemizole, steroid nasal spray, or oral steroids permitted within 6 weeks prior to enrollment Dates: Ragweed season Location: Canada Setting: Outpatient Type(s) of providers: Allergy specialists			Combination 0.241 p < 0.05, BEC vs. astemizole p < 0.05, combination vs. astemizole p = ns, combination vs. BEC Eye drop use: Astemizole 0.707 Beclomethasone 1.016 Combination 0.354 Asthma aerosol use: Astemizole 0.195 Beclomethasone 0.049 Combination 0.113 3) Adverse events: 16 astemizole (9 drowsiness, 3 hunger, 3 dryness, 1 headac he) 16 beclomethasone (4 drowsiness, 3 hunger, 2 dryness, 2 nasal bleeding, 1 headache, 2 thirst, 2 skin irritation) 20 combination (4 drowsiness, 4 hunger, 2 dryness, 3 nasal bleeding, 3 headache, 1 thirst, 1 skin irritation, 2 nausea) 4) Treatment compliance: No differences between groups: Astemizole 99.3% pills, 91.8% placebo spray Beclomethasone 100.2% placebo pills, 94.1% spray Combination 99.2% pills, 91.3% spray	

Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Lanier, Gross, Marks, et al., 2001	Design: RCT, parallel-group Interventions: 1) Loratadine 10 mg once per day + olopatadine ophthalmic solution 0.1%, one drop in each eye 2 times per day (n = 45) 2) Loratadine 10 mg once per day (n = 49) Duration of study treatment: 1 week No mention of rescue med; immunotherapy and inhalers OK if use greater than 3 months Trial preceded by 1-week washout period Dates: May- Nov 1998 Location: US Setting: 3 outpatient sites Type(s) of providers: Family practice	No. of subjects at start: 94 Dropouts/withdrawals: 10 pts without follow-up or did not meet criteria for efficacy analysis 12 pts (6 per group) withdrew (3 AEs, 2 lost to follow-up, 4 protocol violations, 3 screen failure – numbers overlap with above). No. of subjects at end: 84 Inclusion criteria: Age ≥ 7; moderate-severe seasonal allergic conjunctivitis for at least one season (ocular itching, conjunctival redness); positive skin test Exclusion criteria: Pregnant; lactating; other ocular disorder; ocular surgery within 3 months; concomitant systemic, ocular, or nasal medications with potential to interfere with response to therapy Age: Mean 38, range 9-74 Sex: 33 (35%) M, 61 (65%) F Race: 81 (86%) white, 9 (10%) black, 4 (4%) other Other:	1) Patient-assessed symptom severity (*in-clinic*): During clinic visits on days 0, 3, and 7, patients graded ocular itching on scale of 1 (none/never) to 4 (very frequently/2 or more times each day) 2) Patient-assessed symptom severity (*diary data*): ocular itching and redness graded 4 times each day on scale of 0 (none) to 9 (severe) 3) Investigator-assessed symptom severity (immediate, post-dose ocular itching and redness) 4) Patient global assessment of efficacy for ocular symptoms: graded relative to baseline during clinic visits on days 3 and 7 on scale of 0 (clinical cure) to 5 (significantly clinically worse) 5) Investigator global assessment of efficacy for ocular symptoms 6) Quality of life: Assessed using the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) at baseline and end-of-treatment (day 7) clinic visits	1) Patient-assessed symptom severity (*in-clinic*): Itching (day 7): Combination 2.21, loratadine 2.74, P = 0.0436 2) Patient-assessed symptom severity (*diary data for 7 days*): Values shown in figures. Itching significantly lower on days 3, 4, and 6 in combination group (P < 0.05). Redness significantly lower on day 6 for combination. 3) Investigator-assessed symptom severity: Not abstracted 4) Patient global assessment of efficacy for ocular symptoms: Ocular symptoms (day 7): Combination 1.49, loratadine 2.15, P = 0.0022 5) Investigator global assessment of efficacy for ocular symptoms: Not abstracted 6) Quality of life: Overall mean score day 7: Combination 1.45 Loratadine 2.09 P < 0.05 Significant differences also noted for sleep, eye symptoms, activities, and emotions domains. 7) Adverse events: 13 total AEs from 10 patients 2 AEs due to loratadine use (1 asthenia and dry mouth, 1 dyspepsia); patients continued with study 2 AEs caused withdrawal (1 bronchitis,	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Not applicable Objectively confirmed: Not applicable Outcome measures valid: Yes Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: No Blinding adequate: Not applicable Dropouts described: Yes Intention-to-treat: Yes Note: Patients not blinded to treatment (no placebo eye drops).

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Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
			7) Adverse events: Both spontaneous and elicited AEs recorded throughout study (method of eliciting not described); AEs defined as "any changes from baseline other than efficacy parameters in a patient's ophthalmic or medical condition"	1 allergy exacerbation)	
Lau, Wei, Van Hasselt, et al., 1990	Design: RCT, parallel-group Interventions: 1) Budesonide nasal aerosol 200 µg bid + oxymetazoline nasal drop pipette (0.5 mg/ml), 3 drops 15 minutes before administration of budesonide for first 3 days only (n = 47) 2) Budesonide nasal aerosol 200 µg bid (n = 48) 3) Terfenadine 60 mg bid (n = 47) Duration of study treatment: 3 weeks No mention of rescue med No pre-trial washout period; pts who had received other steroid treatment during previous 4 weeks were excluded Dates: June 1986-May 1988 Location: Hong Kong Setting: Outpatient	No. of subjects at start: 142 Dropouts/withdrawals: 12 4 due to AEs (1 nasal pain due to budesonide, 1 HA from budesonide, 2 ulcer pain from taking terfenadine) 8 lost to follow-up No. of subjects at end: 130 Inclusion criteria: Age 15-70; perennial rhinitis for 2 years; blocked nose and 2 other symptoms (runny nose, itchy nose, sneezing) Exclusion criteria: Steroid treatment within 4 weeks; infection; nasal polyps; septal deviation; pregnant; lactating Age: Mean 26.7 (range 15-68) Sex: 65 M, 77 F Race: 140 Chinese, 2 Indian Other:	1) Patient-assessed symptom severity: blocked nose, runny nose, itchy nose, sneezing bouts, sore eyes, and runny eyes graded once per day on scale of 0 (no symptoms) to 3 (severe/ sufficiently troublesome to interfere with daily activity or sleep) 2) Patient global assessment of efficacy: treatment graded as ineffective, slightly effective, moderately effective, and extremely effective during last clinic visit (3 weeks) 3) Adverse events: AEs noted on diary cards; patients asked non-leading question about AEs during clinic visits at 1 and 3 weeks	1) Patient-assessed symptom severity: Values shown in figures. Improvement for all nasal symptoms in the two budesonide groups compared to baseline ($P < 0.05$). Terfenadine improved only in nasal blockage compared to baseline ($P < 0.05$). Between-group comparison showed two budesonide groups better than terfenadine group ($P < 0.05$) Budesonide with oxymetazoline showed faster relief than budesonide alone, 1 day vs. 7 days, $P < 0.05$. 2) Patient global assessment of efficacy: No significant differences among the three groups. 3) Adverse events: N = 6 budesonide + oxymetazoline (2 nasal irritation, 2 throat irritation, 2 headache, 1 GI distress) N = 10 budesonide (3 nasal irritation, 2 headache, 2 GI distress, 1 each dizziness, nausea, and other) N = 17 terfenadine (10 gi distress, 3 nasal irritation, 1 each dizziness, nausea, dry mouth, and other)	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: No Objectively confirmed: No Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Can't determine Note: Double-dummy blinding technique employed. *(continued on next page)*

Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Type(s) of providers: Otolaryngology				
Meran, Morse, and Gibbs, 1990	Design: RCT, crossover Interventions: 1) Acrivastine 8 mg + pseudoephedrine 60 mg, 3 times daily 2) Acrivastine 8 mg, 3 times daily 3) Pseudoephedrine 60 mg, 3 times daily 4) Placebo Duration of study treatment: 6 days each treatment period, with a 1-day washout between periods No rescue med permitted Trial preceded by washout period of 24 hours to 1 month, depending on pre-trial medication Dates: Apr-Jul 1984 Location: Switzerland Setting: Outpatient Type(s) of providers: Otolaryngology	No. of subjects at start: 40 (3 with perennial rhinitis, 37 with seasonal rhinitis) Dropouts/withdrawals: 5 noncompleters – 3 withdrew due to lack of treatment effect (placebo group), 1 left country, 1 due to headache associated with pseudoephedrine. Data up to withdrawal included in analysis. No. of subjects at end: 40 Inclusion criteria: Age 12-70; seasonal allergic rhinitis; positive skin test to mixed grasses Exclusion criteria: Nasal deformity; patients who operated dangerous machinery; other acute or chronic disease; pregnant, lactating, or not on contraception Age: Mean 28, range 17-56 Sex: 15 M, 25 F Race: NR Other:	1) Patient-assessed symptom severity: sneezing, itchy nose/throat, runny nose, blocked nose, watery eyes, itchy eyes, and overall symptoms graded at end of each day on scale of 0 (no symptoms) to 9 (very severe) 2) Patient global assessment of efficacy: graded on day 7 of each treatment period as excellent, good, satisfactory, poor, or abysmal 3) Investigator global assessment of efficacy 4) Acceptability/patient preference: Patients asked on day 7 of each treatment period if they would continue with the current treatment if that treatment were available 5) Adverse events: Incidence of AEs recorded during day 7 clinic visit of each treatment period, as reported spontaneously or in response to indirect questioning	1) Patient-assessed symptom severity: Overall symptom score: Placebo 3.37, pseudoephedrine 2.92, acrivastine 2.04 **, combination 1.66** ** P < 0.01 vs. placebo. No significant difference between acrivastine and combination. Combination significantly better than acrivastine, P < 0.01, for symptoms of sneezing, itchy nose/throat, runny nose, blocked nose, and watery eyes (mean values available from table). 2) Patient global assessment of efficacy: Values shown combine patient and investigator responses; no significant differences between patient and MD responses. Pseudoephedrine better than placebo (P < 0.01); acrivastine alone or in combination better than placebo or pseudoephedrine (P < 0.01). 3) Investigator global assessment of efficacy: Not abstracted 4) Acceptability/patient preference: 45% placebo, 69% pseudoephedrine, 82% acrivastine,** 87% for combination** **P < 0.01 vs. placebo 5) Adverse events: 16 placebo group 18 pseudoephedrine group 7 acrivastine group 19 combination group More insomnia with pseudoephedrine	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: [??] Intention-to-treat: Yes Note: Double-dummy blinding technique employed.

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Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
				than with placebo or acrivastine, P < 0.05. More fatigue with placebo than with pseudoephedrine, P < 0.01.	
Negrini, Troise, Voltolini, et al., 1995	Design: RCT, parallel-group Interventions: 1) Astemizole 10 mg + pseudoephedrine 240 mg once daily (n = 102) 2) Beclomethasone nasal spray (0.05 mg/ml), 2 puffs per nostril twice per day (n = 102) Duration of study treatment: 4 weeks Vasoconstrictor eye drops (phenylephrine, xylo-metazoline, or naphazoline) provided for use as rescue med Trial preceded by washout period ranging from 3 days to 6 weeks, as follows: decongestants (3 days); oral antihistamines (3 days, except for astemizole [6 weeks]); topical corticosteroids and sodium cromoglycate (2 weeks); oral corticosteroids (1 month); immunotherapy (1 month) Dates: 1992 hay fever season Location: Austria, Belgium, Germany, Italy Setting: Outpatient	No. of subjects at start: 204 Dropouts/withdrawals: Total of 31 patients (15 astemizole-D group, 16 beclomethasone); 12 withdrew due to AEs (9 and 3, respectively); 8 withdrew from treatment inefficacy (4 per group); 1 lost to follow-up; 1 lack of symptoms in beclomethasone group No. of subjects at end: 173 Inclusion criteria: Age 12-70 with 1-year history of seasonal allergic rhinitis requiring therapy; positive skin test or RAST for pollen; moderately severe nasal congestion and at least one other nasal symptom of moderate severity Exclusion criteria: Pregnancy; serious concurrent medical illness; concomitant therapy that could interfere with assessment Age: Astemizole-D mean 28.4 (range 12-66) Beclomethasone mean 29.2 (13-66) Sex: Astemizole-D 56 M/46 F Beclomethasone 54 M/48 F Race: NR Other:	1) Use of rescue med (eye drops): recorded by patients in study diaries 2) Investigator-assessed symptom severity 3) Patient-assessed symptom severity: sneezing, rhinorrhea, nasal itching, congestion, and concurrent ocular symptoms graded daily on scale of 0 (absent) to 3 (severe); severity of rhinitis also graded daily using a visual analog scale ranging from "absent" to "very severe" 4) Investigator global evaluation of efficacy 5) Patient global evaluation of efficacy: effect of therapy graded at end of trial as "excellent," "good," "moderate," or "poor" 6) Adverse events: recorded by patients in study diaries	1) Use of rescue med (eye drops): Astemizole-D: 16% of patients, mean frequency of use 5.5% of treatment days (P < 0.05 compared to beclomethasone) Beclomethasone: 29%, mean frequency of use 10% of treatment days 2) Investigator-assessed symptom severity: Not abstracted 3) Patient-assessed symptom severity: Mean (SEM) Area under the Curve results shows in Figure 1 (1st 2 weeks of therapy) and Figure 2 (entire study period) No significant difference in nasal congestion, sneezing, rhinorrhea, nasal itching, VAS rhinitis, total nasal, or total symptom scores. Trend towards fewer ocular symptoms on astemizole-D (P = 0.07) at end of study (at 2 weeks P = 0.03). 4) Investigator global evaluation of efficacy: Not abstracted 5) Patient global evaluation of efficacy: Excellent or good response: Astemizole-D: 63% Beclomethasone: 72% 6) Adverse events: Astemizole-D 38 pts (38%) Beclomethasone 26 pts (27%) No statistically significant difference Most common = headache (7 pts	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Yes Note: Double-dummy blinding technique employed.

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Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Type(s) of providers: Specialists (allergy and ENT)			asthemizole, 3 beclomethasone), dry mouth (9, 1), nausea (4,4), somnolence (5,2) and fatigue (4,1)	
Panda and Mann, 1998	Design: RCT, parallel-group Interventions: 1) Terfenadine 60 mg + pseudoephedrine 120 mg (10 mg immediate-release and 110 mg extended-release), combined in one tablet, 2 times per day (n = 22) 2) Terfenadine 60 mg 2 times per day (n = 19) Duration of study treatment: 2 weeks Rescue med not permitted No pre-trial washout period described; patients who had taken oral or topical steroids or sodium cromoglycate in the previous month, and those who had taken antihistamines or decongestants in the previous 48 hours, were excluded Dates: NR Location: India Setting: Outpatient Type(s) of providers: Otolaryngology	No. of subjects at start: 41 Dropouts/withdrawals: 4 due to AEs (2 per group) 5 lost to follow-up (5 combo, 1 single) No. of subjects at end: 32 completers, but results shown for 31 subjects Inclusion criteria: Moderate-severe allergic rhinitis Exclusion criteria: Hyper-sensitivity to study meds; pregnant, lactating, or not on contraception; renal, cardiac, or respiratory disorder; non-responsive to antihistamines (new and classic); immunotherapy Age: Range 15-56 Sex: 23 M, 18 F Race: NR Other:	1) Patient *and* investigator global assessment of efficacy: graded by patient and physician together (?) at 2 weeks on scale ranging from excellent (virtually all signs and symptoms stopped [reduction of 90% or more]) to poor/no response/deterioration 2) Patient global assessment of efficacy *and* adverse events: graded at 2 weeks on scale ranging from excellent (excellent efficacy with no or mild side effects) to poor 3) Investigator global assessment of efficacy and adverse events 4) Adverse events: Recorded at clinic visits at 1 and 2 weeks	1) Patient *and* investigator global assessment of efficacy: Excellent: 10/22 (45.5%) combination group, 2/19 (10.5%) single treatment group Good: 6/22 (27.3%) combination group, 7/19 (36.8%) single treatment group Fair: 4/19 (21%) single treatment group Poor: 3/19 (5.7%) single treatment group. P = 0.0485 2) Patient global assessment of efficacy: Excellent: 10/22 (45.5%) combination group, 2/19 (10.5%) single treatment group Good: 6/22 (27.2%) combination group, 6/19 (31.5%) single treatment group Fair: 5/19 (26.3%) single treatment group Poor: 3/19 (15.7%) single treatment group. P = 0.0236 3) Investigator global assessment of efficacy and adverse events: Not abstracted 4) Adverse events (treatment discontinued): 2 AEs in combination group (cloudy urine, dizziness/insomnia) 2 AEs in single treatment group (somnolence, insomnia)	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: No Objectively confirmed: No Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Notes:

Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Purello-D'Ambrosio, Isola, Ricciardi, et al., 1999	Design: RCT, parallel-group Interventions: 1) Flunisolide, two 25-µg puffs per nostril twice per day + loratadine 10 mg once per day (n = 15) 2) Flunisolide, two 25-µg puffs per nostril twice per day + placebo once per day (n = 15) Duration of study treatment: 3 weeks Rescue med not permitted Trial preceded by 8-week washout period Dates: NR Location: Italy Setting: Outpatient Type(s) of providers: Allergy specialist	No. of subjects at start: 30 Dropouts/withdrawals: 0 No. of subjects at end: 30 Inclusion criteria: Nonallergic rhinitis with eosinophilia for at least 3 years; symptom score ≥ 5; eosinophil count > 10% Exclusion criteria: Positive skin test or positive IgE tests to common allergens; nasal polyposis or sinusitis; on drugs that would interfere with treatment; severe disease; pregnant or lactating women Age: Mean 38.7 (range 32-48) Sex: 12 M, 18 F Race: NR Other:	1) Patient-assessed symptom severity: sneezes, rhinorrhea, and nasal blockage graded daily on scale of 0 (no symptoms) to 3 (severe symptoms) 2) Investigator-assessed symptom severity 3) Eosinophil counts 4) Adverse events: Patients instructed to record any unexpected symptom on their diary cards, along with its duration, severity, and presumed relationship to treatment	1) Patient-assessed symptom severity: Flunisolide + loratadine group had decrease in sneezing compared to flunisolide alone (change of 73.4% vs. 46.6%, P < 0.000001); rhinorrhea (66.7% vs. 26.7%, P < 0.0006). No differences in nasal blockage (19.9% vs. 20.0%). 2) Investigator-assessed symptom severity: Not abstracted 3) Eosinophil counts: Not abstracted 4) Adverse events: 2 AEs total (1 per group), both subjects with nasal irritation.	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Not applicable Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Yes Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Yes Notes:

Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Ratner, van Bavel, Martin, et al., 1998	Design: RCT, parallel-group Intervention(s): 1) Fluticasone propionate aqueous nasal spray (two 50-µg sprays per nostril once per day + loratadine 10 mg once per day (FP+LOR) (n = 150) 2) Fluticasone propionate aqueous nasal spray (two 50-µg sprays per nostril once per day (FP) (n = 150) 3) Loratadine 10 mg once per day (LOR) (n = 150) 4) Placebo (n = 150) Duration of study treatment: 2 weeks No rescue med permitted Trial preceded by 7- to 30-day run-in period. In addition, patients who had taken following drugs, in time frame indicated, were excluded: loratadine (1 week); astemizole (6 weeks); cromolyn sodium (2 weeks); other OTC or prescription drugs that might affect rhinitis symptomatology (e.g., nasal decongestants) (72 hours); inhaled, intranasal, or systemic corticosteroids (1 month). Dates: Actual dates NR, during mountain cedar allergy season	No. of subjects at start: 600 Dropouts/withdrawals: 31 total 8 due to AEs 13 due to lack of efficacy 7 withdrew from other reasons 3 lost to follow-up No. of subjects at end: 569 Inclusion criteria: Seasonal AR (positive skin test to mountain cedar allergen, nasal mucosa allergic changes, seasonal symptoms over 2 or more seasons); moderate-severe symptoms on diary during run-in period Exclusion criteria: Loratadine within 1 week; astemizole within 6 weeks; cromolyn NA within 2 weeks; OTC nasal meds within 72 hours; steroids (MDI, nasal, oral) within 1 month; septal deviation, nasal polyp; history of nasal septal surg/perforation; candida infection; pregnant/lactating; other impairment Age: 12 or older Sex: 272 M (45.3%), 328 (54.7%) Race: 462 white (77%); 106 Hispanic (17.7%); 32 other (5.3%) Other:	1) Investigator-assessed symptom severity 2) Patient-assessed symptom severity: sneezing, nasal blockage, rhinorrhea, and nasal itching graded once per day on visual analog scale ranging from 0 (absent) to 100 (severe) 3) Investigator global evaluation of treatment efficacy 4) Patient global evaluation of treatment efficacy: overall response to treatment graded at end of trial on 7-point scale ranging from "significant improvement" to "significant worsening" 5) Quality of life: assessed using the Rhinoconjunctivities Quality of Life Questionnaire (RQLQ) at baseline and 2 weeks 6) Adverse events: Defined as any untoward medical occurrence, drug-related or not; recorded by clinicians during clinic visits at 1 and 2 weeks	1) Investigator-assessed symptom severity: Not abstracted 2) Patient-assessed symptom severity: Values shown in Figure 1 FP+LOR vs. FP alone, P = 0.006 days 1-7, and P = 0.017 days 8-14 FP+LOR and FP alone vs. LOR, P < 0.05; vs. placebo, P < 0.001 3) Investigator global evaluation of treatment efficacy: Not abstracted 4) Patient global evaluation of treatment efficacy: Values shown in Figure 3 FP alone and FP+LOR more effective than placebo or LOR alone (P < 0.001). No difference between FP alone vs. FP+LOR. No difference between placebo and LOR. 5) Quality of life (global RQLQ score): Mean change score (SEM): Placebo: -1.3 (0.1) LOR alone: -1.3 (0.1) FP alone: 2.2 (0.1), P < 0.05 vs. placebo or LOR FP+LOR: 2.3 (0.1), P < 0.05 vs. placebo or LOR 6) Adverse events: 5-8% each group with AEs due to study drug 1-2% blood in nasal mucus in active treatment groups, 3% blood in nasal mucus in placebo ≤1% epistaxis all groups ≤2% xerostomia all groups	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: Yes Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Yes Notes: Double-dummy blinding technique employed. Patient population: 90% PC, 10% allergy

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Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Location: South central Texas Setting: Professional research centers Type(s) of providers: Research center MDs				
Simpson, 1994	Design: RCT, parallel-group Interventions: 1) Budesonide nasal spray, 200 µg (2 puffs in each nostril) bid + terfenadine 60 mg bid (n = 32) 2) Terfenadine 60 mg bid (n = 23) 3) Budesonide nasal spray, 200 µg (2 puffs in each nostril) bid (n = 30) 4) Placebo (n = 21) Duration of study treatment: 3 weeks Xylometazoline or metazoline eye drops could be used for "troublesome eye symptoms"; no other rescue med permitted No pre-trial washout period described; patients taking oral corticosteroids at the time of recruitment, or who had had desensitization therapy in previous 12 months, were excluded Dates: May 1-Aug 31	No. of subjects at start: 143 Dropouts/withdrawals: 6 records unusable 20 withdrew due to lack of efficac y (12 from placebo group) 3 withdrew due to AEs 5 noncompliant with follow -up 3 protocol violations No. of subjects at end: 106 Inclusion criteria: Age ≥ 15; hay fever between May 1 and Aug 31 for ≥ 2 years; 2 symptoms (blocked nose, runny nose, itching nose, sneezing) Exclusion criteria: Oral steroids; upper respiratory infection; desensitization treatment within 12 months; hay fever symptoms outside specified period; pregnancy Age: Mean 25.7-29.7 (SD 7.8-12.4) Sex: Placebo 71% M, 29% F Budesonide 43% M, 57% F Terfenadine 53% M, 47% F Combination 41% M, 39% F Higher proportion of men in placebo group	1) Patient-assessed symptom severity: blocked nose, sneezing, nasal itching, runny nose, sore eyes, and runny eyes graded at end of each day on scale of 0 (no symptoms) to 3 (severe symptoms/discomfort experienced during most waking hours) 2) Patient global assessment of efficacy: graded on scale of 0 (ineffective) to 3 (very effective) at end-of-trial clinic visit (3 weeks) 3) Use of rescue med (eye drops): Number of drops used recorded each day by patients on diary cards 4) Adverse events: Not clear who reported/ recorded	1) Patient-assessed symptom severity: Mean symptom scores at 1 week shown in figure. Terfenadine reached maximum efficacy within 1-2 days; budesonide scores were lower than terfenadine after 2-3 days and continued to improve over days 3-7. Combination treatment had similar effect to budesonide alone. Mean symptom scores at week 3 graphically shown. Terfenadine resulted in significant (P < 0.05) reductions in symptom scores for runny and itchy nose compared to placebo. Budesonide alone reduced all mean symptom scores compared to placebo (P < 0.05); also more than terfenadine but only statistically significant for nasal blockage. Combination therapy symptom scores were similar to budesonide for blocked/itchy/runny nose. Combination reduced mean sneezing score than terfenadine or budesonide alone (P < 0.05). 2) Patient global assessment of efficacy: Proportion rating treatment as noticeably effective or very effective: Placebo 40%, terfenadine 46%, 85% budesonide alone or in combination. P < 0.05 for budesonide alone or in combination vs. placebo or terfenadine.	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: No Objectively confirmed: No Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: No Note: Double-dummy blinding technique employed.

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Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Location: UK Setting: Outpatient Type(s) of providers: Primary care	Race: NR Other:		3) Use of rescue med (eye drops): Eye drop use in all groups remained constant; use in budesonide group higher than terfenadine group (NS) 4) Adverse events: 19 total AEs (5 placebo, 2 terfenadine, 7 budesonide, 8 combination). Most common sneezing and nasal irritation (1 combination pt with palpitations) 3 withdrawals due to AE (1 placebo pt with nausea, 1 budesonide patient with fatigue, 1 combination patient with sneezing and headache)	
Sussman, Mason, Compton, et al., 1999	Design: RCT, parallel-group Interventions: 1) Fexofenadine 60 mg + pseudoephedrine 120 mg (extended-release), twice per day (n = 215) 2) Fexofenadine 60 mg twice per day (n = 218) 3) Pseudoephedrine 120 mg (extended-release) twice per day (n = 218) Duration of study treatment: 14-20 days Rescue med not permitted Trial preceded by a 3- to 5-day placebo run-in period; no other washout period described Dates: NR Location: Canada	No. of subjects at start: 651 Dropouts/withdrawals: 63 discontinued therapy (3.8% subject/MD decision, 2.8% AEs) No. of subjects at end: 588 Inclusion criteria: Age 12-65; ragweed allergy confirmed by positive skin test; clinical response to antihistamines Exclusion criteria: Hyper-sensitivity to drug, URI or sinusitis within 30 days, alcohol or drug abuse, pregnant or lactating women Age: Mean 31.7-34.9 (SD 11.12-12.35) Sex: 275 M (42%), 376 F (58%) Race: 566 (87%) white, 35 (5%) black, 42 (6%) Asian, 8 (1%) multiracial	1) Patient-assessed symptom severity: sneezing; rhinorrhea; itchy nose, palate, and/or throat; itchy, watery, or red eyes; and nasal congestion graded twice each day (7 PM and bedtime) on scale of 0 (symptom absent) to 4 (symptom so severe as to warrant an immediate visit to the physician) TSS = total symptom score; NCS = nasal congestion score 2) Adverse events: Patients "were required to record any adverse events" 3) Work-related productivity: Assessed using the Work Productivity Activities Index, completed at	1) Patient-assessed symptom severity: Primary outcome: reduction in 7 PM reflective total symptom/nasal congestion score (TSS-NCS): Combination therapy reduction (2.32) significantly greater than pseudo-ephedrine alone (1.42, P < 0.0001), but not significantly different than fexofenadine alone (2.05, P = 0.1579). Change in 7 PM NCS: Combination therapy reduction (0.56) significantly greater than fexofenadine (0.36, P < 0.0005), but not significantly different from pseudoephedrine (0.45, P = 0.059). Change in individual symptom scores showed significantly greater reductions in combination therapy compared to pseudoephedrine for all symptoms (P-values 0.0002 for all symptoms except P < 0.0001 for sneezing). Combination therapy had greater improvement than fexofenadine for nasal congestion only (P = 0.0005).	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: Yes Intention-to-treat: Yes Notes: Double-dummy blinding technique employed. Pollen levels measured daily throughout study.

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Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Setting: 18 medical centers Type(s) of providers: NR	Other:	baseline and at end of treatment	2) Adverse events: 280/651 (43%) had at least 1 AE. Combination 51.2%, pseudoephedrine 45.4%, 36.2% fexofenadine. P < 0.001 in fexofenadine group. 29% of 651 had treatment-related AEs. Combination 34.9%, pseudoephedrine 36.7%, 16.5% fexofenadine. P < 0.001 compared to fexofenadine group. Most common were headache (combo 9.3%, pseudoephedrine 12.4%, fexofenadine 7.3%) and insomnia (combo 11.2%, pseudoephedrine 12.8%, fexofenadine 1.8%). 3) Work-related productivity: Reduction in work impairment scores: Fexofenadine 9.8%, pseudoephedrine 7.9%, combination 13% (P < 0.0001 for each group compared to baseline). Reductions in combination group significant (P = 0.006) compared to pseudoephedrine group, but not different compared to fexofenadine group. Improvement in work productivity among employed patients: combination 9.3% compared to pseudoephedrine 6.2%, P < 0.05. No difference compared to fexofenadine group 8.1%. Overall work productivity in combination (8.5%) and fexofenadine (8.0%) groups significantly improved from baseline (P < 0.001) compared to pseudoephedrine (4.9%, P < 0.12).	

Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Vuurman, van Veggel, Sanders, et al., 1996	Design: RCT, parallel-group (see Notes) Interventions: Allergic rhinitis patients randomized to one of following treatments during 3-day training period: 1) Acrivastine 8 mg + pseudo-ephedrine 60 mg qid (A+P) (n = 22) 2) Diphenhydramine 50 mg qid (D) (n = 24) 3) Placebo (n = 22) In all three groups, treatment was started the evening before the first of three evening training sessions and continued for 3 days. At the end of the 3-day training period, all allergic rhinitis patients were treated with acrivastine + pseudo-ephedrine, as above, for 14 days, after which they returned for examination phase. Duration of study treatment: 17 days+, as follows: 2-hour introduction phase, 3-day training phase, 14-day interval, and 1-hour examination phase No mention of rescue med No pre-trial washout period described Dates: April - August 1993, Dutch pollen season	No. of subjects at start: 68? with seasonal allergic rhinitis (see Table 1) Dropouts/withdrawals: 1 No. of subjects at end: 67 with seasonal allergic rhinitis (see Notes); complete symptom score data on 59 patients Inclusion criteria: Documented medical treatment for seasonal allergic rhinitis over the prior 2 years; diary symptom score = 9 prior to treatment Exclusion criteria: Severe mental of physical disorders; alcohol or drug abuse; chronic medication use; drug hypersensitivity Age: Overall mean 20.0 (SD 2.3), range 16-25 Control 20.2 (SD 2.6) Acrivastine + pseudophedrine 20.0 (2.7) Placebo 19.8 (2.0) Diphenhydramine 20.1 (1.7) Sex: Control 10 M/18 F Acrivastine + Pseudophedrine: 13 M/9 F Placebo 7 M/15 F Diphenhydramine 14 M/10 F Race: NR Other:	1) Patient-assessed symptom severity (training and examination phases): rhinorrhea, nasal congestion, sneezing, mouth-breathing, itchy nose/throat, and tearing or red eyes graded daily on 5-point scale ranging from "absent" to "very severe, interfering with daily activities" 2) Performance on memory tests (training phase) 3) Performance on learning tests (training and examination phases)	1) Patient-assessed symptom severity: Mean (SEM) values shows in Figure 1. Symptom scores improved for drug treatments (A+P and D groups) compared to placebo. Significant treatment effect on day 1, P = 0.037, but not days 2 and 3. Placebo vs. A+P, P = 0.029 Placebo vs. D, P = 0.024 2) Performance on memory tests (training phase): Not abstracted 3) Performance on learning tests (training and examination phases): Not abstracted	Quality Scoring: Population similar: No Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: No Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: No Dropouts described: Yes Intention-to-treat: No Notes: Study also completed by 28 normal controls with no history of allergic rhinitis, matched for age and intelligence. Study designed primarily to test performance on a didactic computer simulation. Patients randomized to separate treatments during 3-day training phase at start of trial. After training period, all allergic rhinitis patients treated with acrivastine + pseudo-ephedrine for 14 days preceding the examination phase. Examination lasted approximately 1 hour and was designed to assess retention of knowledge acquired during training phase and measure group differences in performance attributable to the combined effects of allergies and treatment during the

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Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Location: The Netherlands Setting: Academic center Type(s) of providers: NR; authors from psychiatry, neuropsychology, and psychopharmacology departments				training period.
Williams, Hull, McSorley, et al., 1996	Design: RCT, parallel-group, randomization stratified to assure uniform sex distribution Interventions: 1) Acrivastine 8 mg + pseudoephedrine 60 mg, combined in a single capsule, four times per day (n = 202-3) 2) Acrivastine 8 mg four times per day (n = 202-3) 3) Pseudoephedrine 60 mg four times per day (n = 202-3) 4) Placebo four times per day (n = 68) Duration of study treatment: 2 weeks No mention of rescue med No pre-trial washout period described; individuals taking antihistamines, decongest-ants, MAOIs, cromolyn sodium, or corticosteroids within specified times prior to study (based on half-lives of respective drugs) were excluded	No. of subjects at start: 676 Dropouts/withdrawals: None reported No. of subjects at end: 676 Inclusion criteria: Age ≥ 18; positive skin test reaction to mountain cedar; 2-year history of symptoms Exclusion criteria: Nasal obstruction (turbinates, septal deviation); vasomotor rhinitis; contraindication to study medications; pregnant, lactating, or not on acceptable form of contraception; use of meds known to effect response to study drug within specified times based on drug half-life Age: Mean 36-37, range 18-76 Sex: 367 F, 309 M Race: 81-91% white per group Other:	1) Patient-assessed symptom severity: runny nose; sneezing; itchy nose/throat; tearing, itching, or redness of eyes; and nasal congestion graded twice each day (upon arising and at bedtime) on scale of 0 (absent) to 5 (very severe) 2) Investigator global assessment of efficacy 3) Adverse events: spontaneous reports of AEs evaluated	1) Patient-assessed symptom severity: Mean diary symptom scores days 1-14: Combination 8.5 Acrivastine 9.8 Pseudoephedrine 10.8 Placebo 11.3 P < 0.001 for combination compared to other 3 treatment groups Mean nasal congestion scores days 1-14: Combination 2.3 Acrivastine 2.7 Pseudoephedrine 2.6 Placebo 2.9 P < 0.001 for combination compared to acrivastine Mean allergy symptom scores days 1-14: Combination 6.2 Acrivastine 7.1 Pseudoephedrine 8.2 Placebo 8.4 P < 0.001 for combination compared to pseudoephedrine 2) Investigator global assessment of efficacy: Not abstracted 3) Adverse events: 12 types of AEs, total number not reported. Most common in	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: Yes Blinding adequate: Yes Dropouts described: yes Intention-to-treat: Yes Note: Precise numbers of patients in active treatment groups not reported (all 202 or 203).

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Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Dates: NR (discussion states season lasts from Christmas through February) Location: South central Texas Setting: 6 outpatient centers Type(s) of providers: NR			combination group relative to placebo group were dry mouth (8%), insomnia (7%), somnolence (7%), and headache (6%).	
Wilson, Dempsey, Sims, et al., 2000	Design: RCT, parallel-group Interventions: 1) Cetirizine 10 mg + mometasone furoate nasal spray 200 µg (two squirts in each nostril), once daily (n = 14) 2) Cetirizine 10 mg + montelukast 10 mg, once daily (n = 11) 3) Cetirizine 10 mg + placebo, once daily (n = 13) Duration of study treatment: 4 weeks No mention of rescue med Trial preceded by placebo run-in period, lasting a minimum of 1 week, during which usual medications were suspended Dates: June-July 1998 Location: Scotland Setting: Outpatient medical school	No. of subjects at start: 40 Dropouts/withdrawals: 2 withdrew during placebo run-in phase prior to randomization No. of subjects at end: 38 Inclusion criteria: Symptomatic seasonal allergic rhinitis; positive skin to at least 1 pollen extract Exclusion criteria: None specified Age: Mean 30 (SEM 1.4), range 16-65 Sex: 26 F, 12 M Race: NR Other:	1) Patient-assessed symptom severity: runny nose, blocked/stuffy nose, itchy nose, sneezing, itchy eyes, watery eyes, red eyes, and tickly throat graded twice each day on scale of 0 (no symptoms) to 3 (maximal symptoms) 2) Patient-assessed impact of symptoms on daily activities: graded twice per day on scale of 0 (no interference with daily activity) to 10 (maximal interference with daily activity) 3) Nasal peak inspiratory flow	1) Patient-assessed symptom severity: Total symptom score mean (SEM) after 4 weeks: Cetirizine 4.3 (1.4) ** Cetirizine + mometasone 2.1 (1.1) *** Cetirizine + montelukast 5.5 (1.2) ** ** P < 0.01 vs. run-in, ***P < 0.001 vs. run-in Cetirizine significantly improved all symptoms at 4 weeks except eye symptoms. Cetirizine + mometasone significantly improved all symptoms at 4 weeks. Cetirizine + montelukast significant improved total, nasal, and eye symptoms only at 4 weeks. 2) Patient-assessed impact of symptoms on daily activities: Daily activity score after 4 weeks Cetirizine 1.1 (0.4) ** Cetirizine + mometasone 0.5 (0.3) *** Cetirizine + montelukast 1.8 (0.5) ** P < 0.01 vs. run-in, ***P < 0.001 vs. run-in Daily activity not improved significantly in cetirizine + montelukast group. 3) Nasal peak inspiratory flow: Not abstracted	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 1b Randomized: Yes Allocation concealed: Not described Double-blind: No Blinding adequate: Not applicable Dropouts described: Yes Intention-to-treat: Yes Notes: Double-dummy blinding technique employed. Pollen levels measured daily during trial. No data on adverse events.

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Evidence Table 4: Combined Treatments (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Type(s) of providers: Allergy specialist				

[†] Quality scoring criteria were as follows:
Population similar: Was the study population described and reasonably similar to an adult working US population? (Yes [described and similar], No [described, but not similar], Not adequately described)
Intervention(s) described: Were the intervention protocols referenced or described in sufficient detail to replicate? (Yes, No)
Comorbidities described: Was the presence of comorbid asthma (or other upper respiratory conditions) described in the study population? (Yes, No)
Diagnosis by MD: Was the diagnosis of allergic rhinitis based on physician diagnosis? (Yes, No, Not applicable [asthma patients only])
Objectively confirmed: If physician-diagnosed, was the diagnosis supported by objective evidence of allergy (e.g., skin prick or serum IgE antibody testing)? (Yes, No, Not applicable)
Outcome measures valid: Were the main outcomes of interest to us measured in a way that has been demonstrated empirically to be valid and reliable (e.g., using a standardized scale such the RQLQ or SF-36)? (Yes, No, Not adequately described)
Level of evidence: Based on Oxford Center for Evidence-Based Medicine Levels of Evidence (1a, 1b, 1c, 2a, 2b, 2c, 3a, 3b, 4, 5)
Randomized: Was the study described as "randomized"? (Yes, No)
Allocation concealed: If the method for concealing allocation from the investigators was described, was it *adequate* (table of random numbers, computer-generated, coin tossing, etc.) or *inadequate* (alternating, date of birth, hospital number, etc.)? (Not described, Yes [described and adequate], No [described, but inadequate])
Double-blind: Was the study described as "double-blind"? (Yes, No)
Blinding adequate: If the method of double-blinding was described, was it *adequate* (e.g., identical placebo, active placebo, injection vs. tablet with double dummy) or *inadequate* (e.g., tablet vs. injection with no double dummy)? (Not described, Yes [described and adequate], No [described, but inadequate])
Dropouts described: Did the study describe dropouts and withdrawals so that all patients entering the trial could be accounted for? (Yes, No)
Intention-to-treat: Was the analysis performed according to the intention-to-treat principle? (Yes, No, Can't determine)

Evidence Table 5: Clinician Specialty Differences

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Brydon, 1993	Design: Prospective before-after comparison Intervention(s): Consultation with allergy nurse practitioner Duration of study treatment: 9 months prior to consultation and 9 months after Dates: 11/90-3/91 Location: UK Setting: Patients referred for consultation by general practitioners (GPs) Type(s) of providers: GPs, nurse practitioners	No. of subjects at start: 53 Dropouts/withdrawals: 14 No. of subjects at end: 39 Inclusion criteria: Referred to nurse practitioner for allergy consultation Exclusion criteria: NR Age: Median 38 yrs Sex: 44% female Race: NR	1) GP visits 2) Number of prescriptions written	1) Of 23 patients with positive skin tests, GP visits dropped 71% ($p < 0.001$) after consultation with the nurse practitioner. 2) Of 23 patients with skin positive skin tests, number of scripts dropped 39% ($p < 0.001$) in the 9 months after consultation with the nurse practitioner.	Quality Scoring: Population similar: Yes Intervention(s) described: No Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 4 Notes: High dropout rate (25%). Article implies that nurse practitioners spend more time with allergy sufferers and better educate them, resulting in better management of allergic rhinitis and decreased GP utilization.
Camilleri, 1991	Design: Case series, survey Intervention(s): None Duration of study treatment: NA Dates: NR Location: Glasgow, UK Setting: Rhinitis clinic Type(s) of providers: Otolaryngologist	No. of subjects at start: NR Dropouts/withdrawals: NR No. of subjects at end: 60 Inclusion criteria: Referred to otolaryngologist rhinitis clinic for the first fine; report previous failed nasal steroid treatment Exclusion criteria: NR Age: Mean 27 years (range 14-68 years) Sex: 52% female Race: NR 80% confirmed to have allergic or	1) Duration of steroid use 2) Mean dose per month 3) Reported symptoms 4) Mean standardized total course steroid dose, calculated based on equivalent budesonide dose	1) Mean duration 4.8 months; only 12% used nasal steroid spray for < 4 weeks 2) Mean 12 mg (range 4.3 – 30.9 mg) 56.5% used recommended dose 15% more than recommended dose 28.5% less than recommended dose 3) Reported symptoms Blocked 51% Catarrh 27% Drip 12% Sneeze 5% Loss of smell 5% 4) Mean 61 mg (range 2 – 228 mg); median 36 mg (equivalent to 4 spray canisters)	Quality Scoring: Population similar: Yes Intervention(s) described: No Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: No Outcome measures valid: No Level of evidence: 4 Notes: Author concluded that no more than 29% of treatment failures could be attributed to lack of patient education.

Evidence Table 5: Clinician Specialty Differences (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Demoly, Allaert Lecasble, et al., 2002	Design: Survey Intervention(s): None Duration of study treatment: NA Dates: May 2000 Location: France Setting: General medical practices throughout France Type(s) of providers: GPs	No. of subjects at start: 3026 patients 1321 physicians Dropouts/withdrawals: NA No. of subjects at end: NA Inclusion criteria: First 4 patients consulting physician for intermittent allergic rhinitis during study period. Exclusion criteria: Patient previously enrolled in a clinical trial or another epidemiological survey. Age: Mean 36.5 ± 13.6 yrs Sex: 47.5% female Race: NR	1) Duration of symptoms at consultation 2) Past allergy consultation 3) Patient-reported impairments 4) Specialist consultation 5) Treatments prescribed 6) Predictors of sick leave based on multivariable analysis of patients ordered sick leave (n=137) versus not. 7) Patient assessment of information/ education needs/ plans	1) Current episode 19.6 ± 40.4 days 2) Past history None 15.3% 55.5% identified allergen 42.2% had previous allergy testing 44% previously treated 3) Patient –reported impairments 79.2% Occupational impairment 91.8% impaired ADL 4) Consultation of specialist for 10.3% 78.8% allergologist 23.2% ENT specialist 11.8% pulmonologist 5) Treatments prescribed Oral antihistamines 92.4% Topical corticosteroids 45.2% Antiallergic eyedrops 32.2% Topical antihistamines 16.8% Local vasoconstrictors 8.7% Systemic corticosteroid 11.7% Two or more meds 74.4% Sick leave ordered in 4.6% for 5.7 ± 4.8d 6) Predictors of ordering sick leave 1st episode p<0.001) impaired work p<0.001 impaired personal life p<0.02 sleeping difficulty p<0.05 7) 79% considered information form physician adequate and easy to understand 58.2% wanted more advice 94.6% from family doctor 13.3% books and magazines 11.6% pharmacist 54.7% completely adherent to treatment	Quality Scoring: Population similar: Yes Intervention(s) described: No Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: No Outcome measures valid: No Level of evidence: 4 Notes:

Evidence Table 5: Clinician Specialty Differences (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Francillon, Burnand, Frei, et al., 1995	Design: Survey Intervention(s): NA Duration of study treatment: NA Dates: 6-8/92 Location: Switzerland Setting: Allergy clinics Type(s) of providers: GP, allergist	No. of subjects at start: NR Dropouts/withdrawals: NR No. of subjects at end: 126 Inclusion criteria: Referral to clinic and willingness to complete survey Exclusion criteria: Chief complaint related primarily to asthma or allergic conditions other than hay fever Age: Adults (age > 16) Sex: 50% female Race: Italian and French	1) Hay fever score 2) Reason for referral	1) Hay fever scores not associated with socioprofessional status, referral pattern, age, sex, duration of symptoms or geographic locations. 2) 30% referred by a physician. Reason for referral because of patients reported symptom severity (63%), or they were looking for a specialist skill (37%). Of those looking for a specialist, 24% wanted optimal treatment, 23% wanted a specific and accurate diagnosis.	Quality Scoring: Population similar: Not adequately described Intervention(s) described: Not applicable Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: No Outcome measures valid: No Level of evidence: 4 Note: No data on whether specialist care offers benefits to patients with allergic rhinitis

Evidence Table 5: Clinician Specialty Differences (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Gani, Pozzi, Crivellaro, et al., 2001	Design: RCT Intervention(s): Patient education adjunct to nasal glucocorticoid spray. 1) written drug information from manufacturer (package insert) 2) training on use of nasal spray and simplified written information 3) detailed lesson on nature of disease All patients received regular therapy with mometasone furoate nasal spray (2 puffs per nostril q.i.d. = 200 mcg/d) Dates: NR Location: Genoa, Italy Setting: Allergy clinic Type(s) of providers: Allergists	No. of subjects at start: 101 Dropouts/withdrawals: 6 No. of subjects at end: 95 Inclusion criteria: 2 year history of SAR solely due to pollens; positive skin test; positive RAST. Referred to nurse practitioner for allergy consultation Exclusion criteria: Sensitization to cat dander, mites or mold; anatomical abnormalities of upper respiratory airways; previous or ongoing SIT; chronic systemic corticosteroid treatment. Age: Mean 30 yrs Sex: 39% female Race: NR 32 patients also had mild asthma and were stratified into 3 treatment groups	1) Compliance rate 2) Nasal symptoms 3) Ocular symptoms 4) Respiratory symptoms (cough, wheezing, tightness) 4) Drug consumption for symptom control	1) Dropout/noncompliance rate A B C Dropouts 4 0 2 Noncompliant 9 3 4 Total 13 3 6 P=0.001 (A vs. B+C) 2) Nasal symptoms Group A 62.6 ± 51 Group B 64.7 ± 50 Group C 54.1 ± 62 P=NS 3) Ocular symptoms Group A 51.3 ± 52.8 Group B 46.0 ± 52 Group C 42.6 ± 55 P=0.02 4) Respiratory symptoms Group A 16.2 ± 24 Group B 11.7 ± 20 Group C 6.0 ± 15 P=0.02 (A vs. C) 1) Drug consumption for sx control Oral antihistamines (tablets taken) Group A 8.3 ± 15 Group B 4 ± 11.3 Group C 1.3 ± 6.1 P=0.08 (A vs. C) 6) Inhaled albuterol (at least one dose) Group A 6 (23.8%) Group B 2 (5.7%) Group C 0 P=0.05 (A vs. B+C); P=0.005 (A vs. C) 7) Any drug (at least one dose) Group A 13 (50%) Group B 12 (34%) Group C 5 (14.7%) P=0.02 (A vs. B+C); P=0.003 (A vs. C)	Quality Scoring: Population similar: Yes Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Randomized: Yes Allocation concealed : Not described Double-blind: No Blinding adequate: NA Dropouts described: Yes Intention-to-treat: No Notes:

Evidence Table 5: Clinician Specialty Differences (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Lane, Pine, and Pillsbury, 2001	Design: Case series Intervention(s): Allergy skin testing by intradermal skin end point titration (SET) with a panel of aeroallergens diluted serially in 5-fold decreasing concentrations of the following antigens: Epidermals, mold mix, *Trichophyton*, *Candida*, and *Epidermophyton* species, cotton, house dust mixture (w/o mite antigens, mite (Der f 1), ragweed, weed mix, grass mix, tree mix, and fescue. Duration of study treatment: NA Dates: 1979-1999 Location: Chapel Hill, NC Setting: Allergy clinic at academic medical center Type(s) of providers: Otolaryngologist, allergy nurses	No. of subjects at start: 3,329 Dropouts/withdrawals: NR No. of subjects at end: NA Inclusion criteria: Referral to clinic for allergy skin testing Exclusion criteria: None Age: 45.2 ± 14.5 years Sex: 58% female Race: NR	1) Positive skin test responses, defined as 3 or more 2+ reactions or 1 or more 3+ reactions 2) Proportion of patients with positive skin test response who underwent immunotherapy 3) Self-rated effectiveness of immunotherapy 4) Proportion of current IT patients who underwent nasal or sinus surgery	1) 2,653 (79.7%) had positive skin test responses. 2) 2,008 (75.7%) patients underwent immunotherapy 3) Among patients undergoing immunotherapy, improvement was 3.9 on a 1- to 5-point scale. Patients with no improvement in nasal congestion symptoms had an average rating of 3.57, significantly lower than all patients (p = 0.015). 4) A survey of 275 patients currently undergoing immunotherapy showed that 84 (30.5%) had a history of nasal or sinus surgery, either before IT (35.6%), after IT (57.8%) or during IT (6%). Nasal congestion was the symptom most often reported to be improved with surgery (74.3%). Surgical procedures (131 procedures in 72 patients) included septoplasty (59 patients), reduction of inferior turbinates (38 patients) or endoscopic sinus surgery (34 patients), with 54% of patients having more than one procedure. The most frequent combination was septoplasty and reduction of inferior turbinates (n = 18). Mean self-reported effectiveness of IT was not significantly different between patients who had and had not undergone surgery.	Quality Scoring: Population similar: Yes Intervention(s) described: Not applicable Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 4

Evidence Table 5: Clinician Specialty Differences (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Scadding, Richards, and Price, 2000	Design: Population-based survey Intervention(s): NA Duration of study treatment: NA Dates: Grass pollen season Location: Southern England Setting: Community Type(s) of providers: NA	No. of subjects at start: NR Dropouts/withdrawals: NR No. of subjects at end: 2139 Inclusion criteria: Adults listed in the UK electoral register followed by telephone contact; screening criteria not listed Exclusion criteria: NR Age: 16-65+ years Sex: 42% M, 58% F Race: NR	1) Consultation distribution 2) Prevalence of seasonal allergic rhinitis 3) Symptoms 4) Satisfaction with treatment	1) GPs were the main point of contact for education and treatment: 54% of patients consulted GPs 27% consulted pharmacists 7% a health food consultant 2% a specialist 2) Prevalence of seasonal allergic rhinitis: 15% overall 23% 16-34 age group 13% 35-54 age group 8% 55+ age group 3) Symptoms (seasonal allergic rhinitis [SAR] vs. perennial allergic rhinitis [PAR]): Symptom / SAR / PAR Sneezing 78% 65% Runny nose 64% 59% Itchy eyes 52% 31% Watery eyes 42% 33% Itchy nose 41% 38% Headache 25% 41% Wheeze 15% 25% Blocked nose 37% 46% Blocked sinuses 37% 21% Sore nose 18% 10% 4) Satisfaction with treatment: Level of Satisfaction / All / SAR / PAR Very 32% 17% 34% Reasonably 28% 36% 27% Some 14% 18% 12% Not 3% 10% 2% Not applicable 24% 19% 25%	Quality Scoring: Population similar: Yes Intervention(s) described: Not applicable Comorbidities described: Yes Diagnosis by MD: No Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 1b Note: Does not really provide any information between health care providers other than the aforementioned distribution regarding consultation.

Evidence Table 5: Clinician Specialty Differences (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
White, Smith, Baker, et al., 1998	Design: Postal survey (cohort) Intervention(s): 1) Nonsedating antihistamine 2) Steroid nasal spray Duration of study treatment: NR Dates: 1994-95 Location: UK Setting: Patients selected from GP practices Type(s) of providers: GPs	No. of subjects at start: 846 Dropouts/withdrawals: 219 No. of subjects at end: 627 (74.1%) Inclusion criteria: Identified as having been prescribed a non-sedating antihistamine and a nasal steroid spray by GP Exclusion criteria: NR Age: 32.8 years ± 13.3 Sex: 54.9% female Race: NR	1) Usage pattern of the antihistamine and steroid spray by the patient in relation to overall control of symptoms	1) 54% of patients reported partial or poor control of their symptoms. 69.4% of these were not taking their meds appropriately. 30.6% of patients were taking their meds appropriately, but did not have full control of their symptoms. At least 15% of the 54% of patients would be suitable for immunotherapy by a specialist.	Quality Scoring: Population similar: Yes Intervention(s) described: No Comorbidities described: No Diagnosis by MD: Yes Objectively confirmed: No Outcome measures valid: No Level of evidence: 2b Note: The article indicates that 54% of the patients seen at the GP clinics are partially/poorly controlled with the medication and dosing regimen they were using. The authors suggest that better control of the symptoms would be achieved with referral to a specialist for immunotherapy but offer no data to support this conclusion.

[†] Quality scoring criteria were as follows:
Population similar: Was the study population described and reasonably similar to an adult working US population? (Yes [described and similar], No [described, but not similar], Not adequately described)
Intervention(s) described: Were the intervention protocols referenced or described in sufficient detail to replicate? (Yes, No)
Comorbidities described: Was the presence of comorbid asthma (or other upper respiratory conditions) described in the study population? (Yes, No)
Diagnosis by MD: Was the diagnosis of allergic rhinitis based on physician diagnosis? (Yes, No, Not applicable [asthma patients only])
Objectively confirmed: If physician-diagnosed, was the diagnosis supported by objective evidence of allergy (e.g., skin prick or serum IgE antibody testing)? (Yes, No, Not applicable)
Outcome measures valid: Were the main outcomes of interest to us measured in a way that has been demonstrated empirically to be valid and reliable (e.g., using a standardized scale such the RQLQ or SF-36)? (Yes, No, Not adequately described)
Level of evidence: Based on Oxford Center for Evidence-Based Medicine Levels of Evidence (1a, 1b, 1c, 2a, 2b, 2c, 3a, 3b, 4, 5)

Evidence Table 6: Racial and Ethnic Variation

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Fagan, Scheff, Hryhorczuk, et al., 2001	Design: Cross-sectional, population-based survey Assessment method: Self-administered survey Definitions: Rhinitis – sneezing or a runny or blocked nose not associated with a cold or the flu Hay fever – "yes" response to the question, "Have you ever had hay fever?" Response rate: 90% Dates: 1993 Location: Illinois, USA	Inclusion criteria: Schoolchildren in grades 7 through 12 Sample size: 2044 Age: 7th to 12th graders Sex: 1034 males; 1010 females Race: 1551 white; 332 Hispanic; 163 African-American; 154 other or not reported	1) Prevalence – unadjusted 2) Prevalence – adjusted for age, gender, family history of asthma, active smoking and exposure to dampness in past 12 months 3) Functional impairment defined as "interferes with daily activities"	1) Unadjusted prevalence: Rhinitis (lifetime) – 36.3% Rhinitis (12 months) – 31.9% Hay fever – 22.4% 2) Adjusted prevalence African-American vs. other: Current rhinitis – Odds ratio 1.0 (95% CI 0.68 – 1.47) Hay fever – Odds ratio 1.18 (95% CI 0.78 – 1.78) 3) Rhinitis functional impairment: Not at all – 79.9% Little – 15.8% Moderate – 3.6% A lot 0.7% African-Americans were significantly more likely to report functional impairment.	Quality Scoring: Population similar: No Intervention(s) described: Not applicable Comorbidities described: Yes Diagnosis by MD: No Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 1b Notes:
Lebowitz, Cassell, and McCarroll, 1972	Design: Prospective incidence study of minor illnesses Assessment method: Weekly interview, using standardized questions to assess 14 symptoms Definitions: Rhinitis – "yes" response to "Did you have a stuffy or runny nose…" that was not associated with a common cold? Dates: 1962 - 1965 Location: New York City, USA	No. of subjects at start: 448 families Dropouts/withdrawals: NR No. of subjects at end: NR Inclusion criteria: Volunteers from a 2-stage cluster sample Average follow-up: 45 weeks; 1168 person-years of observation Age: NR Sex: NR Race: NR Other:	1) Illness episodes (person days) 2) Illness duration (mean) 3) Illness incidence by sex, age, and race	1) Illness episodes: Out of 61,893 person-days of illness, 4255 (6.9%) were due to rhinitis 2) Illness duration: Average duration of rhinitis was 7.4 days 3) Incidence of rhinitis per person year: White – 0.7 per person year Black – 0.4 per person year Puerto Rican – 0.3 per person year	Quality Scoring: Population similar: No Intervention(s) described: Not applicable Comorbidities described: No Diagnosis by MD: No Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 1b Notes: No adjustments for age differences in race comparison. Follow-up rate is unclear.

Evidence Table 6: Racial and Ethnic Variation (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
Lower, Henry, Mandik, et al., 1993	Design: Retrospective cohort study Intervention: Immunotherapy given weekly for up to 8 months, then maintenance doses every 2 to 4 weeks for 2 to 4 years Dates: NR Location: Pittsburgh, USA Setting: University-affiliated allergy clinic Type(s) of providers: Allergy specialists	No. of subjects: 315 Inclusion criteria: Allergic rhinitis, asthma, or atopic dermatitis; computerized medical records; immunotherapy treatment based on specific allergens identified by skin testing, begun at least 1 year prior to study start Exclusion criteria: None Age: "Pediatric population" (range, 5-18 years) Sex: 190 male; 125 female Race: 254 white; 59 non-white Other: 52 allergic rhinitis with asthma; 34 allergic rhinitis with atopic dermatitis	1) Non-adherence – patients who had discontinued immunotherapy for ≥ 6 months (presumably prior to completing the full 2- to 4-year course of treatment) 2) Reasons for non-adherence – response to open-ended question administered by telephone 3) Factors associated with non-adherence, including gender, race, and type of health insurance	1) Non-adherence: 138 (44%) 2) Reasons for non-adherence: Inconvenient: 17 Symptoms not decreased: 15 Symptoms improved: 14 Changed clinic: 14 Child refused: 9 Local reaction: 6 Financial burden: 6 Other: 7 Could not contact to determine: 50 3) Non-adherence factors: Non-white race and non-private insurance were associated with non-adherence.	Quality Scoring: Population similar: No Intervention(s) described: Yes Comorbidities described: Yes Diagnosis by MD: Yes Objectively confirmed: Yes Outcome measures valid: No Level of evidence: 2b Notes:
Strachan, Sibbald, Weiland, et al., 1997	Design: International survey (prospective cohort) Definitions: Rhinitis – "yes" response to question, "Have you ever had a problem with sneezing or a runny or blocked nose, when you did not have a cold or the flu?" Hay fever – "yes" response to question, "Have you ever had hay fever?" Assessment: Questionnaire (self- or parent-completed) Dates: NR	No. of subjects 721,601 Response rate: 149 of 155 centers achieved response rates of ≥ 80% in the 13- to 14-year-old groups; 89 of 91 centers achieved response rates of ≥ 70% in the 6- to 7-year-old group Inclusion criteria: School enrollment and appropriate age or grade level Age: 6- to 7- (257,800) and 13- to 14-year-olds (463,801) Sex: NR Race: NR	1) Prevalence – reported as a range and by percentiles for the 155 centers	1) Prevalence: Rhinitis (lifetime): ranged from 2.0% to 80.5% Rhinitis (12 months): ranged from 1.5% to 66.6% Hay fever (lifetime): ranged from 0% to 54.4%	Quality Scoring: Population similar: No Intervention(s) described: Not applicable Comorbidities described: No Diagnosis by MD: No Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 1b Notes: *(continued on next page)*

Evidence Table 6: Racial and Ethnic Variation (continued)

Study	Design and Interventions	Patient Population	Outcomes Reported	Results	Quality Score[†]/Notes
	Location: 155 centers in 56 countries Setting: Schools selected randomly within each participating center	Other:			
Turkeltaub and Gergen, 1991	Design: Population-based survey Definitions: Chronic rhinitis – no physician's diagnosis of hay fever, but frequent nasal and/or eye symptoms that did not vary by both season and pollen during the past 12 months, not counting colds or the flu Allergic rhinitis – physician diagnosis of hay fever or frequent nasal and/or eye symptoms that varied by both season and pollen during the past 12 months, not counting colds or the flu Assessments: Interviews using structured questionnaires Response rate: 73.1% Dates: 1976-1980 Location: USA Setting: Community-based	No. of subjects: 12,742 Inclusion criteria: None Exclusion criteria: None Age: Range, 12-74 years Sex: 6,174 males; 6,568 f emales Race: 11,260 white (88%); 1,482 Black	1) Prevalence, weighted for the sampling design, reported separately for whites and blacks 2) Prevalence, weighted for sampling design, and adjusted for age, sex, smoking, poverty level and urban/rural residence	1) Prevalence (whites, blacks) Chronic rhinitis: 20.4% (SE 0.5); 19.2% (SE 1.2), p = ns Allergic rhinitis: 9.8% (SE 0.5); 8.1% (SE 0.9), p = ns Allergic rhinitis without asthma: 7.8% (SE 0.4); 5.1 (SE 0.6), p < 0.01 Allergic rhinitis with asthma: 2.0% (SE 0.2); 3.1% (SE 0.5), p < 0.05 2) Adjusted prevalence☹whites, blacks) Chronic rhinitis: 20.4% (SE 0.5); 18.8% (SE 1.2), p = ns Allergic rhinitis: 10.0% (SE 0.5); 8.4% (SE 1,1), p = ns Allergic rhinitis without asthma: 7.9% (SE 0.4); 5.3 (SE 0.8), p < 0.01 Allergic rhinitis with asthma: 2.0% (SE 0.2); 3.1% (SE 0.6), p = ns	Quality Scoring: Population similar: Yes Intervention(s) described: Not applicable Comorbidities described: ?? Diagnosis by MD: No Objectively confirmed: Not applicable Outcome measures valid: No Level of evidence: 1b Notes:

[†] Quality scoring criteria were as follows:
Population similar: Was the study population described and reasonably similar to an adult working US population? (Yes [described and similar], No [described, but not similar], Not adequately described)

Intervention(s) described: Were the intervention protocols referenced or described in sufficient detail to replicate? (Yes, No)
Comorbidities described: Was the presence of comorbid asthma (or other upper respiratory conditions) described in the study population? (Yes, No)
Diagnosis by MD: Was the diagnosis of allergic rhinitis based on physician diagnosis? (Yes, No, Not applicable [asthma patients only])
Objectively confirmed: If physician-diagnosed, was the diagnosis supported by objective evidence of allergy (e.g., skin prick or serum IgE antibody testing)? (Yes, No, Not applicable)
Outcome measures valid: Were the main outcomes of interest to us measured in a way that has been demonstrated empirically to be valid and reliable (e.g., using a standardized scale such the RQLQ or SF-36)? (Yes, No, Not adequately described)
Level of evidence: Based on Oxford Center for Evidence-Based Medicine Levels of Evidence (1a, 1b, 1c, 2a, 2b, 2c, 3a, 3b, 4, 5)