Chapter 3. Results

General Observations

The MEDLINE® search identified 3,354 citations. We retrieved 228 articles for evaluation and included 88 into the evidence report. Among these 88 studies, 86 were RCTs and two were prospective cohort studies. Of the 86 randomized trials, 77 were double-blinded, six were single-blinded and in three studies the type of blinding was unstated. Forty-four of the 86 randomized trials reported the source of funding. Ninety-one percent of these 44 trials reported funding by pharmaceutical companies. There were only four trials supported by government funding.

There were no specific studies of the pediatric population. Even though some studies may have enrolled patients in pediatric ranges, separate data was not reported for this subgroup. Therefore, no specific conclusions could be drawn for the pediatric population.

Results for Specific Questions

Question 1. How does one diagnose allergic and nonallergic rhinitis (especially vasomotor)?

What differentiates allergic from nonallergic rhinitis with respect to symptoms, signs, physical examination, and diagnostic testing? *(Question 1.1)*

Summary of the evidence on what differentiates allergic from nonallergic rhinitis. No studies addressing these questions met the criteria described in the methods section of this report. Specifically, no studies were identified which sought to differentiate between allergic and nonallergic rhinitis on the basis of clinical symptoms or signs on physical examination. We found no study that evaluated a test specifically to diagnose nonallergic rhinitis.

One study was identified which sought to develop criteria for the definition of allergic rhinitis through a systematic evaluation of the relative importance of symptoms, signs and investigative tests (Ng, Warlow, Chrishanthan, et al., 2000). This study compared patients with diagnosed allergic rhinitis to normal individuals. It did not attempt to differentiate symptoms and signs between allergic and nonallergic rhinitis. It was suggested in that study that in establishing a diagnosis of allergic rhinitis the relative importance of skin prick testing is equal to a history of allergen-induced nasal and ocular symptoms. However, most authorities recommend confirmatory testing (Dykewicz, Fineman, Skoner, et al., 1998). Discordance between history and skin tests (or other diagnostic tests) is observed.

Due to the lack of studies that directly address this question, we therefore undertook an analysis of the inclusion criteria employed in those randomized controlled clinical trials addressing treatment issues in vasomotor rhinitis. In the majority of cases (7 out of 10 evaluable studies: Broms and Malm, 1982; Graf, Enerdal, and Hallen, 1999; Jokinen and Sipila, 1983; Kirkegaard, Mygind, Molgaard, et al., 1987; Kirkegaard, Mygind, Molgaard, et al., 1988; Nelson and Jacobs, 1982; Sjogren, Jonsson, Koling, et al., 1988) exclusion of allergic disease by an absence of positive allergy skin tests or negative results by RAST is the usual prerequisite criterion for diagnosing vasomotor rhinitis. The term vasomotor rhinitis will be used preferentially, since in all the studies we analyzed every otherwise identifiable form of rhinitis was excluded.

Vasomotor rhinitis can occur as an isolated condition, characterized by an increase in nasal symptoms attributable to exposures to nonspecific irritants such as strong odors, fragrances or perfumes, or indeed to changes in air pressure and temperature. Importantly, however, it can also occur in conjunction with (possibly as a complication of) allergic rhinitis.

Given the absence of well-designed studies addressing these questions, we can only report that, based on current clinical practices and the analysis of the inclusion criteria employed in studies of vasomotor rhinitis, diagnostic testing rather than signs and symptoms is necessary to differentiate isolated vasomotor rhinitis from allergic rhinitis.

What is the *minimum* level of testing necessary to differentiate allergic from nonallergic rhinitis? *(Question 1.2)*

The minimum level of testing necessary to confirm or exclude a diagnosis of allergic rhinitis has not been established. The small study by Ng, Warlow, Chrishanthan, et al. (2000) suggests that total serum IgE may be as useful as specific allergy skin prick tests which in turn are more useful than RAST-type testing in confirming a diagnosis of allergic rhinitis.

Henderson, Swedlund, and Van Delen (1971) conducted a prospective study in an adult allergy clinic and observed elevated serum IgE in 10% of patients with non-allergic rhinitis and in 62% of allergic rhinitis patients. A larger study by Wittig, Belloit and De Fillippi (1980) employed different cutoff levels of serum IgE to look at diagnostic sensitivity and specificity in rhinitic individuals and reported 98% specificty with the highest cutoff level but with a sensitivity of only 30%. Reduction of the cutoff level allowed an increase in sensitivity to 60% but a drop in the sensitivity to 80%. These studies suggest limited value for serum IgE in screening for allergic rhinitis.

Question 2. Is differentiating allergic from nonallergic rhinitis important?

Differentiation of allergic from nonallergic rhinitis is important if treatments are significantly different and if the outcomes of treatment including prevention of complications differ in response to those treatments. As seen in the evidence tables, similar treatments are frequently employed in the two conditions. However, what has been studied in the literature does not imply that differentiation might be important. It is generally believed that environmental control and immunotherapy have relevance only for treatment of allergic rhinitis. Therefore, differentiation is important for these two interventions.

Are treatments different? *(Question 2.1)*

Similar treatment modalities have been employed in RCTs in both conditions and include antihistamines, decongestants, nasal corticosteroids, cromoglycate, ipratropium bromide and other agents.

Are outcomes different? *(Question 2.2)*

The evidence tables and the details elaborated below indicate the difference in success rates of the various treatment modalities.

Question 3. How does one treat nonallergic and allergic rhinitis?

Nonallergic

What is the efficacy of antihistamines (all classes) vs. placebo, nasal corticosteroids vs. placebo, sympathomimetics vs. placebo, leukotriene modifiers, and other agents (anticholinergics, cromoglycate and sympathomimetics)?

(Question 3.1a)

[See Evidence Table 1]

Studies examining the efficacy and safety of the above treatments are summarized in Evidence Table 1. There were a total of 13 RCTs; one studied antihistamines, three nasal corticosteroids, three sympathomimetic agents, five anticholinergic agents, and two cromoglycate (one study examined both antihistamines and sympathomimetic agents). Twelve studies were conducted in Europe and one in the U.S. A total of 338 patients were enrolled and 333 evaluated in 10 evaluable studies. Study participants ranged in age from 14 to 87. Seven of ten evaluable studies required negative skin test results as an entrance criterion.

Summary of the evidence from RCTs comparing antihistamines (all classes) versus placebo. Studies looking at the various treatments employed in the treatment of nonallergic rhinitis are summarized in the evidence tables. Only one study (Broms and Malm, 1982) meeting the criteria for inclusion looked at the role of antihistamines in the treatment of nonallergic rhinitis. In this study, the antihistamine was used as part of antihistamines-decongestants combination product and accordingly, outcomes related to the antihistamine component of this drug cannot be separately identified. The FDA has approved a nasal topical product – azelastine (an H1 antihistamine) for treatment of vasomotor rhinitis.

Table 2. Summary of randomized trials: antihistamines (all classes) versus placebo

Author Year UI	Study size	Applica-bility	Outcome efficacy	Outcome safety	Methodo-logical Quality
Broms 1982 83046227	20	II	PPA reduced symptoms of rhinorrhea and sneezing. No comment on significance.	Headache in all groups. Difficulty in micturition 2 patients in brompheniramine group.	B

Summary of the evidence from RCTs of nasal corticosteroids. A small number of studies have looked at the benefit of nasal corticosteroids in this condition. In a double-blind placebo controlled trial, Wight, Jones, Beckingham, et al. (1992) showed a significant improvement in the symptom of nasal obstruction with each of two doses of budesonide. No other symptoms were altered, no difference was seen between the two doses and no significant side-effects were recorded. Comparisons of nasal corticosteroids and ipratropium in nonallergic rhinitis (NAR) yield conflicting results. Bende and Rundcrantz (1985) compared budesonide with ipratropium and showed a superior effect for budesonide with respect to symptoms of nasal secretion and sneezing. Jessen and Bylander (1990) report a double blind RCT comparing ipratropium and beclomethasone in 24 patients with NAR characterized by hypersecretion. No difference was identifiable between the efficacy of the two medications.

Summary of the evidence from RCTs comparing sympathomimetics versus placebo. Two randomized controlled studies were identified which looked at the role of oral decongestants (phenylpropanolamine) in treatment of nonallergic rhinitis. In both studies emphasis was placed on

relief of symptoms of nasal congestion. One study additionally focused on nasal sneezing while the other study focused additionally on rhinorrhea. The first study (Broms and Malm, 1982) contained data which were difficult to abstract, but did suggest a decrease in symptoms of nasal congestion by phenylpropanolamine. The second study (Renvall and Lindqvist, 1979) indicated that phenylpropanolamine was not superior to placebo in terms of relief of nasal congestion at a dosage of 50 mg per day with approximately 50 percent of patients reporting no improvement or worsening at this dosage. At a dosage of 100 mg per day there was a statistically significant improvement in symptoms of nasal obstruction with respect to placebo and also with respect to phenylpropanolamine 50 mg. The lower dosage was also poorly effective in alleviating symptoms of increased nasal secretion, whereas the 100 mg per day dosage was significantly more effective in relieving this symptom than the lower dose. The FDA has urged companies marketing that decongestant, phenylpropolamine, to voluntarily withdraw the drug from the marketplace, while it initiated regulatory actions to mandate such withdrawals.

Table 3. Summary of randomized trials: sympathomimetics versus placebo

Author Year UI	Study Size	Applica-bility	Outcome Efficacy	Outcome Safety	Method-ological quality
Renvall 1979 79214155	70	II	100 mg doses significantly reduced congestion and rhinorrhea. 100 mg PPA significantly more efficacious than 50 mg.	No major adverse effects. Minor effects: Drowsiness, flushing, nausea, increased alertness.	B

Summary of the evidence from RCTs of leukotriene modifiers versus placebo. No studies were identified looking at the efficacy of leukotreine modifiers in the treatment of nonallergic rhinitis.

Summary of the evidence from RCTs comparing anticholinergic agents versus placebo. Five randomized controlled clinical trials were identified addressing the efficacy of anticholinergic agents in the treatment of nonallergic rhinitis. All of the studies are rated B for methodological quality and the median grade for applicability is rated II. Each of these five trials studied intranasal ipratropium bromide, and each of the five studies documented efficacy for ipratropium in reducing nose blowing frequency and rhinorrhea. The first study (Kirkegaard, Mygind, Molgaard, et al., 1988) (n=38) documented a significant reduction in mean daily episodes of nose blowing by treatment with 80 micrograms q.i.d. of ipratropium. The second study (Sjogren, Jonsson, Koling, et al., 1988) (n=24) documented a dose-dependent decrease in methacholine induced nasal secretions by treatment for one day with doses of ipratropium of 40 micrograms, 100 micrograms and 200 micrograms. The third (Jokinen and Sipila, 1983) documented a physician rated significant reduction in the symptoms on rhinorrhea with ipratropium but no effect on the symptoms of nasal congestion, sneezing or nasal itching. The fourth study (Kirkegaard, Mygind, Molgaard, et al., 1987) compared two doses of ipratropium (80 micrograms q.i.d. versus 400 micrograms q.i.d.) to placebo. Both doses resulted in a significantly decreased mean daily number of nose blowing episodes compared to placebo, but 400 micrograms q.i.d. being significantly more effective than 80 micrograms q.i.d. No effect was observed on symptoms of nasal congestion or sneezing. The final study (Malmberg, Grahne, Holopainen, et al., 1983) also documented a

significant reduction in the number of nose blowing episodes as well as a significant reduction in the symptom of rhinorrhea with ipratropium compared to placebo. No effect was seen on nasal congestion.

Table 4. Summary of individual RCTs comparing anticholinergics versus placebo

Author Unique Identifier	Study Size	Applic-ability	Outcome Efficacy	Outcome Safety	Method-ological quality
Jokinen 1983 84120896	30	II	Significant reduction in nasal hypersecretion with ipratropium, but no effect on nasal blockage, sneezing, or tickling.	11 pts with mild side-effects on active treatment 7 with placebo: nasal irritation, nasal dryness, mild throat irritation.	B
Malmberg 1983 84082739	34	III	Active treatment reduced nasal discharge and nasal secretion.	18 active patients complained of nasal irritation, 9 placebo. 15 active complained of excessive drying of mucosa, 8 placebo.	B
Kirkegaard 1987 87167181	36	II	Number of nose-blowings 47% lower during active treatment than placebo, some slight reduction with high dose treatment but not statistical significant. Active treatment had no effect on number of sneezes or nasal blockage index.	Side-effects slight w/low dose treatment, but high dose caused unpleasant nasal dryness.	B
Kirkegard 1988 89074206	38	II	Ipratropium significantly reduced mean daily number of nose-blowing episodes compared with placebo.	Nasal dryness noted in both groups.	B
Sjogren 1988 89086030	24	II	All doses of ipratropium reduced volume of methacholine-induced nasal secretions vs placebo nasal symptoms. No significant difference between doses.	No major adverse effects. Sweating with high-dose ipratropium.	B

Summary of the evidence from RCTs comparing cromoglycate versus placebo. Two RCTs were identified looking at the effects of cromoglycate in nonallergic rhinitis. Both studies recorded improvement in symptoms of rhinitis with active treatment compared to placebo. In the first study (Balle and Illum, 1977) cromoglycate resulted in a significant decrease in sneezing and congestion

scores. In the second (Nelson and Jacobs, 1982) cromoglycate was documented to produce a significant decrease in nasal itching but no change in the other three symptoms evaluated.

Table 5. Summary of randomized trials: cromoglycate versus placebo

Author Year UI	Study size	Applic-ability	Outcome Efficacy	Outcome Safety	Method-ological quality
Balle 1977 78016773	25	II	Cromoglycate significantly reduced mean monthly scores for sneezing and nasal congestion.	No adverse events.	B

What are the side-effects/adverse events due to: antihistamines, nasal corticosteroids, sympathomimetics, leukotriene modifiers, anticholinergics and cromoglycate? *(Question 3.1b)*

[See Evidence Table 1]

Adverse events of antihistamines described included drowsiness, nausea, and headache. This study (Broms and Malm, 1982) involving a combination product (antihistamine plus decongestants) also had patients who described micturition difficulties. This is presumed to be related to the anticholinergic activity of the antihistamine component.

In three of the five studies looking at ipratropium in treatment of nonallergic rhinitis, significant side-effects of nasal dryness and nasal irritation were recorded (Jokinen and Sipila, 1983; Kirkegaard, Mygind, Molgaard, et al., 1988; Malmberg, Grahne, Holopainen, et al., 1983).

In the two studies looking at cromoglycate in nonallergic rhinitis no significant adverse effects were associated with use of this medication (Balle and Illum, 1977; Nelson and Jacobs, 1982).

[See Evidence Table 1]

Allergic: Seasonal

What is the efficacy of antihistamines (all classes) vs. nasal corticosteroids, antihistamines vs. immunotherapy (desensitization, NOT sublingual), nasal corticosteroids vs. immunotherapy (NOT sublingual), sedating vs. nonsedating antihistamines, other agents (cromolyn, leukotriene modifiers, sympathomimetics, ipratropium) *(Question 3.2a)*

[See Evidence Tables 2-5]

Summary of the evidence from RCTs comparing antihistamines versus nasal steriods. Studies examining the efficacy and safety of the above treatments are summarized in evidence table 2. There were a total of 18 RCTs. Eight studies were conducted in Europe, 1 in Canada and 9 in the U.S. A total of 3,557 patients were enrolled and 3,333 evaluated. Study participants ranged in age from under 12 to 90 years old, with 12 of 18 studies enrolling both adult and pediatric patients. Thirteen of 18 studies required positive allergen skin test results as an entrance criterion. The median grade for methodological quality of these studies is rated B and the median grade for applicability is rated II.

A recent meta-analysis of 17 RCTs published up to 1997 compared intranasal corticosteroids with antihistamines in the treatment of seasonal and/or perennial allergic rhinitis (Weiner, Abramson, and Puy, 1998). The analysis included several different nasal corticosteroid preparations and several different antihistamines including both nonsedating and sedating

antihistamines. The analysis reported that for the six nasal symptoms studied as well as for overall nasal symptoms score nasal corticosteroids produced significantly greater relief than did oral antihistamines. The specific symptoms that were improved included nasal blockage, nasal discharge, sneezing, or nasal itching and postnasal drainage. There were no significant differences identified between treatments for nasal discomfort, nasal resistance or eye symptoms. Three of the 17 RCTs address the issue cost effectiveness of intranasal corticosteroids versus oral nonsedating antihistamines with results favoring use of nasal corticosteroids in each case.

Our search identified eight additional studies that were not included in the meta-analysis undertaken by (Weiner, Abramson, and Puy, 1998). Seven of the studies favored intranasal corticosteroids over antihistamines both with respect to improvement in global nasal symptoms as well as most individual nasal symptoms. One study (D'Ambrosio, Gangemi, Merendino, et al., 1998) showed better symptom improvement with cetirizine alone over fluticasone alone. Thus, the overwhelming majority of studies show very clear benefits for the use of intranasal corticosteroids over either sedating or nonsedating antihistamines for relief of symptoms of nasal allergy. These results are similar for seasonal allergic rhinitis and perennial allergic rhinitis.

Table 6. Summary of randomized trials: antihistamines versus nasal corticosteroids

Author Year UI	Study size	Applic-ability	Outcome-efficacy	Outcome-safety	Method-ological quality
Munch 1983 84050113 SAR	61	II	Budesonide significantly improved rhinorrhea, nasal congestion and sneezing scores compared to dexchlorpheniramine.	No major adverse effects. Minor adverse effects-sedation.	B
Backhouse 1986 86165329 SAR	99	II	Terfenadine + flunisolide significantly improved sneezing, nasal blowing, nasal congestion and ocular symptoms scores compared to flunisolide alone.	No major adverse effects: Minor adverse effects: nasal irritation, drowsiness, and nausea.	B
Wood 1986 86245576 SAR	74	I	No significant difference between astemizole and beclomethasone for all nasal symptoms.	No major adverse effects Minor adverse effects: Drowsiness.	C
Juniper 1989 89175902 SAR	90	II	Both beclomethasone and beclomethasone + astemizole significantly improved sneezing, nasal congestion and rhinorrhea symptom scores compared to astemizole.	No major adverse effects. Minor adverse effects: nasal bleeding, headache, thirst, skin rash and nausea.	B

Author Year UI	Study size	Applic-ability	Outcome-efficacy	Outcome-safety	Method-ological quality
Robinson 1989 90002391 PAR	20	III	Beclomethasone significantly reduced rhinorrhea, sneezing, and nasal inflammation scores compared to terfenadine. Significant patient preference for beclomethasone.	No major adverse effects. Minor adverse effects: Nausea, sedation and epistaxis.	B
Darnell 1994 95196117 SAR	214	II	Fluticasone significantly improved nasal symptoms compared to terfenadine for sneezing, rhinorrhea, and nasal congestion.	No major adverse effects. Minor adverse effects: Fatigue, epistaxis, oral burning, asthma, headache, and breathlessness.	B
Van Bavel 1994 95085365 SAR	232	II	Fluticasone significantly Improved rhinorrhea, nasal congestion, sneezing, nasal itch, and total nasal symptom scores compared with terfenadine.	No major adverse effects. Minor adverse effects: asthma and headache	B
Hilberg 1995 96098156 SAR	18	II	Budesonide significantly increased nasal cross-sectional areas and nasal secretion volume. Budesonide significantly improved nasal congestion.	No adverse effects noted.	B
Schoenwetter 1995 96070357 SAR	298	I	Triamcinolone significantly improved sneezing, nasal congestion, nasal itch, postnasal drip, rhinorrhea, and ocular symptom scores compared to loratadine.	No major adverse effects. Minor adverse effects: Epistaxis, headache and rhinitis.	A

Author Year UI	Study size	Applic-ability	Outcome-efficacy	Outcome-safety	Method-ological quality
Bernstein 1996 96213647 SAR	239	II	Triamcinolone significantly improved nasal itch, nasal congestion, postnasal drip, rhinorrhea, sneezing and total nasal symptom scores compared with astemizole.	No major adverse effects Minor adverse effects: pharyngitis, headache, and weight gain	B
Bronsky 1996 96194242 SAR	348	I	Fluticasone significantly improved sneezing, rhinorrhea, nasal obstruction, nasal itch and total nasal symptom scores when compared with terfenadine.	No major adverse effects Minor adverse effects: headache	A
Jordana 1996 96191239 SAR	242	II	Fluticasone significantly improved nasal congestion, sneezing, nasal itch, and rhinorrhea scores compared to loratadine.	No major adverse effects Minor adverse effects: headache and pharyngitis	B
Gehanno 1997 97332767 SAR	114	II	Fluticasone significantly improved rhinorrhea, nasal congestion, sneezing and nasal itch. Scores compared with loratadine.	Major adverse effects Convulsions Minor adverse effects: nausea, asthma attack, dizziness, sweating, and weakness	A
Juniper 1997 97286890 SAR	61	I	Fluticasone significantly improved all nasal symptoms compared to terfenadine.	Major adverse effects: nausea. No minor adverse effects.	B
D'Ambrosio 1998 99133169 SAR	60	II	Cetirizine and cetirizine + fluticasone significantly improved sneezing, rhinorrhea, nasal itch and total nasal scores compared to fluticasone alone.	No major adverse effects. Minor adverse effects: Burning throat & nose, dizziness, gastric disorders, and visual disturbances.	B

Author Year UI	Study size	Applic-ability	Outcome-efficacy	Outcome-safety	Method-ological quality
Ratner 1998 98390023 SAR	600	I	Fluticasone and fluticasone + loratadine significantly improved rhinorrhea, nasal congestion, sneezing, and nasal itch scores compared to loratadine.	No major adverse effects. Minor adverse effects: blood in nasal mucosa, epistaxis, and xerostomia.	B
Ortolani 1999 20068053 SAR	288	II	Fluticasone significantly improved rhinorrhea, nasal congestion, sneezing, and nasal itch scores compared to levocabastine.	No major adverse effects. Minor adverse effects: respiratory symptoms, and exacerbations of nasal symptoms.	B
Condemi 2000 20289854 SAR	351	I	Triamcinolone significantly improved rhinorrhea, sneezing, and nasal congestion scores compared with loratadine.	Major adverse effects: Chest pain. Minor adverse effects: Headache.	B

Summary of the evidence from RCTs comparing antihistamines versus immunotherapy. No RCTs were identified directly comparing immunotherapy with antihistamines in the treatment of seasonal and/or perennial allergic rhinitis. Immunotherapy is generally considered a long-term disease modifying treatment measure requiring months to years of treatment whereas antihistamines are often used for immediate symptom relief. Therefore direct comparisons with respect to efficacy are not likely to be undertaken.

Summary of the evidence from RCTs comparing nasal corticosteroids versus immunotherapy. No RCTs were identified directly comparing immunotherapy with intranasal corticosteroids in the treatment of seasonal and/or perennial allergic rhinitis.

Summary of the evidence of effectiveness of immunotherapy. The efficacy of subcutaneous specific allergen immunotherapy has been documented in more than 40 placebo-controlled trials in allergic rhinitis. These studies frequently employ immunotherapy as an add-on treatment and do not compare it to other active treatment. Efficacy has been demonstrated in allergic rhinitis for many different inhalant allergens including tree pollens, grass pollens, ragweed pollens, other pollens, dust mite, cat and the mold alternaria (Bousquet, Lockey, and Malling, 1998; Bousquet 2001).

Summary of the evidence from RCTs comparing sedating versus nonsedating antihistamines. Studies examining the efficacy and safety of the above treatments are summarized in Evidence Table 3. There were a total of 12 RCTs, 10 in seasonal allergic rhinitis patients and two in perennial allergic rhinitis patients. The median grade for methodological quality is rated B and the median grade for applicability is rated II. Seven studies were conducted in Europe, one in Canada and four in the U.S. A total of 1,693 patients were enrolled and 1,562 evaluated. Study participants ranged in age from under 12 to 92 years old, with eight of 12 studies focusing on the

15-66 age group. Seven of 10 seasonal allergic rhinitis studies required a positive allergen skin test result as an entrance criterion.

Eight randomized controlled clinical trials were identified in which a direct comparison between nonsedating and sedating antihistamines in the treatment of seasonal allergic rhinitis were undertaken. Three of these studies (including approximately 589 patients) implicated superior relief of nasal symptoms by the sedating antihistamines (Gutkowski, Del Carpio, Gelinas, et al., 1985; Johansen, Bjerrum, and Illum, 1987; Thoden, Druce, Furey, et al., 1998). One other study (including approximately 138 patients) indicated superior relief of nasal symptoms by the nonsedating antihistamine (Backhouse and Rosenberg, 1987). The remaining four studies (including approximately 507 patients) showed no difference with respect to nasal symptoms between the two treatment arms (Buckley, Buchman, Falliers, et al., 1988; Hugonot, Hugonot, and Beaumont, 1986; Malmberg, Grahne, Holopainen, et al., 1983; Pastorello, Ortolani, Gerosa, et al., 1987). These results are interpreted as indicating no consistent benefit of sedating antihistamines over nonsedating antihistamines with respect to symptom alleviation in allergic (seasonal) rhinitis. In most of these studies an array of symptoms was evaluated (including nasal itching, sneezing, rhinorrhea, nasal congestion, post nasal drainage), and in most cases changes in symptoms tended to correlate with one another with respect to favoring either sedating or nonsedating antihistamines. Accordingly, emphasis is placed upon the global evaluation of symptom change for the purpose of this reporting. Changes in ocular symptoms were not included in this data analysis.

Two additional studies did not give outcomes in terms of improvement of nasal symptoms. Gastpar and Dieterich (1982) studied changes in IgE values, and Weiler, Bloomfield, Woodworth, et al. (2000) studied side-effects.

An additional two RCTs were identified in which a direct comparison between nonsedating and sedating antihistamines in the treatment of perennial allergic rhinitis were undertaken. One of these studies (Brostoff and Lockhart, 1982) showed no statistical difference between the groups with respect to treatment of nasal symptoms with both treatments being assessed as extremely effective. The other study (Druce, Thoden, Mure, et al., 1998) showed significant benefits in favor of the sedating antihistamine brompheniramine over loratadine with respect to each nasal symptoms evaluated. These results are interpreted as indicating no consistent benefit of nonsedating antihistamines over nonsedating in perennial allergic rhinitis.

Table 7. Summary of randomized trials: sedating versus nonsedating antihistamines

Author Year UI	Study size	Applic-ability	Outcome-efficacy	Outcome-safety	Method-ological quality
Brostoff 1982 83014720 PAR	60	III	No statistical difference between chlorpheniramine and terfenadine. Both antihistamines not extremely effective in perennial rhinitis treatment.	Major adverse effects: Upset stomach, headache, and fatigue. Minor adverse effects: sedation.	B
Gastpar 1982 83100633 SAR	20	III	Significant decrease in IgE values with terfenadine compared to clemastine.	No major adverse effects. Minor adverse effects: sedation, and conjunctivitis.	B

Author Year UI	Study size	Applic-ability	Outcome-efficacy	Outcome-safety	Method-ological quality
Malmberg 1983 83253693 SAR	51	II	No significant difference between chlorpheniramine and astemizole in all nasal symptoms studied.	No major adverse effects. Minor adverse effects: Fatigue, palpitations, headache, GI upset.	B
Gutkowski 1985 86030956 SAR	177	II	Dexchlorpheniramine significantly improved rhinorrhea, nasal congestion, sneezing, itchy nose and total nasal symptom scores compared to terfenadine.	No major adverse effects. Minor adverse effects: Dizziness, somnolence, headache, and dry mouth.	B
Hugonot 1986 86248368 SAR	147	II	No significant differences between terfenadine and mequitazine in all nasal symptoms studied.	No major adverse effects. Minor adverse effects: Headache, blurred vision, somnolence, dizziness, and nausea.	B
Backhouse 1987 89062246 SAR	138	II	Terfenadine significantly improved sneezing, rhinorrhea, nasal blowing and nasal congestion scores compared to chlorpheniramine.	No major adverse effects.	B
Johansen 1987 87205847 SAR	42	II	Dexchlorpheniramine significantly improved sneezing, nasal congestion, and nasal itch scores compared to terfenadine.	No adverse effects noted.	B
Pastorello 1987 88016480 SAR	65	II	No significant difference between terfenadine and dexchlorpheniramine in effect on sneezing, rhinorrhea, congestion, itchy throat and ocular symptom scores.	No major adverse effects. Minor side-effects unspecified.	C
Buckley 1988 88131974 SAR	244	II	No significant difference between terfenadine and chlorpheniramine on all nasal symptoms studied.	No major adverse effects. Minor adverse effects: Headache, sedation, nausea, dryness of mouth, nose and throat	B

Author Year UI	Study size	Applic-ability	Outcome-efficacy	Outcome-safety	Method-ological quality
Druce 1998 98250349 PAR	338	II	Brompheniramine significantly improved rhinorrhea, nasal congestion, sneezing, nasal itch, itchy throat and ocular symptoms scores compared to loratadine.	Major adverse effects: Hypertension. Minor adverse effects: somnolence and dizziness.	A
Thoden 1998 98413360 SAR	370	II	Brompheniramine significantly improved sneezing, nasal congestion, rhinorrhea, and nasal itch scores compared to terfenadine.	No major adverse effects. Minor adverse effects: somnolence.	B
Weiler 2000 20143057 SAR	41	I	Mean coherence value 0.88 with diphenhydramine, 0.915 with fexofenadine, 0.92 with alcohol, and 0.9 with placebo.	No adverse effects.	A

Summary of the evidence from RCTs comparing other agents (cromolyn, leukotriene modifiers, sympathomimetics, ipratropium). Studies examining the efficacy and safety of cromoglycate and other agents are summarized in Evidence Table 4. There were two studies examining sympathomimetic agents, one study of an anticholinergic agent, and 32 studies of cromoglycate. Twenty-one randomized controlled studies were in seasonal allergic rhinitis patients and 14 in perennial allergic rhinitis patients. Twenty-four studies were conducted in Europe, one in Canada, one in South Africa, one in New Zealand, two in Australia, one in India, and five in the U.S. A total of 1,320 patients were enrolled and 1,212 evaluated. Study participants ranged in age from 12 to 76 years old. Fourteen of 21 seasonal allergic rhinitis studies required positive allergen skin test result as an entrance criterion.

In all studies except for two, significant improvements in symptoms of allergic rhinitis were reported in those patients treated with cromoglycate compared to those patients treated with placebo.

In 16 of the studies, three or more of the five common symptoms associated with allergic rhinitis (nasal itch, sneezing, rhinorrhea, nasal congestion, or postnasal drainage) were significantly improved by treatment with cromoglycate compared to placebo. No consistent pattern of nonresponsiveness to cromoglycate with respect to a given symptom was identifiable across the studies. In five of the 13 studies that indicated failure of some symptoms to respond to treatment with cromoglycate, congestion was identified as one of the nonresponsive symptoms.

Eighteen studies (14/18 studies of seasonal allergic rhinitis and 4/11 studies of perennial allergic rhinitis) included documentation of patient preference or patient willingness to use the drug in the future. In 17 studies there was a clear-cut preference for the active ingredient

(cromoglycate). One study of cromoglycate in perennial allergic rhinitis fails to document a significant improvement in symptoms or a patient preference for future usage.

Overall, cromoglycate is an effective treatment for reducing symptoms associated with allergic rhinitis (30 of 32 studies). It seems to have higher efficacy in seasonal allergic rhinitis than it does in perennial allergic rhinitis. In those studies that looked at different dosing regimens, higher doses (including higher frequency of dosing) were more effective.

A single study was identified in seasonal allergic rhinitis looking at the efficacy of nedocromil compared with placebo in reducing symptoms of allergic rhinitis. It showed a significant reduction in daily nasal itch and rescue antihistamine usage. It showed no benefits for symptoms of sneezing, rhinorrhea, and nasal congestion even though 63 percent preferred this medication and 30 percent preferred placebo.

Oral alpha-adrenergic agents, such as pseudoephedrine, phenylephrine and phenylpropanolamine cause nasal vasoconstriction. Two clinical trials were identified looking at the effects of decongestant drugs in allergic rhinitis and suggest some benefit in relief of nasal congestion but not other symptoms.

Table 8. Summary of randomized trials: Other agents (cromolyn, leukotriene modifiers, sympathomimetics, ipratropium)

Author Year UI	Study size	Applic-ability	Outcome-efficacy	Outcome-safety	Method-ological quality
Green 1966 67044478 PAR	33	III	Significantly longer duration of decongestion with oxymetazoline than with phenylephrine.	No major adverse effects. Minor adverse effects- local nasal burning.	C
Coffman 1971 72025239 SAR	35	III	56% successful patient responses with cromoglycate vs 33% successful patient responses with placebo.	No major adverse effects. Minimal minor adverse effects.	B
Engstrom 1971 72012845 SAR	39	II	Cromoglycate significantly improved all nasal symptom scores. No significant difference for ocular symptoms.	ND	B
Holopainen 1971 71066421 SAR	27	II	Cromoglycate significantly reduced sneezing, nasal itch, nasal congestion, and rhinorrhea scores compared with placebo.	No major adverse effects. Minor adverse effects: itchy throat.	B
Anderson 1972 73004602 SAR	18	II	Cromoglycate significantly reduced rhinorrhea, sneezing, and ocular symptoms compared with placebo.	No major adverse effects Minor adverse effects: Nasal irritation, nasal congestion, nausea, and headache.	B

Author Year UI	Study size	Applic-ability	Outcome-efficacy	Outcome-safety	Method-ological quality
Hopper 1972 73166771 PAR	38	II	Cromoglycate significantly improved sneezing, rhinorrhea, and nasal congestion. Significantly higher number of successful treatments with cromoglycate compared to placebo.	Major and minor adverse effects not indicated.	C
Shore 1972 72159215 SAR	41	III	Cromoglycate significantly reduced total nasal symptom score compared to placebo.	No major adverse effects. Minor adverse effects: nausea, sneezing, cough, and rash.	C
Thorne 1972 73089706 PAR	40	II	Cromoglycate significantly reduced sneezing, rhinorrhea, and sense of smell. No significant difference in treatment of nasal congestion and nasal peak flow. Total symptom score of 2608 with cromoglycate vs. score of 3053 with placebo.	No major adverse effects. Minor adverse effects: sneezing and nasal soreness.	C
Blair 1973 74098976 SAR	40	II	Cromoglycate significantly improved rhinorrhea, congestion, itching and sneezing compared with placebo.	No major adverse effects. Minor adverse effects: Nasal irritation, sore throat, headache, and unpleasant taste.	B
Hetherington 1973 73166772 SAR	40	II	Cromoglycate significantly improved total nasal symptom score compared to placebo.	No major adverse effects. Minor adverse effects: nasal irritation.	B
Illum 1973 74133656 SAR	37	II	No significant difference between cromoglycate and placebo for sneezing, rhinorrhea, nasal congestion and nasal itch scores.	No adverse effects.	C

Author Year UI	Study size	Applic-ability	Outcome-efficacy	Outcome-safety	Method-ological quality
Jenssen 1973 74098975 SAR	10	III	Cromoglycate significantly improved nasal resistance.	ND	C
Manners 1973 74098980 SAR	50	II	Cromoglycate significantly reduced sneezing, rhinorrhoea, nasal congestion, nasal itch, and ocular symptom score.	ND	B
Sunderman 1973 73237443 PAR	74	II	Cromoglycate significantly improved rhinorrhea, sneezing, and nasal congestion. Significant preference for cromoglycate compared to placebo: 53 patients preferred cromoglycate, None preferred placebo, and 15 had no preference.	No major adverse effects. Minor adverse effects: sneezing.	C
Brain 1974 76192641 PAR	34	III	Cromoglycate significantly reduced sneezing, rhinorrhea, congestion and nasal itch scores. Significant patient preference for cromoglycate.	No major adverse events. Minor adverse effects: headache, dry/ sore throat, dizziness, and nasal irritation.	C
Blair 1975 75185857 PAR	20	II	Cromoglycate significantly improved sneezing, nasal congestion, and nasal itch compared to placebo. No significance in treatment of rhinorrhea. 14 patients preferred cromoglycate, 3 patients preferred placebo, and 1 patient had no preference.	No major adverse effects. Minor adverse effects: nasal irritation and sore throat.	C

Author Year UI	Study size	Applic-ability	Outcome-efficacy	Outcome-safety	Method-ological quality
Fagerberg 1975 75221540 PAR	23	II	Cromoglycate significantly improved sneezing and rhinorrhea. No significant difference for treatment of congestion and nasal itch. Significantly more preferences for Cromoglycate: 14 patients preferred cromoglycate vs. 5 patients preferred placebo.	No major adverse effects. Minor adverse effects: nasal itch/ irritation, and sneezing.	B
Girard 1975 76042257 PAR	30	II	Cromoglycate significantly reduced sneezing, nasal congestion, nasal itch, eosinophilia count, and nasal outflow resistance. No significant difference in treatment of rhinorrhea. Significant clinician-rated and patient-rated preference for cromoglycate.	No major adverse effects. Minor adverse effects: nasal irritation and headache.	B
Holopainen 1975 76084510 PAR	49	II	Cromoglycate significantly improved nasal congestion, nasal itch, and nasal patency. According to patient diaries only, not clinician evaluation, cromoglycate significantly reduced sneezing and rhinorrhea. Not significant for eosinophilia count or antihistamine use.	No major adverse effects. Minor adverse effects: nasal irritation, headache, eczema, and tiredness.	C
Leiferman 1975 SAR	26	II	Cromolyn sodium significantly reduced sneezing, coughing, nasal congestion, and rhinorrhea scores compared with placebo.	No major adverse effects. Minor adverse effects: nasal irritation.	C

Author Year UI	Study size	Applic-ability	Outcome-efficacy	Outcome-safety	Method-ological quality
Wilson 1975 76101270 SAR	39	II	No significant difference between cromoglycate groups and placebo. 53% preferred cromoglycate vs 21% preferred placebo.	No major adverse effects. Minor adverse effects: nausea, headache, sneezing, nasal dryness and irritation, and epistaxis.	B
Hasegawa 1976 77001950 SAR	38	II	Cromoglycate significantly improved nasal airway resistance and total nasal symptom score compared to placebo.	ND	C
Knight 1976 76238158 SAR	77	II	Significant improvement in total nasal score with cromoglycate vs. placebo.	No major adverse effects Minor adverse effects: sneezing, coughing, and headache.	C
Backman 1977 78120309 PAR	91	II	Higher preference for cromoglycate powder and solution compared to placebo. 23 patients preferred cromoglycate solution vs 10 patients preferred placebo. 31 patients preferred cromoglycate powder vs 3 patients preferred placebo.	No major adverse effects. Minor adverse effects: nasal irritation, headache, eczema, and tiredness.	C
Frostad 1977 78062986 SAR	44	II	Cromoglycate significantly reduced sneezing, rhinorrhea, nasal congestion and total nasal symptom scores compared with placebo.	No major adverse effects. Minor adverse effects: Nasal irritation.	C
Handelman 1977 77119242 SAR	104	II	Cromolyn sodium significantly reduced sneezing and rhinorrhea scores compared with placebo.	No major adverse effects Minor adverse effects- nasal irritation and sneezing.	B

Author Year UI	Study size	Applic-ability	Outcome-efficacy	Outcome-safety	Method-ological quality
Lofkvist 1977 77131029 PAR	49	II	No significant difference between cromoglycate and placebo for symptom-free condition, patient preference, or diary card data.	No major adverse effects. Minor adverse effects: dryness and irritation in nose and throat	B
McDowell 1977 77264819 SAR	17	II	Cromoglycate reduced sneezing and rhinorrhea symptom scores compared with placebo; non-significant difference.	No major adverse effects. Minor adverse effects: Transient burning and stinging, rash, pruritus, nausea, dizziness, epistaxis and headache.	B
Posey 1977 78063003 SAR	34	II	Cromolyn sodium significantly reduced rhinorrhea, nasal congestion, sneezing, nasal itch, itchy throat, mouth breathing, post-nasal drip, nose blowing, and eye irritation compared to placebo.	Major adverse effects: severe chemical rhinitis. Minor adverse effects: Nasal irritation, rhinorrhea, and sneezing.	B
Van der Bijl 1977 78033928 SAR	40	II	Cromoglycate significantly reduced rhinorrhea, nasal congestion, sneezing, nasal itch, and itchy eyes compared to placebo.	No major adverse effects. Minor adverse effects: nasal irritation, dizziness, and sneezing.	B
Warland 1977 77262676 PAR	21	II	No significant difference between two treatments. 6 out of 17 patients preferred cromoglycate vs. 2 preferred placebo. 9 had no preference.	No major adverse effects. Minor adverse effects: Nasal irritation, headache, nausea, and others.	C
Sorri 1979 79205990 SAR	38	II	Cromoglycate significantly improved rhinorrhea score only vs. placebo. Significant patient preference for cromoglycate.	ND	B

Author Year UI	Study size	Applic-ability	Outcome-efficacy	Outcome-safety	Method-ological quality
Sipila 1987 88110026 SAR	59	II	Nedocromil sodium significantly reduced nasal itch and rescue antihistamine usage compared to placebo.	No major adverse effects Minor adverse effects: sneezing, unpleasant taste, nasal and throat irritation, and dizziness.	B
Shaikh 1995 96080200 PAR	118	II	Ephedrine significantly improved sneezing, rhinorrhea, nasal blockage, and postnasal drip. Overall symptom score of 3.5 with ephedrine vs. score of 0.8 with placebo.	Major adverse effects: palpitations. Minor adverse effects: heaviness of head, nasal burning sensation, and swallowing of negligible amounts of fluids	B
Georgitis 1998 98372425 PAR	45	I	No significant differences between dosages of ipratropium. Both significantly reduced rhinorrhea and postnasal drip.	No major adverse effects. Minor adverse effects: pharyngitis, taste perversion, epistaxis, dizziness, dry mouth, chest pain, fever, headache, paresthesia, pruritus, dry skin, anxiety, asthma, bronchitis, dyspepsia, insomnia, pain, emotional upset, and tachycardia.	A

What are the side-effects/adverse events due to: antihistamines, nasal corticosteroids, sympathomimetics, leukotriene modifiers? *(Question 3.2b)*

[See Evidence Tables 2-3]

A majority of the studies reported no major adverse events associated with the use of antihistamines. In those studies where major adverse events were reported, somnolence, dry mouth, dizziness and headache were identified most frequently. These symptoms were seen almost exclusively with the sedating antihistamines.

Epistaxis, headache and pharyngitis were the most frequently reported side-effects of nasal corticosteroids. None of the studies reported systemic side effects from intranasal steriods, in the short-term treatment studies analyzed. However, a recent study (Skoner, Rachelefsky, Meltzer et al, 2000) reported on the suppressive effect of belcomethasone nasal spray on bone growth in children and all nasal steroid preparations in the United States now warn of this adverse event. Agents with less systemic bio-availability may be devoid of these risks (Allen, 2000).

No major adverse events were reported in studies of cromolyn. Minor reported side-effects included a high frequency of nasal irritation (18/29 studies), headache, and nasal congestion.

How do efficacy and side-effects of treatments vary by severity of rhinitis or patient characteristics? *(Question 3.3)*

We found no data to address this question. None of the studies categorized patients by disease severity or concurrent disease when addressing either efficacy or safety.

Meta-analyses

Identify and review relevant published meta-analyses in the following treatment areas:

Antihistamines vs. placebo in allergic rhinitis. No meta-analyses were identified.

Immunotherapy versus placebo in allergic rhinitis. Ross, Nelson, and Finegold (2000) report a meta-ananlysis of the efficacy of specific immunotherapy in the treatment of allergic rhinitis. Inclusion criteria required of the published studies were prospective nature, double blinding, placebo control and citation in MEDLINE® between 1966 and 1996. Data from sixteen studies (including 759 patients) were combined. Fifteen of 16 studies concluded that specific immunotherapy was effective and the analysis showed a significant effect in improvement in both symptom control and symptom medication scores in allergic rhinitis.

Nasal corticosteroids versus placebo in allergic rhinitis. No meta-analysis addressed the specific comparison posed in this question. However a meta-analysis looking at studies which compared nasal corticosteroids to oral antihistamines by Weiner, Abramson, and Puy (1998) is identified and has been discussed above.

The efficacy of treatment in seasonal versus perennial allergic rhinitis. No meta-analyses were identified addressing this question.

Question 4. How does treatment of allergic rhinitis impact on the development of asthma?

What is the likelihood of developing asthma with untreated allergic rhinitis? *(Question 4.1)*

It has long been recognized that there is an association between allergic rhinitis and asthma. A large number of cross-sectional studies have shown the prevalence of allergic rhinitis in asthmatic patients to be between 28 and 78 percent, compared with approximately 20 percent in the general population. In addition, prevalence of asthmatic symptoms amongst allergic rhinitis patients is reportedly between 19 and 39 percent of patients, again significantly higher than the 5 percent rate in the general population (Blair, 1977; Pedersen and Weeke, 1983; Settipane, 1986; Smith, 1983). Other cross-sectional studies have attempted to elucidate the temporal relationship between allergic rhinitis and asthma. In one study of 7662 subjects, 49 percent of patients with both asthma and allergic rhinitis reported onset of rhinitis symptoms prior to asthma symptoms, and 25 percent of patients experienced the onset of asthma within one year of developing allergic rhinitis (Pedersen and Weeke, 1983). Other studies demonstrated a similar temporal relationship. In addition, it is known that patients with allergic rhinitis commonly exhibit bronchial hyperreactivity. However, in order to illustrate a causal relationship between allergic rhinitis and asthma, well-conducted prospective cohort studies are necessary. We identified two such studies in our literature search. The first study (Settipane, Hagy, and Settipane, 1994) followed a group of college students for 23 years and found that those students with allergic rhinitis at the beginning of the study were three times more likely to develop asthma during followup than non-atopic controls. A similar study by Anderson, Pottier, and Strachan (1992) followed 7,225 children from birth to age 23 and found that children with allergic rhinitis were 2.7 to 3.0 times more likely to develop asthma during followup.

How does treatment of allergic rhinitis affect the likelihood of developing asthma? *(Question 4.2)*

No study was identified which addressed the question of whether treatment of allergic rhinitis can actually prevent the development of asthma. The data, however, suggest a mechanistic link between these two diseases and an ability to impact certain characteristics of asthma by use of nasal corticosteroids in treatment of allergic rhinitis. Conventional doses of cetirizine, loratadine and oral decongestants have been reported to improve asthma symptoms and pulmonary function in patients with allergic rhinitis (Corren, Harris, Aaronson, et al., 1997; Grant, Nicodemus, Findlay, et al., 1995).

How does treatment of allergic rhinitis affect the likelihood of developing bacterial sinusitis? *(Question 4.3)*

It is known that there is a link between allergic rhinitis and rhinosinusitis. Cross-sectional studies have shown an increased prevalence of acute and chronic bacterial sinusitis amongst allergic rhinitis patients. Similarly there is an increased prevalence of atopy and allergic rhinitis amongst patients with chronic bacterial sinusitis. However, in order to determine the effect of treatment of allergic rhinitis on the development of bacterial sinusitis, data from prospective studies on the outcomes of treated and untreated allergic rhinitis are required. We identified no studies meeting these criteria in our literature search.