Review

Evaluating approved medications to treat allergic rhinitis in the United States: an evidence-based review of efficacy for nasal symptoms by class

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Objective: To evaluate how well the medications currently approved in the United States for allergic rhinitis (AR) treat nasal symptoms when examined according to Food and Drug Administration–indicated uses and dosages.

Data Sources: MEDLINE (1966 onward), EMBASE (1974 onward), and the Cochrane Library (2007) were systematically searched according to the following criteria defined at a roundtable meeting of the authors: randomized controlled trial, at least a 2-week duration, and approved indication and dosage in the United States.

Study Selection: Data from studies that met the inclusion criteria were extracted into evidence tables, which were reviewed twice by the full panel of authors. Individual panel members also were asked to comment on abstracts, articles, and summary tables based on their known expertise. The entire faculty approved the selection of studies included in this review.

Results: Fifty-four randomized, placebo-controlled studies involving more than 14,000 adults and 1,580 children with AR met the criteria for review: 38 studies of seasonal allergic rhinitis (SAR; n = 11,980 adults and 946 children) and 12 studies of perennial allergic rhinitis (PAR; n = 3,800 adults and 366 children). The median percentage changes from baseline for total nasal symptom score for SAR were as follows: nasal antihistamines, −22.2%; oral antihistamines, −23.5%; intranasal steroids (INSs), −40.7%; and placebo, −15.0%. For PAR, the changes were as follows: oral antihistamines, −51.4%; INSs, −37.3%; and placebo, −24.8%. Data for mediator antagonists were limited.

Conclusions: The data, although limited, confirm that INSs produce the greatest improvements in nasal symptoms in patients with SAR. In addition, INSs are effective for PAR, but the data were of variable quality, and oral antihistamines may be equally effective for some patients. The reporting of published data should be standardized to permit better comparisons in future studies.

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INTRODUCTION

Allergic rhinitis (AR), the second leading cause of chronic disease in the United States, affects up to 60 million Americans, approximately 1 person in every 4 households. Of those affected, more than half have experienced symptoms for longer than 10 years.[1]

AR is often dismissed as a nuisance disorder by physicians and patients, and its management is frequently complicated

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by delayed diagnosis and treatment because of the patient's attempts at self-treatment.[1] The characteristic symptoms of AR are sneezing, rhinorrhea, nasal itching, nasal discharge, nasal congestion, and itchy, red, and watery eyes. Patients also frequently report postnasal drip, throat clearing, headaches and/or facial pain, itchy throat and palate, snoring, and sleep disturbance.[1–5] Addressing this illness early can have significant clinical benefit, substantially improving the patient's quality of life while reducing the incidence and/or severity of comorbid disorders, including asthma, rhinosinusitis, otitis media, eustachian tube dysfunction, allergic conjunctivitis, and sleep apnea.[2,3,6] Proper treatment can help contain costs by reducing absenteeism and presenteeism, decreasing complications of AR (including reducing hospitalizations related to comorbid asthma), and avoiding costly adverse effects of over-the-counter medications.[1,7–10]

In 2008, evidence-based updates to 2 documents providing guidance for managing AR, the Allergic Rhinitis and its Impact on Asthma (ARIA)/World Health Organization guidelines[3] and the US Practice Parameters,[2] were published. Despite some points of disparity with regard to defining severity and redefining a step-care approach to treatment, no significant differences were found regarding pharmacotherapeutic options for treatment. Both guidelines emphasize that AR is a chronic inflammatory condition and recommend targeting nasal airway inflammation as an important treatment strategy for all patients.[2,3]

Four classes of medication target the underlying inflammation of AR: antihistamines (H_1-receptor inverse agonists, formerly referred to as H_1-receptor antagonists), intranasal steroids (INSs), leukotriene receptor antagonists (LTRAs), and cromolyn sodium. Table 1 summarizes the effects of these medication classes on AR symptoms according to descriptions presented in the ARIA guidelines and US Rhinitis Practice Parameters. Various reiterations of this table have been published and presented, but the lack of head-to-head comparisons and use of studies with different designs and subjects make such tables an oversimplification. The trends as shown may be appropriate for one group of patients studied for a specific duration time (eg, patients with perennial AR [PAR], studied for 4 to 6 weeks) but not for another (eg, patients with seasonal AR [SAR], studied for 2 weeks). Likewise, outcomes may differ for studies of patients with moderate to severe AR compared with those with mild persistent AR.

These observations were discussed by an expert panel convened in November 2007 with the objective of evaluating the efficacy of currently used AR medications in the United States. A systematic review of the published literature was proposed to address the question, "How well do the currently approved classes of medications approved for AR in the United States treat nasal symptoms, when looked at according to Food and Drug Administration (FDA)–indicated uses and dosages?" The focus was narrowed to nasal symptoms because of the volume of data. This publication presents the outcomes, covering more than 3 decades of clinical experience and compiling appropriate data for comparisons and statistical analyses as possible. It is the first evidence-based review comparing the medication classes for AR as they are used in clinical practice (ie, for their approved indications and approved dosages).

METHODS

The review panel, chaired by Michael Benninger, MD, determined the question and criteria for the systematic review at a roundtable discussion (Detroit, Michigan, November 2007). The question was, "What are the comparative efficacies of currently used classes of medications to treat AR on nasal symptoms?" The criteria were as follows: medications targeting multiple nasal symptoms and approved for treating AR in the United States; FDA-approved dosages; controlled studies of 20 patients or more with physician-documented histories of AR; end-of-treatment data (2-week treatment duration for SAR and 4- to 6-week duration for PAR); if not included in study results, appropriate data to calculate percentage changes from baseline for comparison purposes; primary efficacy variable of total nasal symptom score (TNSS) defined as the sum of individual scores for sneezing, rhinorrhea, congestion, and nasal itching; secondary efficacy variables of individual nasal symptom scores; and data reported using 3-point and 4-point scales not by visual analog scales. Medications were combined by classes: oral antihistamines, nasal antihistamines, INSs, LTRAs, and cromolyn sodium.

Systematic Review of the Literature

Multiple MEDLINE searches from 1966 through September 2008, limited to English language and human subjects, were conducted. The primary topic header, *allergic rhinitis* (including *perennial* and *seasonal*) combined with *randomized controlled trial* (as publication type and keyword), was

Table 1. Symptom Management of Allergic Rhinitis (Based on Allergic Rhinitis and its Impact on Asthma Guidelines and US Rhinitis Practice Parameters)[2,3]

Medication class	Sneezing	Itching	Congestion	Rhinorrhea	Eyes	Inflammation
Oral antihistamines	++	++	+/−	++	+	+
Intranasal antihistamines	++	++	+	++	+/−	+
Intranasal steroids	++	++	++	++	+	++
Leukotriene receptor antagonists	+/−	+/−	−	+/−	+/−	+
Cromolyn sodium	+	+	−	+	+	+

Symbols: ++, substantial benefit; +, modest benefit; +/−, little or no benefit.

searched by treatment class: *(intra)nasal (cortico)steroids*, *(intra)nasal antihistamines*, *(oral) antihistamines*, *mast cell stabilizer*, and *leukotriene receptor antagonist*. Subsequent searches used specific medications within each treatment class: INSs: budesonide, beclomethasone, flunisolide, triamcinolone, mometasone, and fluticasone (propionate and furoate); oral antihistamines: fexofenadine, cetirizine, terfenadine, levocetirizine, desloratadine, and loratadine; nasal antihistamines: olopatadine and azelastine; and cromolyn sodium and montelukast as mediator-based therapies. Later searches included the first-generation antihistamines chlorpheniramine, brompheniramine, diphenhydramine, and clemastine.

All terms were searched as keywords and as headers, if available in the database. For the latter, the subheader *therapeutic use* was applied. Studies that reported only nasal challenges with specific allergens or nonclinical outcomes (eg, in vitro data) were excluded.

Studies were also identified from searches of EMBASE and the Cochrane Library (including the Cochrane Database of Systematic Reviews and the Cochrane Controlled Trial Register abstracts and protocols), from reference lists of published articles, and by the faculty.

Data from studies that met the inclusion criteria were extracted into evidence tables, which were reviewed twice by the full panel. Individual panel members also were asked to comment on abstracts, articles, and summary tables based on their known expertise. The entire faculty reviewed and approved the final 2 drafts of the manuscript, including the statistical findings.

Statistical Analysis

Statistical analyses were performed as possible based on sufficient data. Where there were not sufficient data for quantitative analysis, the aggregated data were described and evaluated qualitatively.

Between-class treatment differences were evaluated using the Wilcoxon rank sum test. Because determining the percentage changes from baseline eliminated any measures of dispersion (spread) based on actual symptom scores within each study (eg, SD or SEM per study at baseline and at 2 weeks), it was not possible to use any meta-analysis software (eg, CMA, STATA, or RevMan) to produce forest tree graphs or adjusted estimates.

Dispersion was evaluated using the interquartile range (IQR), which is the difference between the 75th and 25th percentiles of the data. The IQR is robust to outliers compared with the difference between the maximum and minimum values, which by definition includes all outliers. The IQR, thus, provides a measure of consistency for the results within a particular medication class: the broader the IQR, the greater the variability among studies.

RESULTS

Studies That Met the Inclusion Criteria

Of an initial 2,267 citations, 131 articles were obtained and evaluated according to the inclusion criteria (Fig 1). Fifty-four articles describing randomized, placebo-controlled studies involving more than 14,000 adults and 1,580 children with AR met the criteria for review.[11–64] Table 2 and Table 3 summarize the articles, including 31 that were used for statistical analyses (Table 2) and 23 that were not (Table 3).

Of these, 29 included oral antihistamines (n = 5,219 adults and 747 children), 7 included nasal antihistamines (n = 1,125 adults), 17 included INSs (n = 2,210 adults and 24 children), 6 included LTRAs (n = 1,354 adults and 49 children), and 2

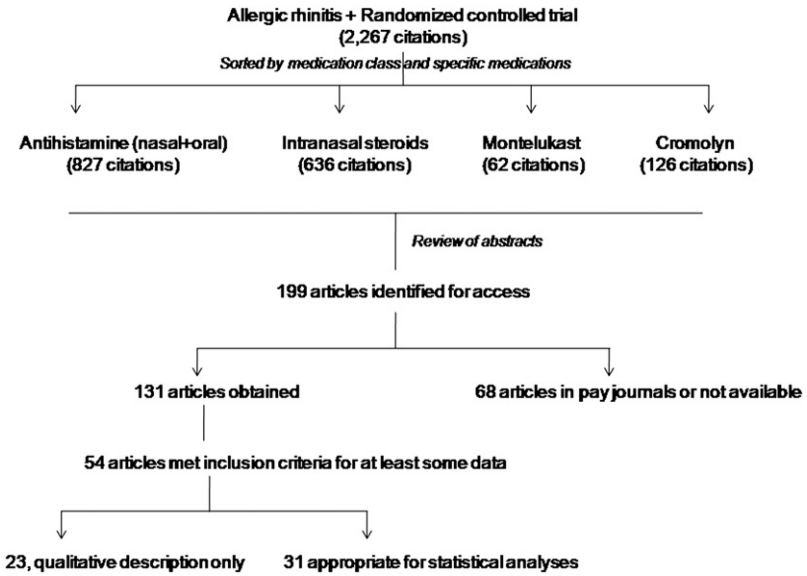

Figure 1. Articles selected for inclusion in this review.

Table 2. Data Summary for Studies That Contained Data Appropriate for Statistical Analyses

Study	Design	Patients	Percent change from baseline
Adults with SAR, percentage change at 2 weeks			
Anolik et al,[11] 2008	MC, R, PG, DB, PC TX: MOM, 200 μg (n = 176), LOR, 10 mg (n = 181), MOM + LOR (n = 169), P (n = 176); all once daily 15 d (3–7 day RI) Efficacy: TNSS Scale, 0–3	N = 702 patients with SAR Mean age: 26 y (11–71 y) Mean duration AR, 14 y (2–60 y) At entry, NC ≥2 and TNSS ≥6	TNSS: MOM + LOR, −35, MOM, −32, LOR, −22, P, −15 Rh: MOM + LOR, −33.3, MOM, −33.3, LOR, −19.1, P, −14.3 NC: MOM + LOR, −30.4, MOM, −31.8, LOR −17.4, P, −13.6 Sn: MOM + LOR, −44.4, MOM, −41.2, LOR −35.3, P, −23.5 NI: MOM + LOR, −38.9, MOM, −35.3, LOR −31.6, P, −21
Berger et al,[15] 2003	MC, R, DB, PC, PG TX: AZE, 2 sprays per nostril twice daily (n = 108); AZE + LOR, 10 mg once daily (n = 110); DES, 5 mg once daily (n = 111); P (n = 111) 2 wk (1 wk screening then 1 wk with LOR, 5 mg twice daily) Efficacy, TNSS Scale, 0–3	N = 428 with SAR, still symptomatic after 1 wk with LOR, 5 mg Mean age, 35.9–36.9 y (12–79 y) Mean duration AR, not specified Score required at entry, TNSS ≥8	rTNSS: P, −11.1; AZE, −21.9; AZE + LOR, −21.5; DES, −17.5 NC: P, −13.5; AZE, −17.6; AZE + LOR, −18.4; DES, −16 NI: P, −12.4; AZE, −23.4; AZE + LOR, −23.5; DES, −18.1 Rh: P, −11; AZE, −21.6; AZE + LOR, −20.2; DES, −16.7 Sn: P, −7; AZE, −26.1; AZE + LOR, −24.8; DES, −19.9
Berger et al,[14] 2002	R, MC, PG, DB TX: DES, 5 mg (n = 168), P (n = 163); both once daily 4 wk (3–14 d RI) Efficacy: TNSS Scale, 0–3	N = 331 with SAR + mild seasonal allergic asthma (FEV_1 ≥70%) Mean age, 32–32.5 y (15–75 y) Mean duration AR, 19.4–21.2 y (2–73 y) At entry, TNSS ≥6	rTNSS3 (TNSS without NC): DES, −31.7; P, −19.3 NC: DES, −23.5; P, −16.4
Berger et al,[13] 2006	MC, R, DB, PG TX: AZE, 2 sprays per nostril twice daily (n = 179), CET, 10 mg once daily (n = 175) 2 wk (1 wk SBRI) Efficacy: rTNSS Scale, 0–3	N = 360 with moderate-to-severe SAR Mean age, 34.3–35.1 y (12–74 y) Mean duration AR, 18.6 y (range not specified) At entry, rTNSS ≥8; rNC ≥2	rTNSS: AZE, −23.9; CET, −19.6
Bjerrum and Illum,[18] 1985	DB, DD BUD, 2 sprays per nostril (50 μg per spray) twice daily (n = 22), CROM, 1 spray per nostril (2.6 mg per spray) 5 times daily (n = 21) 3 wk (7 d RI) Efficacy: TNSS (TSS) Scale, 0–3	N = 40 with SAR >2 y Mean age, 29 y (15–55 y) Mean duration AR, not specified At entry, not specified	TNSS: BUD, −37.7; CROM, +24.3 NC (blockage): BUD, −37.2; CROM, +14.8 Rh (secretion): BUD, −58.3; CROM, +31.6 Sn: BUD, −21.3; CROM, +34.6 NI: BUD, −18.2; CROM, +17.9
Bronsky et al,[19] 1997	MC, DB, PC, DR TX: MOM 50 μg (n = 94), 100 μg (n = 94), 200 μg (n = 96), 800 μg (n = 95); P (n = 95); all once daily 28 d (RI not specified) Efficacy: TNSS Scale, 0–6	N = 480 with SAR Mean age, 37–38 y (18–66 y) Mean duration AR, 18–20 y (2–56 y) At entry, TNSS ≥10, NC ≥2, and ≥1 other Sx ≥2	TNSS: P, −27; MOM 50 μg, −45; 100 μg, −46; 200 μg, −50; 800 μg, −50
Chervinsky et al,[23] 2005	MC, R, DB, PG TX: DES + PSE 2.5/120 mg twice daily (n = 214); DES 5 mg once daily (n = 214); PSE 120 mg twice daily (n = 222) 2 wk (3 d screening) Efficacy: TNSS Scale, 0–3	N = 650 with autumn SAR Mean age, 36 y (range not specified) Mean duration AR, 18.5 y (range not specified) At entry, TNSS ≥6	rTNSS, no NC: DES + PSE, −42; DES, −35; PSE, −34 NC: DES + PSE, −36; DES, −24; PSE, −32
Kaiser et al,[30] 2007	R, DB, PC, PG TX: FF, 110 μg (n = 151); P (n = 148); both once daily 28 d, 5–21 d RI Efficacy, TNSS Scale, 0–3	N = 299 with SAR Mean age, 35 y (12–74 y) Mean duration AR, not specified, but 71% >10 y At entry, TNSS ≥6 and NC ≥3	rTNSS: P, −21.6, FF, −35.6
LaForce et al,[33] 2004	MC, R, DB, PC, PG TX: AZE, 2 sprays per nostril (n = 112), AZE + FEX, 60 mg (n = 112), P (n = 110); all twice daily 2 wk (1 wk OL with FEX, 60 mg twice daily, before study) Efficacy: TNSS Scale, 0–3	N = 334 with SAR still symptomatic after 1 wk with FEX Mean age, 35 y (12–80 y) Mean duration AR, not specified At entry, TNSS ≥8 and improved by <33% with FEX ≥3 d of RI	TNSS: P, −10.5; AZE, −18.5; AZE + FEX, −18.3 NC: P, −11.6; AZE, −15.3; AZE + FEX, −13.6 Sn: P, −9.6; AZE, −21.4; AZE + FEX, −20.8 Rh: P, −9; AZE, −18.6; AZE + FEX, −18.9 NI: P, −11.4; AZE, −19.4; AZE + FEX, −20.9
Lumry et al,[34] 2007	R, DB, PC, PG (2 studies: S1, S2) TX: AZE, 1 spray per nostril (n = 139, 132), P (n = 141, 137); both twice daily 2 wk (1 wk SBRI) Efficacy: TNSS Scale, 0–3	N = 554 with moderate-to-severe SAR (in 2 studies, S1 and S2) Mean age, 33–36 y (12–75 y) Mean duration AR, not specified At entry, TNSS ≥8	TNSS: S1: P, −7.6; AZE, −16.5; S2: P, −14.9; AZE, −22.1 NC: S1: P, −8.4; AZE, −11.4; S2: P, −11.7; AZE, −18.6 Sn: S1: P, −7; AZE, −22.2; S2: P, −18.2; AZE, −27.7 NI: S1: P, −8.3; AZE, −17.7; S2: P, −15.2; AZE, −23 Rh: S1: P, −6.7; AZE, −15.6; S2: P, −14.8; AZE, −20.6

Table 2. Continued

Study	Design	Patients	Percent change from baseline
Meltzer et al,[37] 2000	R, MC, DB, PC, PG TX: MON, 10 mg (n = 95), 20 mg (n = 90); LOR, 10 mg (n = 92); MON + LOR, 10/10 mg (n = 90); P (n = 91); all once daily 2 wk, 1 wk SBRI Efficacy: DT-TNSS; NT score = NC on awakening, difficulty falling asleep, awakenings during night; Composite = DT-NSS + NT Score Scale, 0–3	N = 460 with SAR Median age, 30–37 y (15–75 yr) Mean duration AR, 17–19 y (range not specified) At entry, Total DT-TNSS ≥42 (of 84) + total DT NC ≥13 (of 21)	DT-TNSS: P, −12.1; MON10, −17.0; MON20, −14.4; LOR, −16.4; MON + LOR, −28.6 NT Score: P, −7.8; MON10, −19.2; MON20, −14.8; LOR, −12.7; MON + LOR, −22.8 Composite: P, −13.5; MON10, −21.0; MON20, −17.5; LOR, −17.6; MON + LOR, −29.5
Meltzer et al,[36] 2005	R, MC, DB, PC TX: OLO, 0.4% (n = 189), 0.6% (n = 184); P (n = 192); all twice daily (No. of sprays per nostril not specified) 2 wk (3–21 d SBRI) Efficacy: TNSS Scale, 0–3	N = 565 with SAR Mean age, 35 y (12–80 y) Duration of AR, not specified At entry, TNSS ≥36 (of possible 72) on 3 of 4 d of RI	rTNSS: P, −27.0; OLO 0.4, −35.8; OLO 0.6, −39.2 rNC: P, −22.0; OLO 0.4, −25.7; OLO 0.6, −24.5 rNI: P, −27.8; OLO 0.4, −38.1; OLO 0.6, −39.1 rSn: P, −29.0; OLO 0.4, −49.5; OLO 0.6, −51.7 rRh: P, −24.9; OLO 0.4, −33.0; OLO 0.6, −38.5
Nayak et al,[42] 2002	MC, R, DB, PC, PG TX: MON, 10 mg (n = 155); LOR, 10 mg (n = 301); MON + LOR (n = 302); P (n = 149); all once daily 2 wk, 1 wk SBRI Efficacy: DT-TNSS NT score = NC on awakening, difficulty falling asleep, awakenings during night; composite = DT-TNSS + NT score Scale, 0–3	N = 907 with SAR Mean age, 35–38 y (15–82 y) Mean duration AR, 18–20 y (2–67 y) At entry, Cumulative DT-TNSS ≥42 over 7 d	DT-TNSS: P, −12.9; MON, −23.3; LOR, −24.9; MON + LOR, −28.9
Oei,[44] 1988	R, DB, PC, PG TX: LOR, 10 mg (n = 22), AST, 10 mg (n = 22), P (n = 21); all once daily 2 wk, 3–5 d SBRI Efficacy: TSS = TNSS Scale, 0–3	N = 65 with SAR Mean age, 25–27 y (15–82 y) Mean duration AR, 7.5 y (range not specified) At entry, not specified	TNSS: LOR, −49; AST, −52; P, −40
Pleskow et al,[45]2005	MC, R, DB, DD, PG TX: Des + PSE, 5/240 mg (n = 372); DES, 5 mg (n = 372); PSE, 240 mg (n = 377); all once daily 2 wk, 2 wk screen Efficacy, TSS = TNSS + ocular Sx + itchy ears and palate Scale, 0–3	N = 1,047 with SAR Mean age, 35 y (12–78 y) Mean duration AR, 16.5–18 y (2–55 y) At entry, Rh ≥2 + NC ≥2 + TNSS ≥6 + TNNSS ≥5	rTSS, no NC: DES + PSE, −39; DES, −34; PSE, −32 rNC: DES + PSE, −33; DES, −28; PSE, −29
Ratner et al,[48] 2005 (data also reported in Hampel et al,[27] 2006)	R, MC, DB, PC	N = 675 with SAR	rTNSS: P, −18.7; OLO 0.4, −27.6; OLO 0.6, −30.1
	TX: OLO. 0.4% (n = 229), 0.6% (n = 222); P (n = 224); all twice daily (No. of sprays per nostril not specified) 2 wk, 3–21 d SBRI Efficacy: TNSS Scale, 0–3	Mean age, 39 y (12–81 y) Mean duration of AR, not specified At entry, TNSS ≥36 (of possible 72) on 3 of 4 d of RI	rNC: P, −13.2; OLO 0.4, −21.3; OLO 0.6, −21.7 rNI: P, −19.4; OLO 0.4, −30.8; OLO 0.6, −32.4 rSn: P, −18.8; OLO 0.4, −33.4; OLO 0.6, −35.7 rRh: P, −18.4; OLO 0.4, −22.3; OLO 0.6, −30.0
Ratner et al,[71] 2008	DB, DD, R, PG TX: AZE NS, 2 sprays per nostril twice daily (n = 49), FP, 2 sprays per nostril once daily (n = 49), both TX (n = 52) 2 wk, 5 d RI Efficacy: TNSS Scale, 0–3	N = 151 with moderate to severe Sx to mountain cedar Mean age, 37.2 y (12–73 y) Mean duration AR, 17 y (3–51 y) At entry, TNSS ≥8 at 3 evaluations	TNSS: AZE + FP, −37.9, AZE −22.2, FP, −24.5% NI: AZE + FP, −39.9, AZE, −25.4, FP, −25.5 NC: AZE + FP, −31.2, AZE, −19.2, FP, −21.1 Rh (Runny nose): AZE + FP, −36.4, AZE, −20.5, FP, −23% Sneezing: AZE + FP, −46.4, AZE, −34.2, FP, −31.8
Storms et al,[53] 1989	R, MC, DB, PC, PG TX: LOR + PSE, 5/120 mg (n = 111), LOR, 5 mg (n = 109), PSE, 120 mg (n = 109), P (n = 106); all twice daily 2 wk, 3–5 d SBRI Efficacy: TNSS Scale, 0–3	N = 65 with SAR Mean age, 30–32 y (12–60 y) Mean duration AR, 14–15 y At entry, NC ≥2, Rh ≥2, TNSS ≥6	TNSS: LOR + PSE, −49, LOR, −43, PSE, −43, P, −33 NC (Stuffiness): LOR + PSE, −42, LOR, −22, PSE, −38, P, −28 NI: LOR + PSE, −55, LOR, −42, PSE, −45, P, −32 Rh (Discharge): LOR + PSE, −42, LOR, −46, PSE, −42, P, −30

Table 2. Continued

Study	Design	Patients	Percent change from baseline
Sussman et al,[55] 1999	MC, R, DB, PG TX: FEX, 60 mg (n = 218), PSE, 120 mg (n = 218), FEX + PSE (n = 215), all twice daily 2 wk, 3–5 d SBRI Efficacy: TSS = Rh + Sn + INPT + NC + WIRE Scale, 0–4	N = 651 with SAR Mean age, 31.7–34.9 y (12–66 y) Mean duration AR, 14.9–15.9 y (1–55 y) At entry, rTSS ≥6 and NC ≥2 and ≥2 Sx ≥2	rTSS, no NC: FEX + PSE, −29.6; FEX, −25; PSE, −17.8 rNC: FEX + PSE, −22.9; FEX, −15.3; PSE, −19.2
Tinkelman et al,[57] 1990	DB, PC, PG INS TX: TAA 1 spray (13.75 μg) per nostril (n = 81); P (n = 87); both 4 times daily 4 wk (5 d BL) Efficacy: nasal index = NC + Rh + Sn; TSS = nasal index + ocular Sx Scale, 0–3	N = 168 with SAR Mean age, 33 y (18–65 y) Mean duration AR, not specified At entry, TSS ≥24 and Nasal index ≥16	Nasal index: TAA −52.7, P −25.3 NC (nasal stuffiness): TAA −45.8, P −23.8 Rh (nasal discharge): TAA −53, P −25.2 Sn: TAA −61.6, P −27
Adelsberg et al,[58] 2003	R, MC, DB, PC, PG TX: MON, 10 mg (n = 448), LOR, 10 mg (n = 180), P (n = 451); all once daily in the morning 4 wk (3–5 d SBRI) Efficacy: DT-TNSS NT score = difficulty going to sleep + NT awakenings + NC on awakening Composite score = DT-TNSS + NT score Scale, 0–3	N = 1,079 with SAR Mean age, 36–39 y (15–82 y) Mean duration AR, 20 y (range not specified) At entry, not specified	DT-TNSS: P, −10.7; MON, −15.0, LOR, −20.2 NT score: P, −10.9; MON, −16.6, LOR, −14.1 Composite score: P, −10.8; MON, −15.2, LOR, −17.7
Wilson et al,[61] 2002	R, SB, DD, PC, CO TX: FEX, 120 mg (n = 37), MON, 10 mg + LOR, 10 mg (n = 37), P (n = 37); all once daily 2 wk during grass pollen season, 7–10 d SBRI and WO Efficacy: TNSS Scale, 0–3	N = 37 with SAR to grass pollen Mean age, 37 y (range not specified) Mean duration of AR, not specified At entry, not specified	rTNSS: P, −8.6; FEX, −38.3; MON + LOR, −50.6 NC: P, −10.3; FEX, −31; MON + LOR, −44.8 NI: P, 0; FEX, −38.9; MON + LOR, −44.5 Rh: P, −5.9; FEX, −52.9; MON + LOR, −70.6 Sn: P, −10; FEX, −45; MON + LOR, −55
Wilson et al,[62] 2002	R, DB, PC, CO TX: FEX, 180 mg (n = 49); DES, 5 mg (n = 49); both once daily 2 wk, 7–10 d SBRI Efficacy: TNSS Scale, 0–3	N = 49 with SAR Mean age, 32 y (not specified) Mean duration AR, not specified At entry, not specified	TNSS: FEX, −21.9; DES, −23.5 NC: FEX, −18.2; DES, −25.0
Wilson et al,[64] 2001	R, SB, PC, DD, CO TX: MOM, 200 mcg (n = 22); MON, 10 mg + CET, 10 mg; all once daily 2 wk, 7–10 d RI, WO with P Efficacy: TNSS Scale, 0–3	N = 22 with SAR Mean age, 35 y (not specified) Mean duration AR, not specified At entry, not specified	NI: MOM, −52.9; MON + CET, −58.8
Adults with SAR, percentage change at 4 weeks			
Bende et al,[12] 2002	R, MC, PC, PG TX: BUD, 128 μg (n = 110), BUD, 256 μg (n = 107), MOM, 200 μg (n = 106), P (n = 114); all once daily 4 wk, 2 wk RI Efficacy: NIS = TNSS with NI and Sn combined into one score Scale, 0–3	N = 437 with PAR Mean age, 29.9–32.0 y (range not specified) Mean duration AR, 9.5–11.0 y At entry, NIS ≥3 and NC ≥31 for 4 RI d	Morning/evening NIS: P, −11.1/−14.4; BUD 128, −34.6/−38.1; BUD 256, −39.0/−42.4; MOM, −32.6/−36.5 NC: P, −7.8/−12.4; BUD 128, −27.5/−30.1; BUD 256, −25.9/−30.6; MOM, −27.5/−30.1 Rh: P, −11.8/−14.2; BUD 128, −35.5/−36.6; BUD 256, −44.0/−44.0; MOM, −32.7/−37.1 NI/Sn: P, −16.0/−18.6; BUD 128, −45.0/−47.8; BUD 256, −58.1/−59.8; MOM, −43.0/−46.6
Adults with PAR, percentage change at 4 weeks			
Ciebiada et al,[22] 2006	R, DB, PC, CO A). MON, 10 mg, LCET, 5 mg, or combination or P (n = 20); all once daily in evening B). MON, 10 mg, DES, 5 mg, or combination (n = 20) or P; all once daily in evening 6 wk (2 wk RI and WO) Efficacy: DT-TNSS Scale, 0–3	N = 40 with PAR Mean age, 28.9 y (18–65 y) Mean duration of AR, 5.7–7.9 y (range not specified) At entry, not specified	6 wk TNSS (DT-TNSS): A-P, −37.2; MON + LCET, −73.1; MON, −56.7; LCET, −6; B-P, −25.6; MON + DES, −60.5; MON, −53.2; DES, −51.4 NC: A-P, −39.2; MON + LCET, −70.2; MON, −57.3; LCET, −60.8; B-P, −17; MON + DES, −55.2; MON, −45.2; DES, −43.5 Sn: A-P, −30.3; MON + LCET, −77.4; MON, −58.5; LCET, −65.6 B-P, −26.5; MON + DES, −60; MON, −51.9; DES, −48.1 Rh: A-P, −32.7; MON + LCET, −63.9; MON, −43.4; LCET, −52.7; B-P, −21; MON + DES, −54.3; MON, −54.3; DES, −50.5 NI: A-P, −31.7; MON + LCET, −85; MON, −72.1; LCET, −72.9; B-P, −44.8; MON + DES, −77.9; MON, −66.2; DES, −70.3

Table 2. Continued

Study	Design	Patients	Percent change from baseline
Kim et al,[32] 2006	R, MC, DB, PC TX: DES, 5 mg (n = 591), P (n = 588); both once daily 4 wk (RI, not specified) Efficacy: TNSS Scale, 0–4	N = 1,179 with PAR Mean age, 35 y (12–76 y) Mean duration AR, not specified At entry, TNSS ≥5	TNSS: P, −19.8; DES, −23.7
Murris-Espin et al,[40] 1998	R, MC, DB, PG TX: CET, 10 mg (n = 106), EB, 10 mg (n = 108); both once daily 4 wk, RI not specified Efficacy: TSS = TNSS Scale, 0–3	N = 214 with PAR Mean age, 31.2 y (17–70 y) Mean duration AR, 9.2–10.7 y At entry, TNSS ≥6	TNSS = CET, −53.7; EB, −44.7
Nathan et al,[41] 2008	MC, DB, vehicle C, PG FF, 110 μg (n = 149); P (n = 153); both 2 sprays, once daily in the morning 4 wk (7–14 d screening) Efficacy: TNSS Scale, 0–3	N = 302 with PAR ≥2 y Mean age: 36.7 y (range not specified) Duration of AR: 53% ≥10 y At entry, TNSS ≥6 for prior 8 assessments (4 d) of screening	rTNSS: FF, −32.3; P, −23.9 rNC: FF, −28; P, −22.3 rRh: FF, −31.3; P, −23.6 rNI: FF, −32.9; P, −25.2 rSn: FF, −28; P, −25
Spector et al,[52] 1990	R, DB, PC TX: TAA, 25 μg/ nostril (n = 94), P (n = 94); all 4 times daily 12 wk (1 wk BL) Efficacy: TSS = NC (nasal stuffiness) + Rh (nasal discharge) + Sn + ocular Sx; nasal index = NC + Rh + Sn Scale, 0–3	N = 188 with PAR Mean age, 36.8 y (16–65 y) Mean duration of AR, not specified At entry, TSS ≥24 on last 4 d of 1 wk BL	NC (nasal stuffiness): TAA, −34.7, P, −19.6 Rh (nasal discharge): TAA, −38.9, P, −23 Sn: TAA, −51.5, P, −32.3 Nasal index: TAA, −40.8, P, −24.2
Warland,[60] 1982	DB, PC, CO FLU 0.25% (n = 34), P (n = 34), 2 sprays twice daily (=200 μg of FLU) 4 wk, 2 wk BL, 2 wk WO Efficacy: Sx scores (Sn, NS (stuffiness), Rh (runny nose, nose blowing, PND) Scale, 0–3	N = 34 with PAR Mean age, 32.5 y (16–76 y) Mean duration AR, 5.9 y (1–20 y) At entry, not specified	Sn: FLU, −44.4, P, 0 NC (stuffiness): FLU, −46.7, P, −6.7 Rh (Runny nose): FLU, −57.1, P, −14.3 Nose blowing: FLU, +16.7, *P,* +116.7

Abbreviations: AR, allergic rhinitis; AST, astemizole; AZE, azelastine; BDP, beclomethasone dipropionate; BL, baseline; BUD, budesonide; C, controlled; CET, cetirizine; CO, crossover; CROM, cromolyn sodium; DB, double-blind; DD, double dummy; DES, desloratadine; DM, double masked; DR, dose-ranging; DT, daytime; EB, ebastine; EEU, environmental exposure unit; FEX, fexofenadine; FF, fluticasone furoate; FLU, fluticasone; FP, fluticasone propionate; HDM, house dust mite; HRQL, health-related quality of life; IE, itchy eyes (also referred to as ocular pruritus); IN, intranasal; INPT, itchy nose/palate/throat; LCET, levocetirizine; LEVO, levocabastine; LOR, loratadine; MC, multicenter; MOM, mometasone; MON, montelukast; NC, nasal congestion (also referred to as nasal stuffiness, nasal obstruction, or nasal blockage); NI, nasal itching (also referred to as nasal pruritus); NIS, nasal index score; OA, onset of action; OL, open-label; OLO, olopatadine; PAR, perennial allergic rhinitis; PC, placebo-controlled; PG, parallel group; PND, postnasal drip; PSE, pseudoephedrine; r, reflective; R, randomized; RE, red eyes; Rh, rhinorrhea (also referred to as runny, drippy nose, or nasal discharge); RI, run in; RQLQ, Rhinitis Quality of Life Questionnaire; SAR, seasonal allergic rhinitis; SBRI, single-blind run-in; Sn, sneezing; Sx, symptoms; TAA, triamcinolone acetonide; TNSS, total nasal symptom score (NI + Sn + NC + Rh); TNNSS, total nonnasal symptom score (defined according to study); TSS, total symptom score (defined according to study); TX, treatment; WIRE, watery, itchy, red eyes; WO, washout.

included cromolyn sodium (n = 21). A total of 6,655 patients (5,872 adults and 783 children) received placebo in these studies.

Patients

Most studies were conducted in patients with SAR (38 studies; n = 11,980 adults ad 946 children) compared with 12 studies in patients with PAR (n = 3,800 adults and 366 children). One pediatric study evaluated treatment efficacy for SAR but included 271 children who had both PAR and SAR.[59]

According to their methods, all studies included patients who had a physician-documented history of AR for 2 years or more. However, patient demographics cited ranges of less than 2 years for 2 SAR studies[29,55] and for 1 PAR study.[60] The mean duration of AR for 23 SAR studies in which it was reported was 17.1 years (range, 7.5–20.5 years) for adults and adolescents. Duration was reported for 4 PAR studies in adults and adolescents (mean, 8.3 years; range, 5.9–10.3 years). The pediatric studies did not report duration of AR.

The mean ages of the adults and adolescents were 34.5 years (range, 26–40 years) in SAR studies and 33 years (range, 28.9–36.8 years) in PAR studies. In the 28 SAR studies that specified age ranges, adolescents (defined as those aged 12–18 years) were included in 24 studies. One study included at least 1 child younger than 12 years.[11] Seven of 9 PAR studies that specified age ranges included adolescents. Again, 1 study included at least 1 child 11 years old.[51] Six of the 7 pediatric trials included school-aged children (defined as those 6–12 years old; mean age, 10.1 years; range, 8.8–11.5 years). One of these studies included children as young as 5 years,[59] and 3 included adolescents: the trials by deBlic et al[24] and by Razi et al[50] included children up to 13 years old, and the study reported by Strem et al[54] included children up to 15 years old. Chen et al[21] looked at 60 preschool children (defined as those between 2 and 6 years old) with PAR.

Table 3. Data Summary for Studies With Data That Could Not Be Used in the Statistical Analyses

Study	Design	Patients	Percentage change from baseline
Adults with SAR, percentage change at 2 weeks			
Bernstein et al,[16] 1996	MC, DB, DD, PG TX: TAA, 2 sprays, 110 μg per nostril (n = 104), ASTEM, 10 mg (n = 105); both once daily 4 wk (5 d RI) Efficacy: TSS = TNSS + PND + ocular Sx Scale, 0-3	N = 239 with SAR Mean age, 35.7 y (range not specified) Duration of AR, not specified At entry, TSS≥24 for 4 of 5 RI d	At 4 wk TNSS [defined as including PND]: TAA, −50; AST, −37 NI: TAA, −54; AST, −42 NC: TAA, −43; ASTEM, −27 Rh: TAA, −51; ASTEM, −39 Sn: TAA, −56; ASTEM, −42 PND: TAA, −45; ASTEM, −35
Bernstein et al,[17] 1997	R, MC, DB, PC TX: FEX, 60 mg (n = 141), 120 mg (n = 144), 240 mg (n = 144), P (n = 141); all twice daily 14 d (3 d SBRI) Efficacy: rTSS3 = Rh + NI + Sn; NC reported separately Scale, 0–4	N = 570 with moderate-to-severe ragweed SAR Mean age, 32.5 y (12–66 y) Mean duration AR, 17 y (2–60) At entry, rTSS ≥6	rTSS3: P, −16.9; FEX 60 mg, −28.1; 120 mg, −25.5; 240 mg, −28.1
Bronsky et al,[20] 1998	R, MC, DB, PC TX: FEX, 40 mg (n = 135), 60, mg (n = 138), 120 mg (n = 135), P (n = 137); all twice daily 14 d (3 d SBRI) Efficacy: TSS = NI + Rh + Sn + INPT + WIRE NC reported separate Scale, 0–4	N = 545 with autumn SAR Mean age, 33 y (12–65 y) Mean duration AR, 17 (range not specified) At entry, TSS ≥6, ≥2 Sx ≥2, no Sx = 4	rTSS: P, −14; FEX 40, mg, −21; 60 mg, −21; 120 mg, −25
Gehanno et al,[25] 1997	R, MC, DD, PG TX: FP, 200 μg (n = 248), LOR, 10 mg (n = 247); both once daily 4 wk (5–7 d SBRI) Efficacy: TSS = nighttime obstruction + daytime obstruction + Sn + Rh Scale, 0–3	N = 495 with moderate-to-severe SAR Mean age, 34.8 y (12–70 y) Mean duration AR 17.3 y (range not specified) At entry, TSS ≥6	rTSS: FEX, −19; CET, −21.6
Hampel et al,[28] 2003	R, MC, DB, DD, PG TX: FEX, 180 mg (n = 248), CET, 10 mg (n = 247); both once daily 2 wk (5–7 d SBRI) Efficacy: TSS= Sn + Rh + WIRE + INPT Scale, 0–4	N = 495 with moderate-to-severe SAR Mean age, 34.8 y (12–70 y) Mean duration AR 17.3 y (range not specified) At entry, TSS ≥6 + ≥2 Sx rated ≥2 + no Sx rated severe	rTNSS: FEX, −19; CET, −21.6
Hampel et al,[28] 2004	R, DB, PC, PG TX: EB, 20 mg (n = 186), 10 mg (n = 188); LOR, 10 mg (n = 189); P (n = 186); all once daily 4 wk (4–28 d RI) Efficacy: TSS = TNSS + WIRE; TNSS (nasal index) Scale, 0–3	N = 749 with SAR Mean age, 37.6 y (12–70 y) Mean duration AR, 19.9 y (2–69 y) At entry, rTSS ≥42, ≥1 Sx ≥2	4 wk rTSS: P, −28.2; EB20, −39.3; EB10, −35.9); LOR, −33.3 TNSS (nasal index): P, −27.7; EB20, −38.0; EB10, −34.3; LOR, −32.2
Howarth et al,[29] 1999	R, MC, DB, PC, PG TX: FEX, 120 mg (n = 211), 180 mg (n = 202), CET, 10 mg (n = 207), P (n = 201); all once daily 2 wk. (3–5 d SBRI) Efficacy: TSS = Sn + Rh + INPT + WIRE NC reported separately Scale, 0–4	N = 821 with SAR to grass pollen Mean age, 33 y (12–66 y) Mean duration AR, 14.5 y (0–61 y) At entry, TSS ≥5, ≥2 Sx ≥2 (excluding NC), no Sx = 4	rTSS: P, −26.0; FEX180, −44.6; FEX120, −41.7; CET, −45.2
Kammer-Meyer et al,[31] 1977	DB, vehicle C, PG TX: FLU 0.025%, vehicle control; both 2 sprays per nostril twice daily 4 wk (2 wk BL) Efficacy: TSS = Sn + NC (stuffy nose)+ Rh (nasal secretions)+ throat itch + Eye itch Scale, 0–4 (based on time: 0 = none, 1 = barely noticeable, 2 = definitely present <1 h, 3 = present 1–2 h, 4 = present >2 h)	N = 50 with poorly controlled SAR ≥2 y Age ≥18 y Mean duration AR, 10 patients ≤10 y, 39 patients >10 y At entry, not specified	4 wk Sn: FLU, −36.2, control, +2.3 NC (stuffy nose): FLU, −30.6, control, +16.9 RH (nasal secretions): FLU, −31.1, control, +16.2
Martin et al,[35] 2006	MC, R, DB, DD, PG TX: FP, 200 μg (n = 367), MON, 10 mg (n = 369), both once daily 2 wk (7 d RI) Efficacy: DT-TNSS NT score = NC at awakening + difficulty falling asleep due to nasal Sx + awakenings due to nasal Sx Scale, DT-TNSS, 0–100 (VAS); NT score, 0–3	N = 736 with SAR Mean age, 40 y Mean duration AR, 15.2 y (range not specified) At entry, DT-TNSS ≥200 (of 400) for 4 of 7 d RI	TSS: FP, −43.7; MON, −32 NC: FP, −39.9; MON, −39.4 NI: FP, −44.7; MON, −33.7 Rh: FP, −43.9; MON, −30.8 Sn: FP, −46.6; MON, −34.5
Murray et al,[39] 2002	MC, R, DB, PC, PG TX: CET, 10 mg (n = 431), P (n = 431); both once daily 2 wk (1 wk SBRI) Efficacy: TSSC = Sn + Rh + NI + PND + ocular Sx; NC reported separately Scale, 0–3	N = 865 with SAR to ragweed Mean age, 37 y (18–65 y) Mean duration AR, 19.5–21.0 y (2–65 y); 1 patient, 3 mo At entry, TSSC ≥ 6, ≥1 Sx ≥2 excluding NC and PND	TSSC: P, −17.4; CET, −30.3

Table 3. Continued

Study	Design	Patients	Percentage change from baseline
Noonan et al,[43] 2003	R, DB, PC, PG, MC TX: CET, 10 mg (n = 202), P (n = 198); both once daily 2 wk (1 wk SBRI) Efficacy, TSSC = Sn + Rh + NI + PND + ocular Sx; NC reported separately Scale, 0–3	N = 403 with SAR Mean age, 35.8–37.4 y (18–65yr) Mean duration AR, 19.3–20.9 y (2–55 y) At entry, 2 of 5 Sx (Sn, NI, Rh, WE, IE) ≥2, TSSC ≥5 on 4 d	TSSC: P, −21.4; CET, −35.5 DT-TNSS: FP, −44; MON, −31.5 NC: FP, −40.5; MON, −29 Rh: FP, −43.4; MON, −32 NI: FP, −45; MON, −31.9 Sn: FP, −47.5; MON, −32.9 NT score: FP, −48.7; MON, −38.9 NC on awakening: FP, −42.4; MON, −32.3 Difficulty falling asleep: FP, −52.5; MON, −43.2 Awakenings: FP, −55.1; MON, −44.4
Ratner et al,[49] 2003	R, MC, DB, DD, PG TX: FP, 200 μg (n = 353), MON, 10 mg (n = 352); both once daily 15 d, 7 d RI Efficacy, DT-TNSS NT-score = NC on awakening + difficulty falling asleep due to nasal Sx + awakenings due to nasal Sx Scale, DT = TNSS, 0–100 (VAS); NT-score, 0–3	N = 705 with SAR Mean age, 38.2 y Mean duration, 15.6 y At entry, DT-TNSS ≥200 (of 400) for 4 of 7 RI d	
Wilson et al,[61] 2001	R, SB, DD, PC, CO TX: Inh + IN BUD, 400 μg/200 μg (n = 21); MON + CET, 10 mg/10 mg (n = 21); all once daily 2 wk (7–10 d RI) Efficacy: TNSS Scale, 0–3	N = 21 with SAR and mild asthma (10 also had PAR) Mean age, 32 y (range not specified) Mean duration AR, not specified At entry, not specified	TNSS: P, −18.3; IN BUD, −52.7; MON + CET, −66.8 NC: P, −41.5; IN BUD, −63.8; MON + CET, −64.6
Adults with PAR, percentage change at 4 weeks			
Meltzer et al,[38] 1988	MC, DB, PC, CO TX: AZE, 1 mg (n = 92), 2 mg (n = 93), P (n = 184) 4 wk (7 d RI, 1 wk placebo WO) Efficacy: TSS = Sn + Rh (runny nose)+ NC (stuffy nose) + itchy nose or eyes + itchy ears or throat + nose blows Scale, 0–4	N = 192 with PAR > 2yr Mean age, 29.8 y (23–34 y) Mean duration AR, not specified At entry, TSS ≥7 on at least 4 d of RI and WO with ≥1 Sx ≥3	TSS: AZE, 1 mg, −14.8; P, −4.2; AZE, 2 mg, −18.2; P, −5.3 Rh (runny nose): AZE, 1 mg, −23.7; P, +12.5; AZE, 2 mg, −23.3; P, +9.5 NC (stuffy nose): AZE, 1 mg, −2.9; P, −7.4; AZE, 2 mg, −3.5; P, −3.7 Sn: AZE, 1 mg, −11.6; P, +13.4; AZE, 2 mg, −22.5; P, +4.1 Nose blows: AZE, 1 mg, −9.9; P, +19.9; AZE, 2 mg, −13.4; P, +10.6 IE/itchy nose: AZE, 1 mg, −13.1; P, −4.3; AZE, 2 mg, −10.3; P, −4.0
Potter et al,[47] 2003	R, DB, PC, MC TX: LCET, 5 mg (n = 150), P (n = 144); both once daily 6 wk (2 wk RI) Efficacy: TSS = NI + Rh + Sn + IE; NC reported separately Scale, 0–3	N = 294 with PAR to HDM Mean age, 29 y (12–70 y) Mean duration AR, not specified At entry, TSS ≥5	TNSS: P, −29.5; LCET, −44.7
Simons et al,[51] 2003	R, MC, DB, PC, PG DES, 5 mg (n = 337), P (n = 339); both once daily 4 wk, 4–14 d RI Efficacy: TSS = Rh + NI + Sn + PND + ocular Sx + IE/itchy palate; NC reported separately Scale, 0–3	N = 634 with PAR Mean age, 34.8 y (11–79 y) Mean duration of AR, not specified At entry, TSS + NC ≥10; NC ≤2	rTSS: P, −32.3; DES, −37.9
Sy,[56] 1979	DB, PG, PC TX: FLU, 2 sprays per nostril (300 μg/day total, n = 38), P (n = 29); both 3 times daily 6 wk (2 wk BL) Efficacy: Change from BL in average h/d with Sx and in d with Sx lasting >1 h Sx: Sn, NC (stuffy nose), Rh (runny nose), nose-blowing, PND Scale, 1 = absent, 2 = mild, 3 = moderate, 4 = severe	N = 67 with PAR Average age, 36.7 y (16–65 y) Mean duration of AR, not specified At entry, not specified	% change from BL, d with Sx lasting >1 h Sneezing: FLU, −15.8, *P,* +6.8 Stuffy nose: FLU, −21, P, 0 Runny nose: FLU, −22.1, *P,* +5.8 Nose-blowing: FLU, −23.2, *P,* +12.5
Children with SAR, percentage change at 2 weeks			
deBlic et al,[24] 2005	R, MC, DB, PC TX: LCET, 5 mg (n = 89), P (n = 88); both once daily 6 wk (1 wk RI) Efficacy: TSS = Sn + Rh + NI + IE Scale, 0–3	N = 177 children with SAR Mean age, 9.9 y (6–13 y) Mean duration AR, not specified At entry, TSS ≥6	TNSS: P, −25.0; LCET, −46.4

Table 3. Continued

Study	Design	Patients	Percentage change from baseline
Razi et al,[50] 2006	R, DB, PG TX: MON, 5 mg (n = 29), P (n = 28); both once daily 2 wk (1 wk RI) Efficacy: DT-TNSS; NT Score = NC on awakening + difficulty sleeping + NT awakenings; composite score = DT-TNSS + NT score Scale, 0–3	N = 57 children with SAR Mean age, 11.5 y (8–13 y) Mean duration AR, 3 y (3–5 y) At entry, not specified	DT-NSS: P, −2.0; MON, − 38.3 Composite: P, −5.1; MON, −36.8
Strem et al,[54] 1978	R, DB, PC TX: FLU, 1 spray (25 μg) per nostril (150 μg total per day), P; both 3 times daily (N per group not specified) 4 wk, 2 wk BL Efficacy: individual Sx: Sn, NC (stuffy nose), Rh (runny nose) measured as Change from BL, during TX week 2; also, days when Sx present >2 h, and days when Sx absent	N = 48 children with SAR to ragweed Mean age, 10.5 y (6–15 y) Mean duration AR, not specified At entry, not specified	% change from BL, days when Sx absent: Sn: FLU, +23.8, P, −29.2 NC (stuffy nose): FLU, + 77.3, P, −51.6 Rh (runny nose): FLU, + 49.3, P, −17.8 % change from BL, days when Sx present >2 h: Sn: FLU, −62.5, *P,* +80 NC (stuffy nose): FLU, −55, *P,* +21.8 Rh (runny nose): FLU, −65.9, *P,* +31.5
Wahn et al,[59] 2003	R, MC, DB, PC, PG TX: FEX, 30 mg (N = 464), P (n = 471); both twice daily 2 wk (1 wk SBRI) Efficacy: TSS = Sn + Rh + ocular Sx + IE and INPT; NC reported separately Scale, 0–4	N = 935 children with SAR (271 had PAR, asthma ok) Mean age, 8.8 y (5–12 y) Mean duration AR, not specified At entry, rTSS ≥6, ≥2 Sx ≥2	Morning rTSS, no NC: P, −13.2; FEX, −24.6
Children with PAR, percentage change at 4 weeks			
Chen et al,[21] 2006	R, DB, PC TX: MON, 4 mg (n = 20), CET, 5 mg (n = 20), P (n = 20); all once daily 12 wk (RI/BL not specified) Efficacy: TSS = TNSS + throat itch + IE + conjunctival hyperemia + tearing Scale, 0–3	N = 60 children (2–6 y) with PAR to HDM (≥6 mo history) Mean age, 4.4–4.5 y (2–6 y) Mean duration AR, not specified At entry, not specified	TSS: P, −8.5; CET, −15.9; MON, −15.0 12 wk: P, −8.5; CET, −43.5; MON, −33.9
Potter et al,[46] 2005	R, DB, PC TX: LCET, 5 mg (n = 154), P (n = 152); both once daily 4 wk (1 wk RI) Efficacy: TSS = Sn + Rh + NI + IE Scale, 0–3	N = 306 children with PAR to HDM Mean age, 9.9 y (6–12 y) Mean duration AR, not specified At entry, TSS ≥5	TNSS: P, −17.6, LCET, −25.8

Abbreviations: AR, allergic rhinitis; AST, astemizole; AZE, azelastine; BDP, beclomethasone dipropionate; BL, baseline; BUD, budesonide; C, controlled; CET, cetirizine; CO, crossover; CROM, cromolyn sodium; DB, double-blind; DD, double dummy; DES, desloratadine; DM, double masked; DR, dose-ranging; DT, daytime; EB, ebastine; EEU, environmental exposure unit; FEX, fexofenadine; FF, fluticasone furoate; FLU, fluticasone; FP, fluticasone propionate; HDM, house dust mite; HRQL, health-related quality of life; IE, itchy eyes (also referred to as ocular pruritus); Inh, inhaled; IN, intranasal; INPT, itchy nose/palate/throat; LCET, levocetirizine; LEVO, levocabastine; LOR, loratadine; MC, multicenter; MON, montelukast; NC, nasal congestion (also referred to as nasal stuffiness, nasal obstruction, or nasal blockage); NI, nasal itching (also referred to as nasal pruritus); NIS, nasal index score; OA, onset of action; OL, open-label; PAR, perennial allergic rhinitis; PC, placebo-controlled; PG, parallel group; PND, postnasal drip; PSE, pseudoephedrine; r, reflective; R, randomized; RE, red eyes; Rh, rhinorrhea (also referred to as runny, drippy nose, or nasal discharge); RI, run in; RQLQ, Rhinitis Quality of Life Questionnaire; SAR, seasonal allergic rhinitis; SBRI, single-blind run-in; Sn, sneezing; Sx, symptoms; TAA, triamcinolone acetonide; TNSS, total nasal symptom score (NI + Sn + NC + Rh); TX, treatment; VAS, visual analog scale; WIRE, watery, itchy, red eyes; WE, watery eyes; WO, washout.

Table 4. Number of Studies and Aggregated Number of Patients Included in the Statistical Analyses by Medication Class (Monotherapy at Approved Dosages) and Type of Allergic Rhinitis

Medication	SAR		PAR		Total	
	No. of studies	No. of patients	No. of studies	No. of patients	No. of studies	No. of patients
Nasal antihistamines	8	1,125	0		8	1,125
Oral antihistamines	14	2,224	4	737	18	3,698
LTRAs	3	698	2	40	5	738
Intranasal steroids	7	597	4	600	11	1,197
Placebo	17	2,439	7	1,023	24	3,462
Total[a]	25	7,083	8	2,400	33	9,483

Abbreviations: LTRA, leukotriene receptor antagonist; PAR, perennial allergic rhinitis; SAR, seasonal allergic rhinitis.
[a] The number of studies exceeds the number of published reports because Lumry et al[24] and Ciebada et al[24] each described 2 studies that were included in the analyses.

Statistical Findings

The number of studies and the aggregated number of patients included in statistical analyses for each class of medication are given in Table 4. Data were limited for PAR studies overall and for SAR studies of LTRAs. Pediatric data were insufficient for statistical analysis.

Patient demographics for the studies included in the statistical analyses were similar to those cited herein for the full body of data. The mean duration of AR for 14 SAR studies in which it was reported was 16.4 years (range, 7.5–20 years) for adults and adolescents. All PAR studies in which duration was described herein were included in statistical analyses. The mean ages of the adults and adolescents was 34.3 years (range, 26–40 years) in the SAR studies and 32.6 years (range, 28.9–36.8 years) in the PAR studies.

TNSSs

Two-week data for TNSSs for SAR studies were available by treatment class for oral antihistamines, nasal antihistamines, INSs, LTRAs, and placebo (Fig 2). The overall trend observed for reduction in TNSSs shows INSs greater than LTRAs greater than antihistamines equal to nasal antihistamines greater than placebo, but the ranges for the individual treatments are substantial and overlap. The greatest reductions in TNSS occurred with INSs (median, −43.7%; range, −24.5% to −50.0%; $P < .001$) compared with all other treatment classes (Fig 2A). The remaining active treatments all produced reductions of 20% or greater, with wide and overlapping ranges. Only 3 studies met the inclusion criteria for LTRAs; the data are indicative only and should be interpreted with caution. Across the studies, the median reduction in TNSS with placebo was −15.0% (range, −7.6% to −40.0%). Dispersion, measured using the IQR to reduce the effect of outliers, was greatest for oral antihistamines and least for nasal antihistamines.

The 4- to 6-week data for PAR studies were available for oral antihistamines, INSs, and placebo (Fig 2B), with an indicated trend of oral antihistamines greater than INSs greater than placebo. Again, there was wide variability and overlap in the ranges. The median reduction in TNSS was −51.5% (range, −23.7% to −62.0%) for oral antihistamines compared with −37.3% (range, −32.3% to −42.4%) for INSs and −24.8% (range, −14.4% to −37.2%) for placebo. Between-treatment class differences were statistically significant for oral antihistamines compared with placebo at the $P = .05$ significance level. Dispersion was greatest for oral antihistamines.

Individual Nasal Symptom Scores for SAR Studies

Trend analysis for individual symptom scores for the 2-week SAR studies indicates superiority of INSs for all symptoms, with reductions from baseline of approximately 40% or greater (Fig 3). The median reductions from baseline with placebo were 13% to 15% for all symptoms. Data for LTRAs were insufficient for statistical analysis by individual symptom scores, and data for oral antihistamines were limited for all symptoms other than nasal congestion such that interquartile dispersion could not be calculated and interpretation is not clear.

For nasal congestion, the apparent trend was INSs greater than oral antihistamines greater than or equal to nasal antihistamines greater than placebo (Fig 3A). INSs

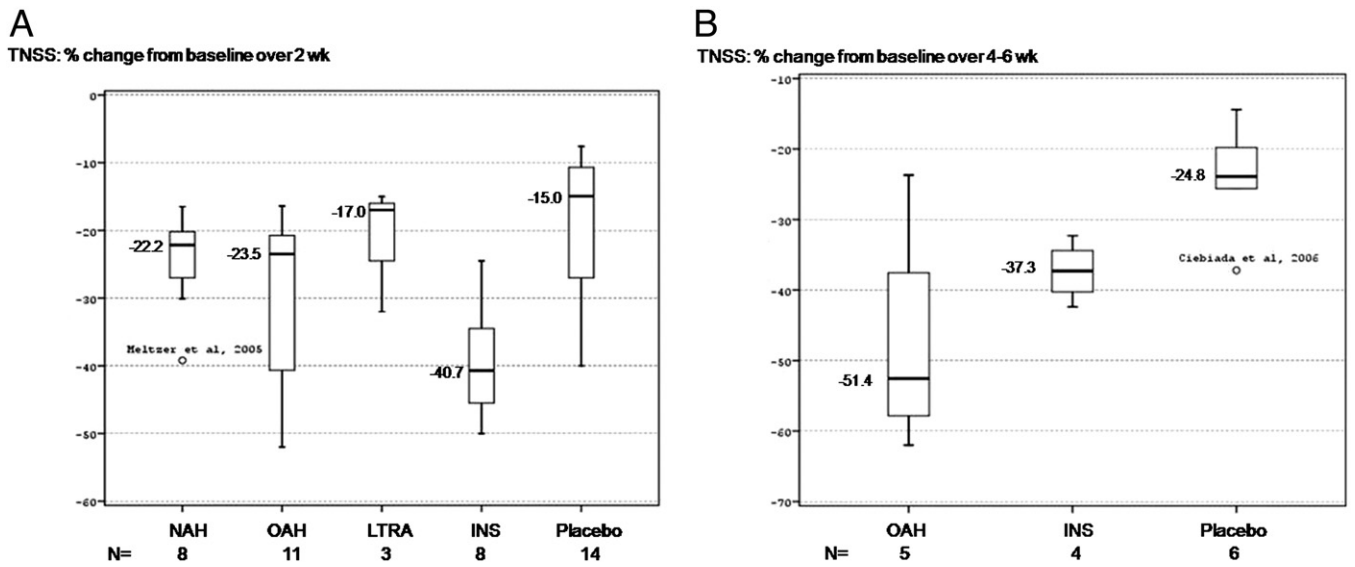

Figure 2. Box plots for the distribution of end-of-treatment scores for total nasal symptom scores (TNSSs). Bold lines represent medians; end points represent minimum and maximum values. Single points show outliers by study. A, Observed values for seasonal allergic rhinitis studies (2-week data). Kruskal-Wallis nonparametric test: $P < .001$ in favor of intranasal steroids (INS) vs all other treatment classes. Leukotriene receptor antagonist (LTRA) data are limited and were not included in the statistical evaluation. B, Observed values for perennial allergic rhinitis studies (4- to 6-week data). Kruskal-Wallis nonparametric test: $P = .03$ in favor of oral antihistamines (OAH) vs placebo. NAH indicates nasal antihistamines.

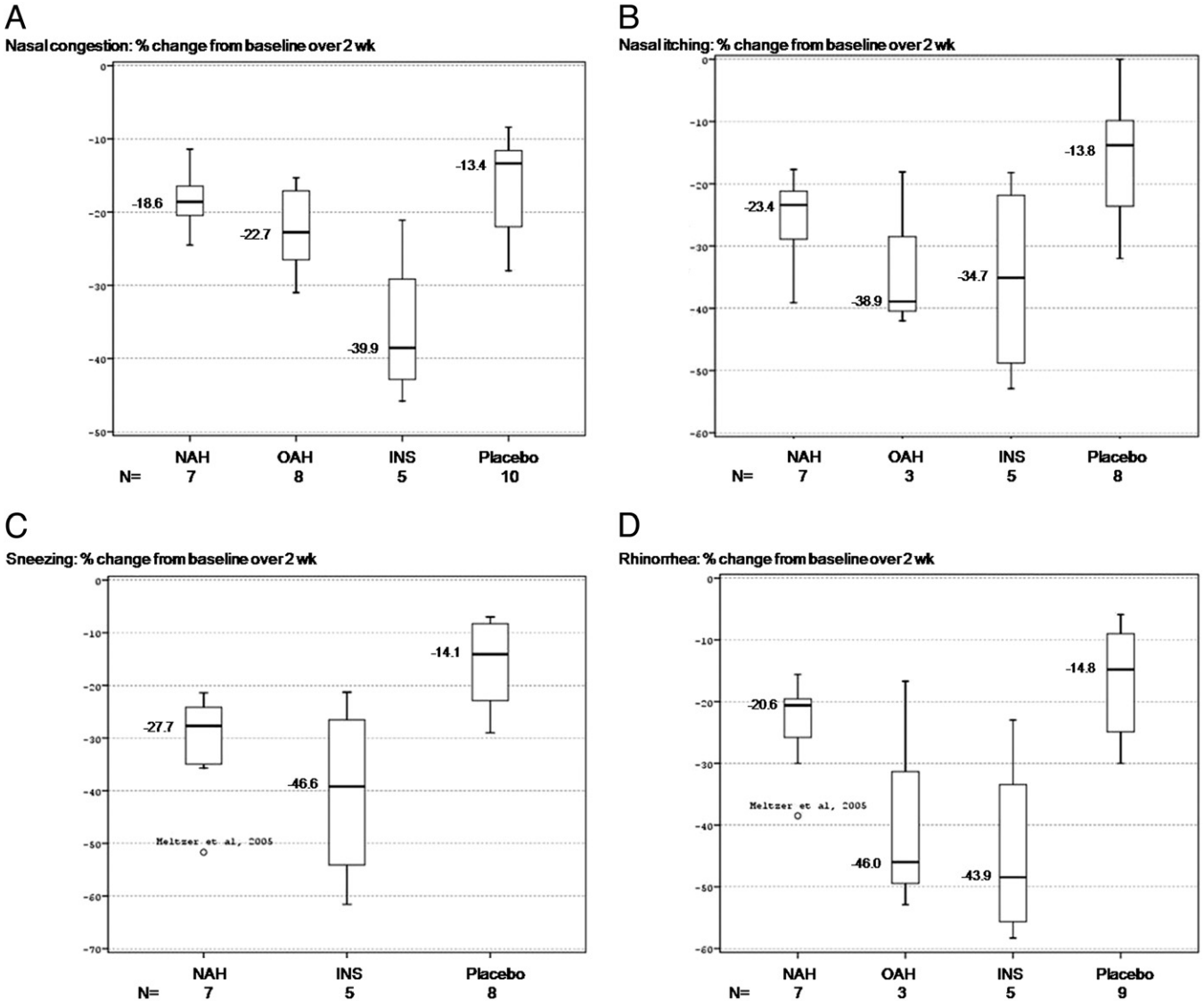

Figure 3. Box plots for the distribution of the observed values for the individual nasal symptoms in the 2-week seasonal allergic rhinitis studies appropriate for statistical evaluation. Bold lines represent medians; end points represent minimum and maximum values. Single points show outliers by study. A, Nasal congestion. Kruskal-Wallis nonparametric test: $P = .007$ in favor of intranasal steroids (INS) vs all other treatment classes. B, Nasal itching. Kruskal-Wallis nonparametric test: $P = .04$ in favor of INS vs placebo. C, Sneezing. Kruskal-Wallis nonparametric test: $P = .02$ in favor of INS vs placebo and nasal antihistamines (NAH). D, Rhinorrhea. Kruskal-Wallis nonparametric test: $P = .01$ in favor of INS vs placebo and NAH. OAH indicates oral antihistamines.

were statistically superior to all other treatment classes ($P = .007$).

For nasal itching, the overall trend is INSs greater than or equal to oral antihistamines greater than nasal antihistamines greater than placebo (Fig 3B), with statistical significance for INSs vs placebo ($P = .04$). Oral antihistamines had a comparable rank value to INSs, but only 3 studies met the inclusion criteria, so the data are indicative and must be interpreted with caution. Dispersion greater than 20% for INSs suggests substantial variability among the studies.

For sneezing, the overall trend is INSs greater than nasal antihistamines greater than placebo (Fig 3C), with statistical significance only for INSs compared with placebo and nasal antihistamines ($P = .02$ for both). Data for oral antihistamines were insufficient for statistical analysis.

For rhinorrhea, the overall trend is oral antihistamines equal to INSs greater than nasal antihistamines greater than placebo (Fig 3D), with statistical significance for INSs compared with placebo and nasal antihistamines ($P = .01$ for both). Only 3 studies met the inclusion criteria for oral

Table 5. Summary Statistics for Percentage Change From Baseline for the Individual Symptom Scores for 4- to 6-Week Perennial Allergic Rhinitis Studies

	No. of studies	Median	Lower quartile	Upper quartile	IQR	Minimum	Maximum
Nasal congestion							
Oral antihistamines	2					−60.8	−43.5
LTRAs	2					−57.3	−45.2
Intranasal steroids	6	−32.7	−39.0	−29.6	−9.4	−46.7	−28.0
Placebo	6	−18.3	−26.5	−11.0	−15.5	−39.2	−6.7
Nasal itching							
Oral antihistamines	2					−72.9	−70.3
LTRAs	2					−72.1	−66.2
Intranasal steroids	4	−47.2				−59.8	−32.9
Placebo	3	−31.7				−44.8	−25.2
Sneezing							
Oral antihistamines	2					−65.6	−48.1
LTRAs	2					−58.5	−51.9
Intranasal steroids	3	−44.0				−51.5	−28.0
Placebo	5	−26.0	−31.3	−12.5	−18.8	−32.3	0.0
Rhinorrhea							
Oral antihistamines	2					−52.7	−50.5
LTRAs	2					−54.3	−43.4
Intranasal steroids	6	−38.0	−47.3	−35.3	−12.0	−57.1	−31.3
Placebo	6	−22.0	−25.9	−14.3	−11.6	−32.7	−14.2

Abbreviations: IQR, interquartile range; LTRA, leukotriene receptor antagonist.

Table 6. Effects of Medication Class on Nasal Symptoms for Seasonal Allergic Rhinitis Based on Systematic Review of the Literature

Medication Class	Sneezing	Itching	Congestion	Rhinorrhea
Oral antihistamines	?	+++[a]	+	+++[a]
Intranasal antihistamines	++	++	+	+
Intranasal steroids	+++	+++	+++	+++
Leukotriene receptor antagonists	?	?	?	?
Cromolyn sodium	?	?	?	?

Symbols: +++, substantial benefit (≥20% difference from placebo); ++, modest benefit (≥10% to 19% difference from placebo); +, Little benefit (≥5% to 10% difference from placebo); +/−, no benefit (<5% difference from placebo); ?, insufficient data.
[a] On the basis of 3 studies; all other data from 5 studies or more.

antihistamines: the data are indicative only and must be interpreted with caution.

Individual Nasal Symptom Scores for PAR Studies

Trend analysis for individual symptom scores is not available for PAR data because of insufficient data for both LTRAs and oral antihistamines (Table 5); appropriate data for calculating the percentage change from baseline are only available for INSs. INSs were statistically superior to placebo for nasal congestion ($P = .04$) and rhinorrhea ($P = .004$); statistical analyses could not be performed for nasal itching and sneezing because of the lack of sufficient data.

DISCUSSION

The data, although limited, confirm that INSs produce the greatest improvements in nasal symptoms in patients with SAR. Table 6 summarizes these data based on clinical benefit assigned as the difference in effect from placebo. INSs are also effective for PAR, but the data were of variable quality, and based on TNSSs, oral antihistamines may be equally effective for some patients.

The lack of appropriate data for statistical analysis is striking and disappointing. On the basis of our criteria, little can be said about the comparative efficacy of LTRAs in clinical studies involving adults and adolescents. Likewise, the data in children are so limited and study methods so variable that no conclusions can be made by medication class for either between-class comparisons or between-age comparisons (ie, adult-child). A Cochrane review of INSs for intermittent and persistent AR in children reported similar findings.[65] Although a large number of randomized controlled trials were identified for the review, few met the set criteria; subsequently, only a descriptive summary of findings could be made because of the insufficient and variable nature of the available data.[65]

The lack of appropriate data for statistical analysis reflects, to a large extent, differences in methods (ie, different severity

scales; different definitions of AR, its symptoms, and total symptom scores), with little (if any) standardization in how studies are reported. Indeed, most studies reported in the published literature do not disclose actual values for symptom scores, which is necessary to calculate percentage changes from baseline for comparisons. In addition, bias in terms of predetermined expectations for study outcomes further complicates data analysis. For example, several studies examining oral antihistamines did not report nasal congestion scores, stating in their "Methods" sections that nasal congestion would not be expected to change.[14,20,23,28,29,39,43] These studies, which defined TNSS as 3 symptoms (nasal itching, sneezing, and rhinorrhea), could not be included in our database. Interestingly, our data indicate that oral antihistamines reduce nasal congestion (median reduction from baseline, −22.7% vs placebo, −13.4%), with little variability among the 8 studies evaluated (IQR, −10.7%); more study is warranted. An agreed-on definition of AR is a necessary starting point for all clinical studies.

This was an extensive, but conservative, exercise, according to the criteria set. Most studies included were of high quality (prospective randomized controlled trials with substantial numbers of patients and well-defined entry criteria and study outcomes).[66] Other evidence-based reviews have been less stringent, even those with statistical analyses, and few have attempted to compare currently used medications in the United States by class. Portnoy et al[67] reported in 2004 a method for developing treatment thresholds for AR therapies and tested it with data from randomized, placebo-controlled studies of nonsedating antihistamines (n = 4), INSs (n = 4), montelukast (n = 1), and azelastine (n = 2) along with allergen immunotherapy (n = 1) and omalizumab (n = 1). This analysis did not specifically control for disease severity or type of study (eg, onset of action vs efficacy), and the outcomes cannot be compared with our findings. However, these authors also cited difficulty with obtaining useful information from the published literature because of insufficient reporting of data.[67]

Systematic reviews and meta-analyses comparing INSs and antihistamines have generally shown INSs to provide greater relief of nasal symptoms than either oral antihistamines[68,69] or nasal antihistamines.[70] A meta-analysis of 16 randomized, double-blind trials of oral antihistamines or INSs for AR reported between 1960 and 1996 showed better outcomes with INSs for all nasal symptoms.[69] However, the analysis did not differentiate studies of SAR from PAR, did not identify a specific treatment period for comparison, and included symptom scores measured on different scales. The authors noted significant heterogeneity in the outcomes for effectiveness that were not related to the use of different INSs or oral antihistamines in the various trials. We tried to control for some of that heterogeneity through our inclusion criteria, and our results support INSs as the most effective medication class for nasal symptoms of SAR based on TNSS. As noted herein, for PAR, our results suggest oral antihistamines may be similarly effective for some patients, a finding that was both surprising and unanticipated. Full analysis is beyond the scope of the current discussion, but further examination is warranted with appropriate controls for population heterogeneity and design inconsistencies.

Considerable overlap was found in the ranges of outcome data, suggesting that some patients responded better than others to specific treatments. Although this type of review cannot distinguish between responders and nonresponders, we looked at response variability in terms of dispersion statistics. Statistically, variation indicated by low IQR values (≤15%, our determination) suggests consistency for observed trends across the studies examined. We believe that IQR values higher than 20% suggest a level of variability among studies that could complicate interpretation of outcomes and that should be examined further. For example, oral antihistamines had an IQR of 23.3% for mean TNSS across ten 2-week SAR studies. Although we looked at class effects only, data from the individual studies (Tables 2 and 3) suggested substantial differences among specific oral antihistamines. This is beyond the discussion or data analysis performed herein but warrants additional review. In addition, INSs had IQR values greater than 20% for all nasal symptoms except congestion across the SAR studies. In this case, the variation likely reflects differences in severity among the SAR patients as described in the entry criteria for the individual studies (Tables 2 and 3), another potential topic for follow-up.

Studies comparing oral and intranasal AR medications used appropriate placebos but often combined the data, which could affect the reported trends. For example, using the appropriate placebo groups (oral, spray) for TNSS in SAR studies (which had sufficient data) yields the following overall trend for the SAR studies: INS greater than nasal antihistamines greater than oral antihistamines, with nasal antihistamines clearly differentiated from oral antihistamines. We did not evaluate other aspects of treatment that, in practice, are important determinants of successful therapy for an individual patient, including onset of action, duration of effect, convenience, preference, and potential adverse effects.

We also did not evaluate the efficacy of combining treatments for patients who have difficulty controlling symptoms of AR while undergoing monotherapy. These treatments are not approved uses in the United States and, thus, did not meet our criteria for evaluation. However, some of the studies included combination arms. Review of the limited data available in Tables 2 and 3 and studies published subsequent to our analysis suggests that there might be some clinical benefit to adding nasal antihistamines to INSs in patients whose conditions are not optimally controlled but no benefit to adding an oral antihistamine to an INS.[11,13,71] The addition of nasal antihistamines to antihistamines does not appear to provide value separate from the use of nasal antihistamines alone, and the data on adding an LTRA to an oral antihistamine were equivocal.[15,33,37,42] Although intriguing, the data are not definitive; more studies are needed to confirm the observations.

A critical take-away from this systematic review is the need for standards in reporting AR studies to allow better comparison. We believe this should include the following: agreed-on inclusion criteria for AR based on a unified definition; agreed-on stratification of disease severity; TNSS based on the 4 nasal symptoms (obstruction, pruritus, rhinorrhea, and sneezing) and reported on a 3-point or 4-point severity scale; standard ocular data for total ocular symptom score; standard quality of life data using a validated survey; and agreed-on age cutoffs (adult studies should include ages ≥18 years; adolescents, 12–18 years old; school-age children, 6–11 years old).

These standards should be used to develop true head-to-head studies with the various classes of medications. In addition, more data are needed for PAR, particularly in relation to comparison of oral antihistamines and INSs. Also, although it was not our purpose to look at the effects of specific treatments within medication classes, the differences between individual oral antihistamines were striking (Tables 2 and 3) and should be revisited.

In conclusion, there is a critical lack of appropriate data for comparison of current medication classes approved to treat AR in the United States, despite a great volume of published studies. The 3 outcomes of this systematic review are that (1) INSs are the most effective treatment for SAR, (2) oral antihistamines may be as effective as INSs for treating PAR, and (3) the reporting of published data should be standardized to permit comparisons among treatments.

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