Original Article

Intranasal Versus Oral Treatments for Allergic Rhinitis: A Systematic Review With Meta-Analysis

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What is already known about this topic? Intranasal and oral medications are part of the mainstay for the treatment of allergic rhinitis. Although intranasal medications are usually recommended, for most of these recommendations, certainty in the evidence was low or very low.

What does this article add to our knowledge? We assessed intranasal corticosteroids or antihistamines versus oral antihistamines or leukotriene receptor antagonists. We found intranasal treatments to be superior to oral interventions at improving nasal and oral symptoms and quality of life.

How does this study impact current management guidelines? This systematic review could help future guideline developers issue recommendations for allergic rhinitis, particularly because the evidence certainty for most comparisons was deemed moderate or high.

BACKGROUND: Treatments for allergic rhinitis include intranasal or oral medications.
OBJECTIVE: To perform a systematic review with meta-analysis comparing the effectiveness of intranasal corticosteroids or antihistamines versus oral antihistamines or leukotriene receptor antagonists in improving allergic rhinitis symptoms and quality of life.

METHODS: We searched four bibliographic databases and three clinical trial datasets for randomized controlled trials (1) assessing patients aged 12 years and older with seasonal or perennial allergic rhinitis, and (2) comparing intranasal corticosteroids or antihistamines versus oral antihistamines or leukotriene receptor antagonists. We performed a meta-analysis of the Total Nasal Symptom Score (TNSS), Total Ocular

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Abbreviations used
AE- Adverse event
AR- Allergic rhinitis
ARIA- Allergic Rhinitis and its Impact on Asthma
CoE- Certainty of evidence
GRADE- Grading of Recommendations, Assessment, Development, and Evaluation
INAH- Intranasal antihistamines
INCS- Intranasal corticosteroids
LTRA- Leukotriene receptor antagonists
MD- Mean difference
OAH- Oral antihistamines
PAR- Perennial allergic rhinitis
RQLQ- Rhinoconjunctivitis Quality of Life Questionnaire
RCT- Randomized controlled trial
RoB- Risk of bias
SAR- Seasonal allergic rhinitis
TNSS- Total Nasal Symptom Score
TOSS- Total Ocular Symptom Score
TSS- Total Symptom Score

Symptom Score, Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ), development of adverse events, and withdrawals owing to adverse events. Certainty of evidence was assessed using Grading of Recommendations, Assessment, Development, and Evaluation.

RESULTS: We included 35 studies, most of which assessed patients with seasonal allergic rhinitis and displayed an unclear risk of bias. Superiority of intranasal treatments was found for all assessed outcomes. Intranasal corticosteroids were more effective than oral antihistamines at improving the TNSS (mean difference [MD], −0.86; 95% CI, −1.21 to −0.51; I^2 = 70%), Total Ocular Symptom Score (MD, −0.36; 95% CI, −0.56 to −0.17; I^2 = 0%), and RQLQ (MD, −0.88; 95% CI, −1.15 to −0.61; I^2 = 0%), which were mostly associated with clinically meaningful improvements. Superiority of intranasal corticosteroids at improving the TNSS was also found against oral leukotriene receptor antagonists (MD, −1.05; 95% CI, −1.33 to −0.77). Intranasal antihistamines were more effective than oral antihistamines at improving the TNSS (MD, −0.47; 95% CI, −0.81 to −0.14; I^2 = 0%) and RQLQ (MD, −0.31; 95% CI, −0.56 to −0.06; I^2 = 0%).

CONCLUSIONS: Randomized controlled trials suggest that intranasal treatments are more effective than oral treatments at improving symptoms and quality of life in seasonal allergic rhinitis. **(J Allergy Clin Immunol Pract 2024;■:■-■)**

Key words: *Allergic rhinitis; Intranasal corticosteroids; Intranasal antihistamines; Oral antihistamines; Leukotriene receptor antagonists; Meta-analysis; GRADE approach*

INTRODUCTION

Intranasal and oral medications are part of the mainstay for the treatment of allergic rhinitis (AR). In particular, the 2020 Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines favor the use of intranasal medications in patients with moderate to severe disease, because they appear to have a faster onset of action and higher effectiveness compared with oral medications.[1] Nonetheless, for most of these recommendations, the certainty of evidence (CoE) was considered low or very low.[1,2] Similarly, although the US 2020 Practice Parameter for Allergic Rhinitis favors using intranasal corticosteroids (INCS) as first-line therapeutics, statements (and the respective evidence) on the comparison between them and oral interventions are lacking.[3] Whereas there have been studies comparing nasal and oral medications, not all used the same methods for outcome assessment and they exhibited inconsistent methodologic rigor.[2] Furthermore, high-quality recent systematic reviews on this topic are missing. A previous systematic review was published in 1998 and compared only INCS with oral antihistamines (OAH),[4]

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whereas another review was limited to studies published after 2003 and excluded studies based on the publication language.[5]

In the context of the 2024 revision of the ARIA guidelines (focusing on the pharmacologic treatment and management of AR), we aim, in this systematic review, to assess the comparative effectiveness and safety of intranasal and oral medications for AR.

METHODS

This systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines.[6] Its protocol is available in PROSPERO (CRD42023495296) and was published elsewhere.[7] A full description is provided in the Supplemental Methods (in this article's Online Repository at www.jaci-inpractice.org).

Eligibility criteria

We included randomized controlled trials (RCTs) with a parallel design assessing patients aged 12 years and older with seasonal allergic rhinitis (SAR) or perennial allergic rhinitis (PAR), comparing intranasal medications (INCS, antihistamines [INAH], and fixed combinations of INCS plus INAH) and oral medications (OAH and leukotriene receptor antagonists [LTRA]) on at least one of the following patient-reported outcome measures: Total Nasal Symptom Score (TNSS), Total Ocular Symptom Score (TOSS), Total Symptom Score (TSS), or Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ). For all these outcomes, an increased score is associated with worsening AR. We included RCTs with a follow-up of at least 2 weeks for SAR and at least 4 weeks for PAR.

Information sources and search strategy

We conducted a systematic search (see Table E1 in this article's Online Repository at www.jaci-inpractice.org) on MEDLINE, Embase, Web of Science, and the Cochrane Central Register of Controlled Trials from database inception to August 2022 (with an updated search in September 2023). We also manually searched the clinicaltrials.gov platform, the GlaxoSmithKline clinical study dataset, and the AstraZeneca Clinical Trials web site.

Study selection and data collection

After removing duplicates, two authors independently accessed each record for eligibility, first by title and abstract and then by full-text reading. Data from each included study were independently extracted by two reviewers using a dedicated online form. Disagreements between reviewers were resolved by a third reviewer.

Risk of bias and critical appraisal of evidence

The risk of bias (RoB) in each included study was independently assessed by two reviewers using the Cochrane RoB tool.[8] Disagreements were resolved by a third reviewer. We assessed the CoE of the different effectiveness outcomes using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.[9]

Quantitative synthesis of results

All outcomes assessed are presented as means (±SDs) at baseline and as values for change from baseline. Safety outcomes are described using absolute and relative frequencies.

For effectiveness outcomes, we performed random-effects meta-analyses of mean differences (MDs) in values for change from baseline. For meta-analytical purposes, we considered only the TNSS to be calculated based on the sum of four symptoms (nasal congestion, itching, sneezing, and rhinorrhea) and the TOSS to be calculated based on the sum of three symptoms (eye itching/burning, tearing/watering, and redness). We conducted an additional analysis for safety outcomes by performing random-effects meta-analyses of risk ratios (RRs). All analyses were performed for SAR. Owing to the insufficient number of included studies, limitations in reporting patient subgroups, and heterogeneity in outcomes, meta-analyses were not performed for PAR.

We used the restricted maximum likelihood approach to estimate between-study variance. Heterogeneity was assessed by estimating the Q-Cochran test P value and the I^2 statistic. We conducted sensitivity analyses to assess the robustness of findings. These included analyses comparing pooled estimates versus those obtained excluding studies with a high risk of bias, studies with imputed SD, studies for which outcomes were not reported at 2 weeks of follow-up, and analyses focusing on specific drug comparisons within each class (eg, individual INCS vs individual OAH).

For subgroup analyses suggesting the existence of effect modification on effectiveness outcomes, the credibility of such an effect modification was assessed using the Instrument to Assess the Credibility of Effect Modification Analyses in a meta-analysis of RCT tool.[10]

We applied a complementary approach to compute the probability that for each pair of interventions, differences would correspond to large, moderate, small, or trivial (no meaningful) effects.[11]

RESULTS

We retrieved 4,631 records from database searches and 55 from clinical trials register databases (Figure 1). After deduplication, 2,998 records were screened and 84 were assessed for eligibility. A total of 35 different studies (published in 49 publications/reports) were included in the systematic review. The characteristics and quantitative results of included studies are summarized in Table I; (see Tables E2-E4 in this article's Online Repository at www.jaci-inpractice.org). We included 25 studies assessing the TNSS, 20 of which reported data on the change from baseline, or baseline and posttreatment, on the four-symptom TNSS and were included in quantitative meta-analysis. Regarding the TOSS, we included a total of seven studies, five of which reported data on the change from baseline, or baseline and posttreatment, on the three-symptom TOSS and were included in quantitative meta-analysis. Twelve studies assessed the TSS, but none were included in quantitative meta-analysis owing to heterogeneity in included symptoms and scale. Finally, we included six studies that assessed the RQLQ, four of which reported data on the change from baseline, or baseline and posttreatment, and were included in the meta-analysis. We found only two studies investigating patients with PAR, but they reported only TSS data. Because of differences in the definition of the TSS, we did not perform a meta-analysis of studies on PAR; all meta-analytical results concerned SAR.

Risk of bias

Figure 2 displays the results of the RoB assessment for the included studies. Overall, the domains most frequently classified as being associated with a low RoB were blinding of participants and personnel, blinding of outcome assessment, and completeness of outcome data. The domains most frequently classified as having an unclear risk of bias were random sequence generation and allocation concealment. This was primarily because of inadequate reporting of these aspects in the included studies rather than a clear indication of bias. On the other hand, the

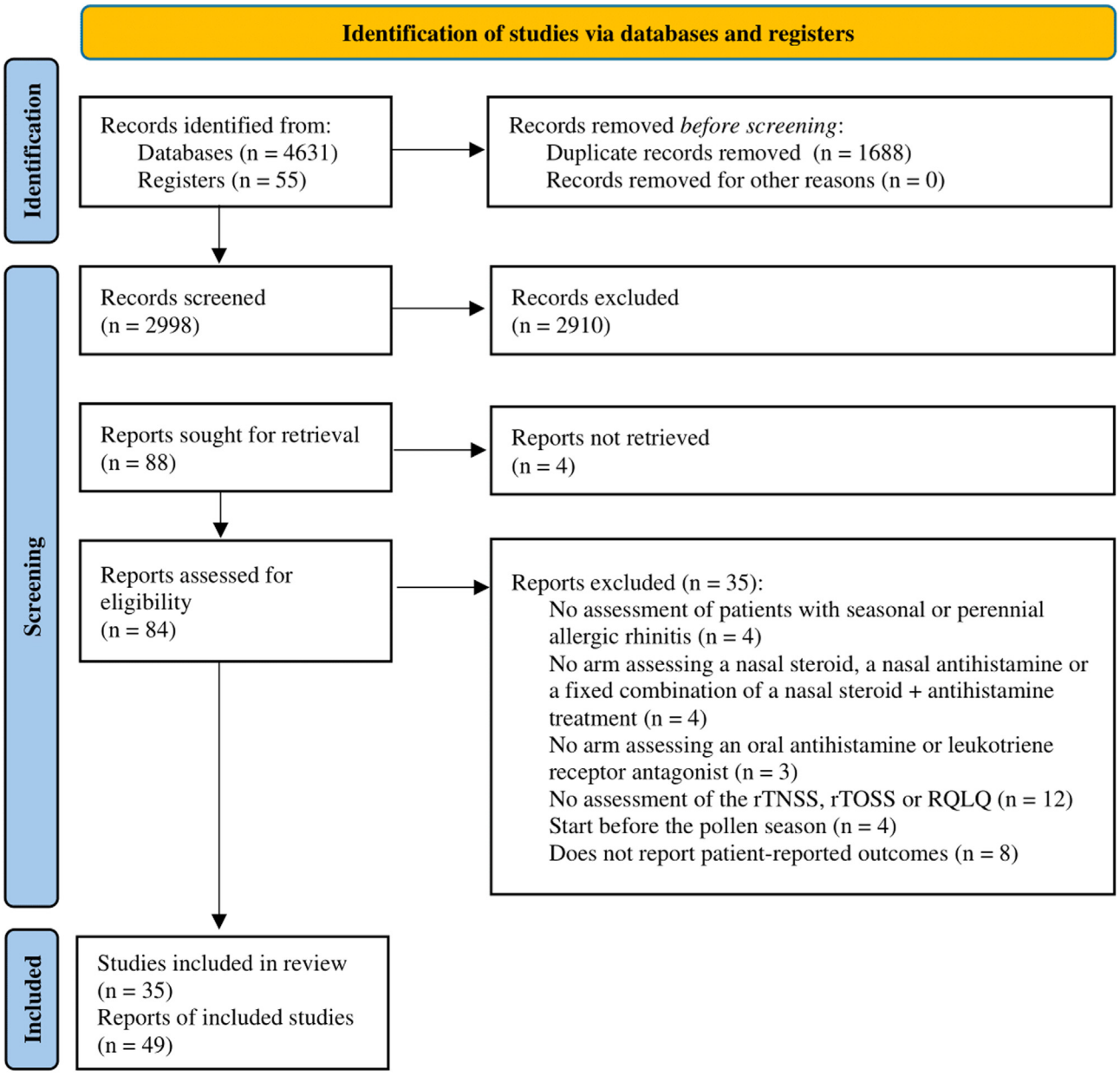

FIGURE 1. Preferred Reporting Items for Systematic Reviews and Meta-analysis flow diagram for study selection. *RQLQ*, Rhinoconjunctivitis Quality of Life Questionnaire. *rTNSS*, Reflective Total Nasal Symptom Score; *rTOSS*, Reflective Total Ocular Symptom Score.

domain most frequently classified as associated with a high risk of bias was selective reporting.

Effectiveness outcomes

Figure 3 shows the main meta-analytical results. Here, we describe the results for the different comparisons for each outcome.

Total Nasal Symptom Score: INAH versus OAH. Three studies (n = 878 participants) comparing INAH and OAH were included in the meta-analysis of TNSS (Figure 4).[12-14] All of these RCTs assessed azelastine as the INAH, whereas the OAH was either cetirizine or desloratadine. All studies had a follow-up of 2 weeks and were classified as having an unclear RoB.

Antihistamines were more effective than OAH at improving the TNSS (MD, −0.47; 95% CI, −0.81 to −0.14; I^2 = 0%), with a probability of 44% of a clinically meaningful improvement (high CoE) (see Table E5 in this article's Online Repository at www.jaci-inpractice.org). Results were consistent in sensitivity analyses after the exclusion of studies with imputed SDs (see Table E6 in this article's Online Repository at www.jaci-inpractice.org).

TABLE I. Characteristics of included studies

Study identification	Disease assessed	Place and period of data collection	Nasal treatment and total daily dose (regimen)	Oral treatment and total daily dose (regimen)	Assessed outcomes	Follow-up	*N* participants			Completers, n (%)	Females, n (%)	Mean age, y	Risk of bias
							Total	Nasal treatment	Oral treatment				
Intranasal antihistamines vs oral antihistamines													
Corren, 2005[12]	Seasonal allergic rhinitis	United States; 2004 fall allergy season	Azelastine NA† (2 sprays/nostril BID)	Cetirizine 10 mg (QD)	rTNSS RQLQ	2 wk	307	152	155	299 (97.4)	190 (35.5)	35	Unclear
Berger, 2006[13]	Seasonal allergic rhinitis	United States; 2005 spring allergy season	Azelastine NA† (2 sprays/nostril BID)	Cetirizine 10 mg (QD)	rTNSS RQLQ	2 wk	354	179	175	345 (97.5)	205 (57.9)	35	Unclear
Ratner, 1994[14]	Seasonal allergic rhinitis	United States; mountain cedar pollen season (January to February, before 1994)	Azelastine 0.55 mg (2 sprays/nostril QD) Azelastine 1.1 mg (2 sprays/nostril BID)	Chlorpheniramine maleate 24 mg (BID)	rTSS	2 wk	187	125‡	62	—§	83 (44.4)	37.7	Unclear
Storms, 1994[15]	Seasonal allergic rhinitis	United States; 1990 (May to August)	Azelastine 0.55 mg (2 sprays/nostril QD) Azelastine 1.1 mg (2 sprays/nostril BID)	Chlorpheniramine maleate 24 mg (BID)	rTSS	2 wk	186	124‖	62	—§	82 (44.1)	32.7	Unclear
LaForce, 1996[16]	Seasonal allergic rhinitis	United States; April to July (before 1994)	Azelastine 0.52 mg (2 sprays/nostril QD) Azelastine 1.04 mg (2 sprays/nostril BID)	Chlorpheniramine maleate 24 mg (BID)	rTSS	4 wk	197	132¶	65	—§	82 (41.6)	29.9	High
Berger, 2003[17]	Seasonal allergic rhinitis	United States; 2002 fall allergy season	Azelastine NA† (2 sprays/nostril BID)	Desloratadine 5 mg	rTNSS	2 wk	219	108	111	—§	139 (63.5)	34.2	Unclear
Antépara, 1998[18]	Seasonal allergic rhinitis	Spain; 1994 (April to August)	Azelastine 0.56 mg (2 sprays QD)	Ebastine 10 mg (QD)	rTSS	2 wk	110	56	54	102 (92.7)	40 (36.4)	31	High
Gastpar, 1994[19]	Seasonal allergic rhinitis	Germany; 1987 (April to October)	Azelastine 0.56 mg (1 spray/nostril BID)	Terfenadine 120 mg (BID)	rTSS	6 wk	167	81	86	162 (97)	59 (35.3)	29.9	Unclear
Gastpar, 1994[19]	Perennial allergic rhinitis	Germany; 1987 to 1997 (May to January)	Azelastine 0.56 mg (1 spray/nostril BID)	Terfenadine 120 mg (BID)	rTSS	6 wk	52	25	27	49 (94.2)	19 (36.5)	30.5	Unclear
Intranasal corticosteroids vs oral antihistamines													
Bhatia, 2005[20]	Seasonal allergic rhinitis	United States; 2003 spring allergy season (March to June)	Budesonide 64 µg (QD)	Desloratadine 5 mg (QD)	rTSS RQLQ	2 wk	61	30	31	61 (100)	33 (54.1)	26	Unclear
Munch, 1983[21]	Seasonal allergic rhinitis	Denmark; 1982 grass pollen season (June)	Budesonide 400 µg (2 sprays/nostril BID)	Dexchlorpheniramine maleate 12 mg (BID)	rTNSS	3 wk	61	—#	—#	60 (98.4)	30 (49.2)	29	Unclear
Kulapaditharom, 2010[22]	Perennial allergic rhinitis	Thailand; NA*	Budesonide 256 mg (2 sprays/nostril QD)	Levocetirizine 5 mg (QD)	rTSS	4 wk	100	50	50	100 (100)	74 (74)	35.7	Unclear
Kim, 2015[23] (NCT01430260)	Seasonal allergic rhinitis	South Korea; 2011 to 2012 (January to July)	Ciclesonide 200 µg (QD)	Levocetirizine 5 mg (QD)	rTNSS	2 wk	49	28	21	—§	—§	—§	High

(continued)

TABLE I. *(Continued)*

Study identification	Disease assessed	Place and period of data collection	Nasal treatment and total daily dose (regimen)	Oral treatment and total daily dose (regimen)	Assessed outcomes	Follow-up	*N* participants			Completers, n (%)	Females, n (%)	Mean age, y	Risk of bias
							Total	Nasal treatment	Oral treatment				
Andrews, 2009[24] (NCT00435461)	Seasonal allergic rhinitis	United States; 2006 to 2007 mountain cedar allergy season	Fluticasone furoate 110 μg (QD)	Fexofenadine 180 mg (QD)	rTNSS rTOSS	2 wk	623	312	311	585 (93.9)	408 (65.5)	38.7	Unclear
Andrews, 2009[24] (NCT00502775)	Seasonal allergic rhinitis	United States; 2007 ragweed pollen season	Fluticasone furoate 110 μg (QD)	Fexofenadine 180 mg (QD)	rTNSS rTOSS	2 wk	451	224	227	423 (93.8)	287 (63.6)	34.2	Unclear
Géhanno, 1997[25] (FNM40071)	Seasonal allergic rhinitis	France; 1991 (March 15 to August 20)	Fluticasone propionate 200 μg (2 sprays/ nostril QD)	Loratadine 10 mg (QD)	rTNSS	4 wk	114	57	57	103 (90.4)	63 (55.3)	39	Unclear
Vervloet, 1997[26]	Seasonal allergic rhinitis	France; NA*	Fluticasone propionate 200 μg (2 sprays/ nostril QD)	Cetirizine 10 mg (QD)	rTSS	3 wk	238	120	118	237 (99.6)	123 (51.7)	29	High
Mackowiak, 1994[27] (FLN-412)	Seasonal allergic rhinitis	United States; 1992 (March to July)	Fluticasone propionate 200 μg (QD)	Astemizole 10 mg (QD)	rTNSS	4 wk	202	102	100	181 (89.6)	93 (46)	32.1	Unclear
Alvarado-Valdés, 1997[28] (FLN-411)	Seasonal allergic rhinitis	United States; 1991 (July to October)	Fluticasone propionate 200 μg (2 sprays/ nostril QD)	Astemizole 10 mg (QD)‡‡	rTNSS	2 wk	207	105	102	189 (91.3)	88 (42.5)	31.9	High
Ford, 2015[29] (NCT01916226; GSK: 200165)	Seasonal allergic rhinitis	United States; 2013 fall allergy season (August 1 to October 16)	Fluticasone propionate 200 μg (2 sprays/ nostril QD)	Cetirizine 10 mg (QD)	rTSS rTNSS rTOSS	2 wk	340	170	170	338 (99.4)	209 (61.5)	39.7	Unclear
Ratner, 1998[30] (FLTA4006)	Seasonal allergic rhinitis	United States; 1995 to 1996 (January to February)	Fluticasone propionate 200 μg (2 sprays/ nostril QD)	Loratadine 10 mg (QD)	rTNSS RQLQ	2 wk	300	150	150	284 (94.7)	163 (54.3)	40.4	High
Stricker, 1998[31] (FLTA4024)	Seasonal allergic rhinitis	United States; 1997	Fluticasone propionate 200 μg (QD)	Loratadine 10 mg (QD)	rTNSS rTOSS	2 wk	327	161	166	312 (95.4)	193 (59)	34.3	Unclear
FNM30034, 2003[32]	Seasonal allergic rhinitis	United States; 2001 (March to June)	Fluticasone propionate 200 μg (2 sprays/ nostril QD)	Loratadine 10 mg (QD)	rTOSS	4 wk	321	158	163	296 (92.2)	211 (65.7)	35.2	Unclear
Bernstein, 2004[33] (FNM30033)	Seasonal allergic rhinitis	United States; 2001 (March to July)	Fluticasone propionate 200 μg (2 sprays/ nostril QD)	Loratadine 10 mg (QD)	rTOSS	4 wk	316	158	158	286 (90.5)	189 (59.8)	34.2	Low
FLTA4004, 2005[34]	Seasonal allergic rhinitis	United States; NA*	Fluticasone propionate 200 μg (2 sprays/ nostril QD)	Loratadine 10 mg (QD)	rTNSS	4 wk	221	109	112	205 (92.8)	96 (43.4)	35.3	Unclear
Bronsky, 1996[35] (FLN-402)	Seasonal allergic rhinitis	United States; spring allergy season (February to May)	Fluticasone propionate 200 μg (2 sprays/ nostril QD)	Terfenadine 120 mg (BID)	rTNSS	4 wk	233	117	116	214 (91.8)	103 (44.2)	30	Unclear
van Bavel, 1994[36] (FLN-401)	Seasonal allergic rhinitis	United States; 1990 to 1991 (December to March)	Fluticasone propionate 200 μg (2 sprays/ nostril QD)	Terfenadine 120 mg (BID)	rTNSS	2 wk	155	78	77	146 (94.2)	81 (52.3)	39.5	Unclear
Anolik, 2008[37] (NCT03855228)	Seasonal allergic rhinitis	United States; 1995 spring allergy season (March to August)	Mometasone furoate 200 μg (QD)	Loratadine 10 mg (QD)	rTSS rTNSS	2 wk	357	176	181	342 (95.8)	180 (50.4)	25.4	Unclear

Nathan, 2009[38]	Seasonal allergic rhinitis	United States; NA*	Mometasone furoate 200 µg (QD)	Loratadine 10 mg (QD)	rTNSS rTOSS	2 wk	—‡‡	—**	—**	340	—**	—**	Unclear
Bernstein, 1996[39]	Seasonal allergic rhinitis	United States; ragweed pollen season	Triamcinolone acetonide 220 µg (2 sprays/ nostril QD)	Astemizole 10 mg (QD)	rTNSS	4 wk	239	120	119	215 (90)	128 (53.6)	35.7	Unclear
Schoenwetter, 1996[40]	Seasonal allergic rhinitis	United States; ragweed pollen season	Triamcinolone acetonide 220 µg (2 sprays/ nostril QD)	Loratadine 10 mg (QD)	rTNSS	4 wk	298	149	149	268 (89.9)	172 (57.7)	31.3	Unclear
Gawchik, 1997[41]	Seasonal allergic rhinitis	United States; NA*	Triamcinolone acetonide 220 µg (2 sprays/ nostril QD)	Loratadine 10 mg (QD)	rTNSS	4 wk	305	152	153	276 (90.5)	174 (57)	33.1	Unclear
Condemi, 2000[42]	Seasonal allergic rhinitis	United States; grass pollen allergy season	Triamcinolone acetonide 220 µg (2 sprays/ nostril QD)	Loratadine 10 mg (QD)	rTNSS RQLQ	4 wk	351	175	176	317 (90.3)	193 (55)	32	Unclear
Intranasal corticosteroids vs oral leukotriene receptor antagonists													
Lu, 2009[43]	Seasonal allergic rhinitis	United States; 1998 (April to June)	Beclomethasone 400 µg (BID)	Montelukast 10 mg (QD) Loratadine 10 mg (QD)	rTSS rTNSS RQLQ	2 wk	401	173	228††	394 (98.3)	251 (62.6)	34.7	High
Ratner, 2003[44] (FNM40195)	Seasonal allergic rhinitis	United States; 2001 to 2002 mountain cedar allergy season (December 12 to February 26)	Fluticasone propionate 200 µg (QD)	Montelukast 10 mg (QD)	rTNSS	2 wk	705	353	352	673 (95.5)	439 (62.3)	38.2	High
Martin, 2006[45]	Seasonal allergic rhinitis	United States; 2001 to 2002 mountain cedar allergy season (December 11 to February 15)	Fluticasone propionate 200 mcg (QD)	Montelukast 10 mg (QD)	rTNSS	2 wk	736	367	369	698 (94.8)	463 (63)	39.7	Unclear

BID, twice per day; *NA*, not available; *QD*, once per day; *RQLQ*, Rhinoconjunctivitis Quality of Life Questionnaire; *rTNSS*, Reflective Total Nasal Symptom Score; *rTOSS*, Reflective Total Ocular Symptom Score; *rTSS*, Reflective Total Symptom Score; *TDD*, total daily dose; *TID*, three times a day.

*Period of data collection is not stated.

†No information on total daily dose (azelastine = 1.1 mg/d); number of patients who completed the nasal treatment = 20; number of patients who completed the oral treatment = 18.

‡Number of patients randomized to azelastine 0.55 mg (2 sprays/nostril QD) = 62; n patients randomized to azelastine 1.1 mg (2 sprays/nostril BID) = 63.

§No information available.

||Number of patients randomized to azelastine 0.55 mg (2 sprays/nostril QD) = 61. Number of patients randomized to azelastine 1.1 mg (2 sprays/nostril BID) = 63.

¶Number of patients randomized to azelastine 0.52 mg (2 sprays/nostril QD) = 66. Number of patients randomized to azelastine 1.04 mg (2 sprays/nostril BID) = 66

#Number of participants randomized per treatment group is not stated; n patients who completed the nasal treatment = 31; n patients who completed the oral treatment = 29.

**Astemizole 30 mg (TID on day 1), 20 mg (BID on day 2) and 10 mg (QD on days 3 - 14).

††Number of patients randomized to montelukast 10 mg (QD) = 112; n patients randomized to loratadine 10 mg (QD) = 116.

‡‡Number of participants randomized is not stated, N patients who completed the nasal treatment = 166, N patients who completed the oral treatment = 174.

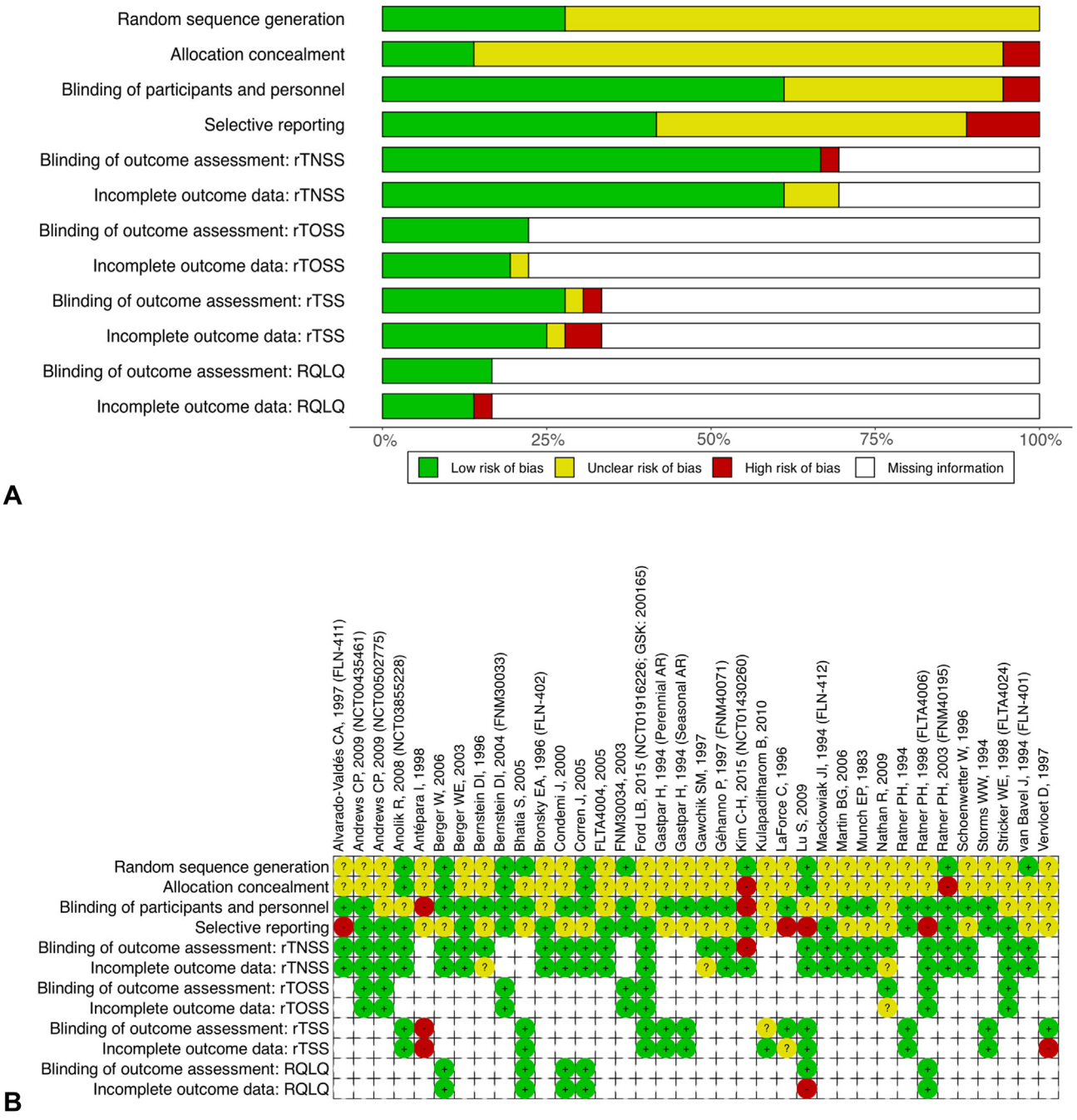

FIGURE 2. Risk of bias (**A**) graph and (**B**) summary for the included studies. *RQLQ*, Rhinoconjunctivitis Quality of Life Questionnaire.

Total Nasal Symptom Score: INCS versus LTRA. Two studies (n = 1,441 participants) reported data for the TNSS regarding the comparison of INCS versus LTRA[44,45] (Figure 4). Both studies compared fluticasone propionate versus montelukast and had a follow-up of 2 weeks, in which one study displayed a high risk of bias.[44]

Intranasal corticosteroids were more effective than LTRA at improving the TNSS (MD, −1.05; 95% CI, −1.32 to −0.77; I^2 = 0%), with a 98% probability of a clinically relevant improvement. The CoE for this comparison was considered high (see Table E7 in this article's Online Repository at www.jaci-inpractice.org). Similar results were found after we excluded the study with a high RoB (Table E6).

Total Nasal Symptom Score: INCS versus OAH. Fifteen studies (n = 4,423 participants) were included in the meta-analysis of TNSS data comparing INCS versus OAH[23-25,28-30,33,34,36-39,41,42] (Figure 4). All studies except one reported results at 2 weeks of follow-up.[34] Three studies displayed a high RoB,[23,28,30] and the remaining had an unclear RoB.

In the meta-analysis, INCS were significantly more effective than OAH at improving the TNSS (MD, −0.86; 95% CI,

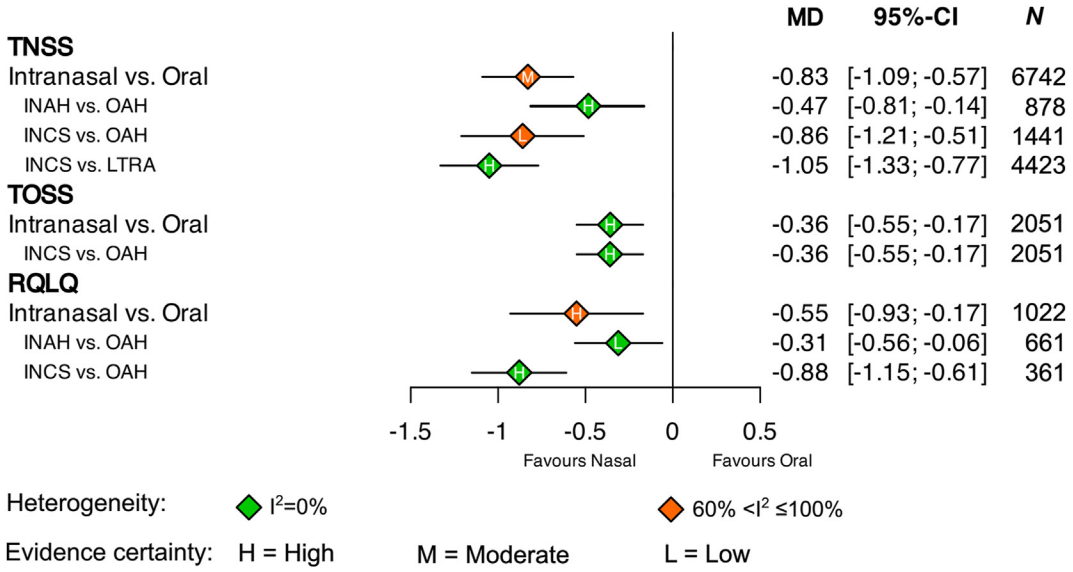

FIGURE 3. Graphical summary of meta-analytical results. *INAH*, intranasal antihistamines; *INCS*, intranasal corticosteroids; *LTRA*, oral leukotriene receptor antagonists; *MD*, meta-analytical mean difference comparing change from baseline values in intranasal treatment versus oral treatment; *OAH*, oral antihistamines; *RQLQ*, Rhinoconjunctivitis Quality of Life Questionnaire; *TNSS*, Total Nasal Symptom Score; *TOSS*, Total Ocular Symptom Score.

−1.20 to −0.51; I^2 = 70%). These results corresponded to a 68% probability of a clinically relevant improvement. The CoE for this comparison was deemed low (see Table E8 in this article's Online Repository at www.jaci-inpractice.org).

Heterogeneity remained substantial in all sensitivity analyses (Table E6). Similar results were found in all analyses, except after we excluded studies with a high RoB (MD, −0.72; 95% CI, −1.07 to −0.36; I^2 = 73%; credibility of the potential effect modification: moderate) (see Figure E1 in this article's Online Repository at www.jaci-inpractice.org).

Total Nasal Symptom Score: Overall intranasal versus overall oral treatments. We included 20 studies (n = 6,742 participants) in the overall comparison of intranasal versus oral treatments (ie, without discriminating between drug classes) in the meta-analysis of the TNSS data[12-14,23-25,28-30,33,34,36-39,41,42,44,45] (Figure 5). Of these studies, 16 were classified as having an unclear RoB whereas four were classified as having a high RoB.[23,28,30,44] All studies except one reported results at 2 weeks of follow-up.[34]

Intranasal treatments likely appeared to be more effective than oral treatment at improving the TNSS (MD, −0.83; 95% CI, −1.09 to −0.57; I^2 = 65%), corresponding to a 70% probability of a clinically relevant improvement. The CoE for this comparison was considered moderate (see Table E9 in this article's Online Repository at www.jaci-inpractice.org).

Heterogeneity remained substantial in all sensitivity analyses (Table E6). We found similar results in all analyses, except after we excluded studies with a high RoB (MD, −0.70; 95% CI, −0.98 to −0.44; I^2 = 67%; credibility of the potential effect modification: low) (see Figure E2 in this article's Online Repository at www.jaci-inpractice.org).

Additional meta-analytical results comparing individual drugs are available in Table E10 (in this article's Online Repository at www.jaci-inpractice.org).

Total Ocular Symptom Score: INCS versus OAH. Five studies (n = 2,051 participants) were included in the meta-analysis comparing intranasal versus oral treatments on TOSS[24,29,32,33] (Figure 6). All studies compared an INCS (either fluticasone propionate or fluticasone furoate) with an OAH. All but one study were classified as having an unclear RoB.[33] All studies reported results at 2 weeks of follow-up.[24,29,32,33]

Intranasal treatments were more effective than oral treatments at improving the TOSS (MD, −0.36; 95% CI, −0.56 to −0.17; I^2 = 0%). These results corresponded to a 21% probability of a clinically relevant improvement. The CoE was considered high (Table E9).

Additional meta-analytical results comparing individual drugs are available in Table E11 (in this article's Online Repository at www.jaci-inpractice.org).

Rhinoconjunctivitis Quality of Life Questionnaire: INAH versus OAH. Two studies (n = 661 participants) comparing INAH and OAH were included in the meta-analysis of RQLQ[12,13] (Figure 7). Both studies compared azelastine versus cetirizine, had a follow-up of 2 weeks, and displayed an unclear RoB.[12,13]

Intranasal antihistamines were possibly more effective than OAH at improving the RQLQ (MD, −0.31; 95% CI, −0.57 to −0.06; I^2 = 0%), with an 81% probability of a clinically relevant improvement. The CoE for this comparison was deemed low (Table E5). We found consistent results after we excluded the study with imputed SDs (see Table E12 in this article's Online Repository at www.jaci-inpractice.org).

Rhinoconjunctivitis Quality of Life Questionnaire: INCS versus OAH. Two studies (n = 361 participants) reported the RQLQ on the comparison between INCS versus OAH[20,30] (Figure 7). Both studies had a follow-up of 2 weeks, and one study was classified as having a high RoB.[30]

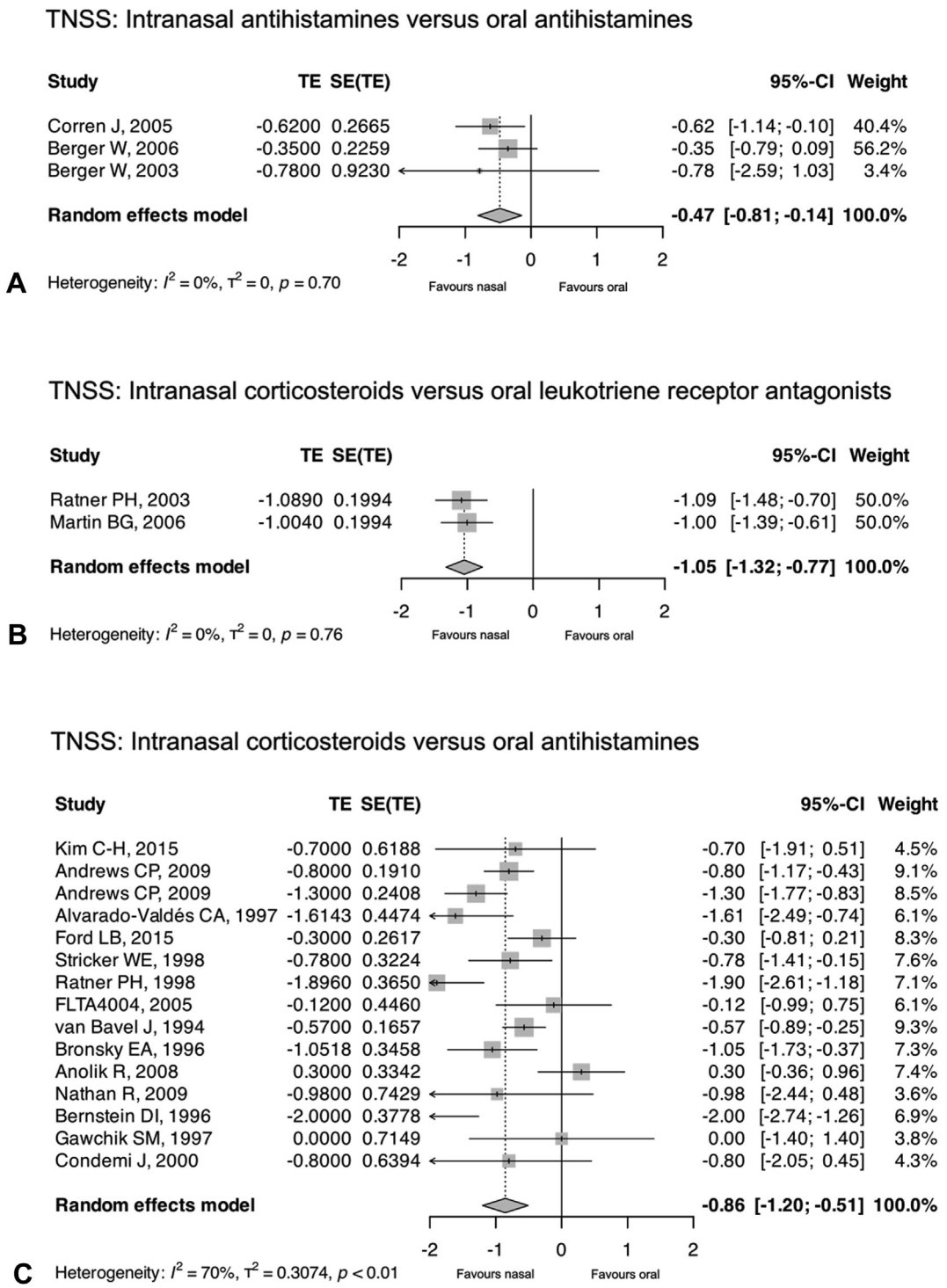

FIGURE 4. Forest plots summarizing meta-analytical results of Total Nasal Symptom Score (TNSS) data on comparison between (**A**) intranasal antihistamines versus oral antihistamines, (**B**) intranasal corticosteroids versus oral leukotriene receptor antagonists, and (**C**) intranasal corticosteroids versus oral antihistamines. *TE*, treatment effect.

Intranasal corticosteroids were more effective than OAH at improving the RQLQ (MD, −0.88; 95% CI, −1.15 to −0.61; I^2 = 0%), corresponding to a 72% probability of a large clinically relevant improvement and 28% probability of moderate improvement. The CoE for this comparison was considered to be high (Table E8).

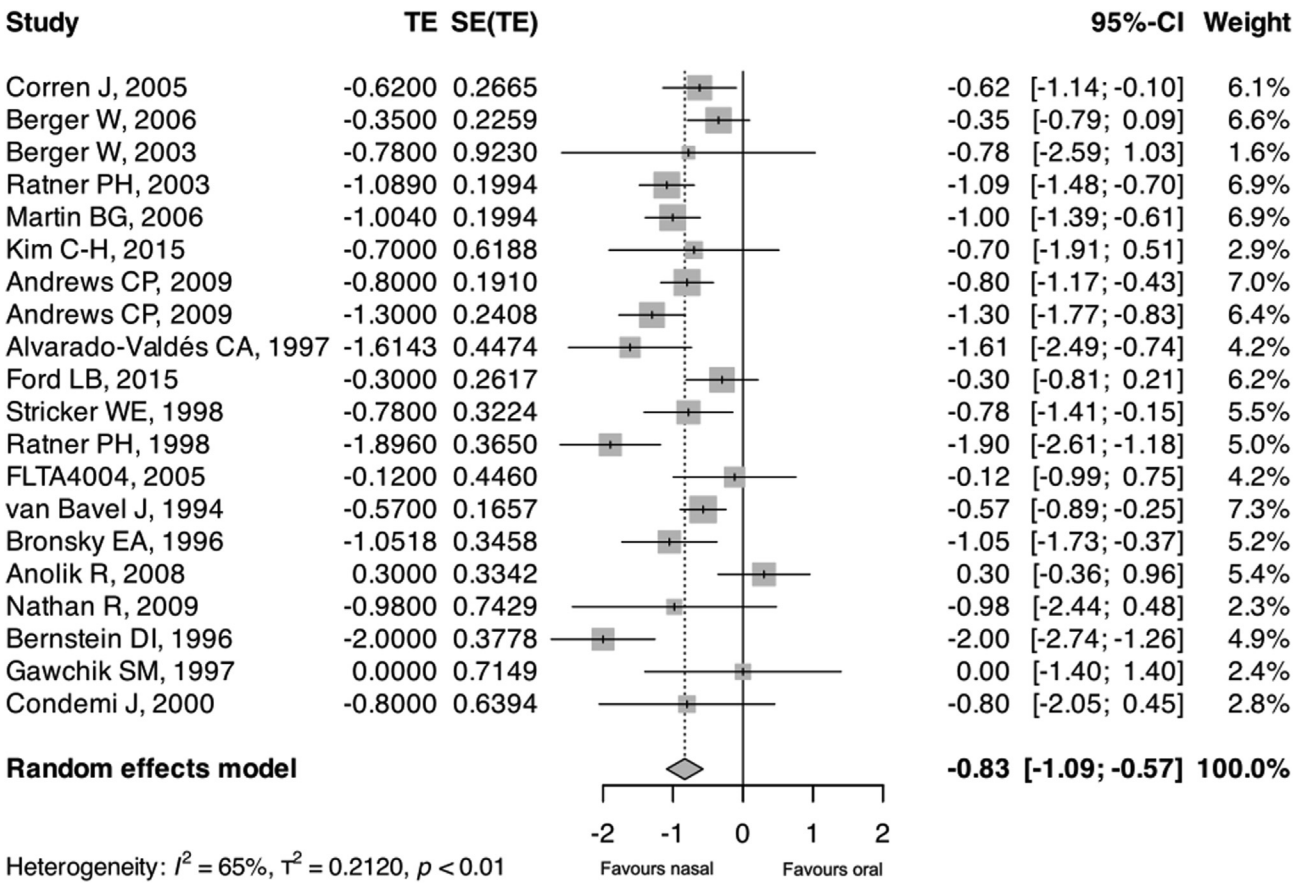

FIGURE 5. Forest plots summarizing meta-analytical results of Total Nasal Symptom Score (TNSS) data on comparison between intranasal versus oral treatments.

Rhinoconjunctivitis Quality of Life Questionnaire: overall intranasal versus overall oral treatments. We included four studies (n = 1,022 participants) in the overall comparison of intranasal versus oral treatments regarding the RQLQ[12,13,20,30] (Figure 7). All studies had a follow-up of 2 weeks, and one study displayed a high RoB.[30]

Intranasal treatments were more effective than oral treatments at improving the RQLQ (MD, −0.55; 95% CI, −0.94 to −0.17; I^2 = 68%), corresponding to a 28% probability of a moderate clinically relevant improvement and a 59% probability of a small improvement. The CoE for this comparison was considered high (Table E9). We found similar results after we excluded studies with imputed SDs, although heterogeneity remained high (MD, −0.58; 95% CI, −1.06 to −0.10; I^2 = 76%) (Table E12).

Additional meta-analytical results comparing individual drugs are available in Table E13 (in this article's Online Repository at www.jaci-inpractice.org).

Safety outcomes

Adverse events: overall intranasal versus overall oral treatments. We included 22 studies (n = 6,520 participants) comparing overall intranasal and oral treatments on the number of patients developing at least one adverse event (AE)[18,19,21,23-37,41,44,45] (see Figure E3 in this article's Online Repository at www.jaci-inpractice.org). Six studies displayed a high RoB,[18,23,26,28,30,44] whereas one study was classified as having a low RoB.[33] Twelve studies had a follow-up of 2 weeks; the others had a follow-up ranging from 3 to 6 weeks.

We found no difference in the risk of AE when we compared intranasal versus oral treatments (relative risk [RR] = 1.02; 95% CI, 0.94-1.09; I^2 = 0%), corresponding to a nonclinically meaningful effect. The CoE for this comparison was considered moderate (Table E9). Similar results were found in sensitivity analyses (see Table E14 in this article's Online Repository at www.jaci-inpractice.org).

We found similar results comparing different classes, except when we compared INAH versus OAH, in which INAH were associated with a higher risk of AE than OAH (RR = 2.10; 95% CI, 1.04-4.26; I^2 = 0%), corresponding to a probability (1) of 35% of a large clinically relevant increase in the risk of AE, and (2) of a 36% moderate increased risk. The CoE for this comparison was considered low (Table E5). Additional meta-analytical results comparing different classes or individual drugs are described in the Supplemental Results (in this article's Online Repository at www.jaci-inpractice.org) and in Figures E4-6 and Tables E14 and E15 (in this article's Online Repository at www.jaci-inpractice.org).

Withdrawals due to AE: overall intranasal versus overall oral treatments. We included 30 studies (n = 8,792 participants) in the comparison between overall intranasal

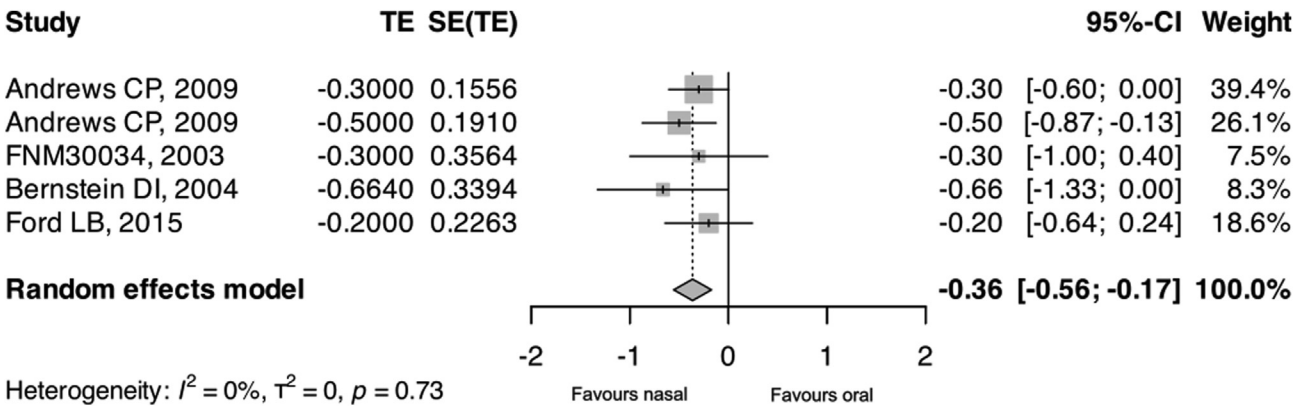

FIGURE 6. Forest plots summarizing meta-analytical results of Total Ocular Symptom Score (TOSS) data on comparison between intranasal versus oral treatments.

and oral treatments on the number of patients withdrawing owing to AE[12-14,23-25,28-30,33,34,36,37,44,45] (Figure E3). Seventeen studies had a follow-up of 2 weeks; the remainder reported results at 3 to 6 weeks. Six studies were classified as having a high RoB[18,23,26,28,30,43,44] and one displayed a low RoB.[33]

There was no difference in the risk of withdrawals when we compared intranasal and oral treatments (RR = 1.00; 95% CI, 0.72-1.38; I^2 = 0%), corresponding to a nonclinically meaningful effect. The CoE for this comparison was considered moderate (Table E9). Consistent results were found in all sensitivity analyses (see Table E16 in this article's Online Repository at www.jaci-inpractice.org).

Additional meta-analytical results comparing different classes or individual drugs are described in the Supplemental Results and Figures E7 to 9 and Tables E16 and E17 (in this article's Online Repository at www.jaci-inpractice.org).

Serious adverse events. A total of 26 studies reported on serious AE. Most studies (20) reported no AE with either nasal or oral treatments. In total, two serious AE were reported with INCS and five with OAH (unlikely to be related to the treatments).

DISCUSSION

In this systematic review, we found INCS or INAH to be more effective than OAH or LTRA at improving both nasal and ocular symptoms in SAR, as well as quality of life. In most cases, this effect was deemed clinically relevant. Regarding safety outcomes, we found no differences when we compared intranasal with oral treatments, except for the comparison between INAH versus OAH on the occurrence of AE. Overall, for most comparisons, a moderate or high CoE was associated with these results.

In this systematic review, the differences in nasal symptoms were most pronounced between INCS and LTRA. This was followed by the comparison between INCS and OAH, for which the differences, although significant, were less pronounced. Finally, the smallest difference was observed between INAH and OAH. Similar results were found for the RQLQ, except for the comparison between INCS and LTRA, for which no evidence was available. Finally, regarding the TOSS, evidence was available exclusively comparing INCS and OAH, showing a significant effect of INCS in improving ocular symptoms. We found no studies assessing the effect of INAH on the TOSS. Future studies assessing the effect of treatments for AR on ocular symptoms, particularly INAH, are needed.

However, our meta-analysis included only studies assessing patients with SAR. For PAR, only two studies were found, both assessing solely the TSS (one assessed intranasal azelastine vs oral terfenadine whereas the other assessed intranasal budesonide vs oral levocetirizine).[19,22] Although both studies displayed a nonsignificant trend favoring intranasal treatments,[19,22] these studies presented a heterogeneous methodology, unclear risk of bias, and small sample sizes. Because the pathophysiology of SAR and PAR is similar, results from SAR trials may be transportable to patients with PAR,[46] but more evidence from RCTs or real-world secondary data would be beneficial.

There have been previous systematic reviews comparing intranasal versus oral treatments for rhinitis. However, they were not recent, assessed fewer drug classes, and restricted study selection based on publication dates or languages.[4,5] In addition, neither of the previous systematic reviews appraised the CoE using GRADE. Importantly, results from previous systematic reviews consistently suggest a superiority of intranasal over oral medications.

This systematic review has some limitations primarily related to the included studies. First, there was insufficient evidence on PAR, hindering the possibility of performing meta-analysis and limiting the generalizability of our findings to this population. Future research should prioritize addressing this gap and investigating the comparative effectiveness of intranasal and oral treatments for PAR. Second, only a minority of studies had been classified as having a low RoB. Although we conducted sensitivity analyses, the potential influence of bias on the results should be considered when interpreting the findings. Third, there is considerable heterogeneity in the measurement and reporting of outcomes. Five studies computed the TNSS based on three or five symptoms; hence they were excluded from quantitative synthesis of TNSS computed based on four symptoms. The same happened with studies reporting data on the TOSS: whereas most studies calculated the TOSS based on three symptoms, two studies computed the TOSS based on two or four symptoms. We opted not to include the latter studies in the meta-analyses because we believed they represented

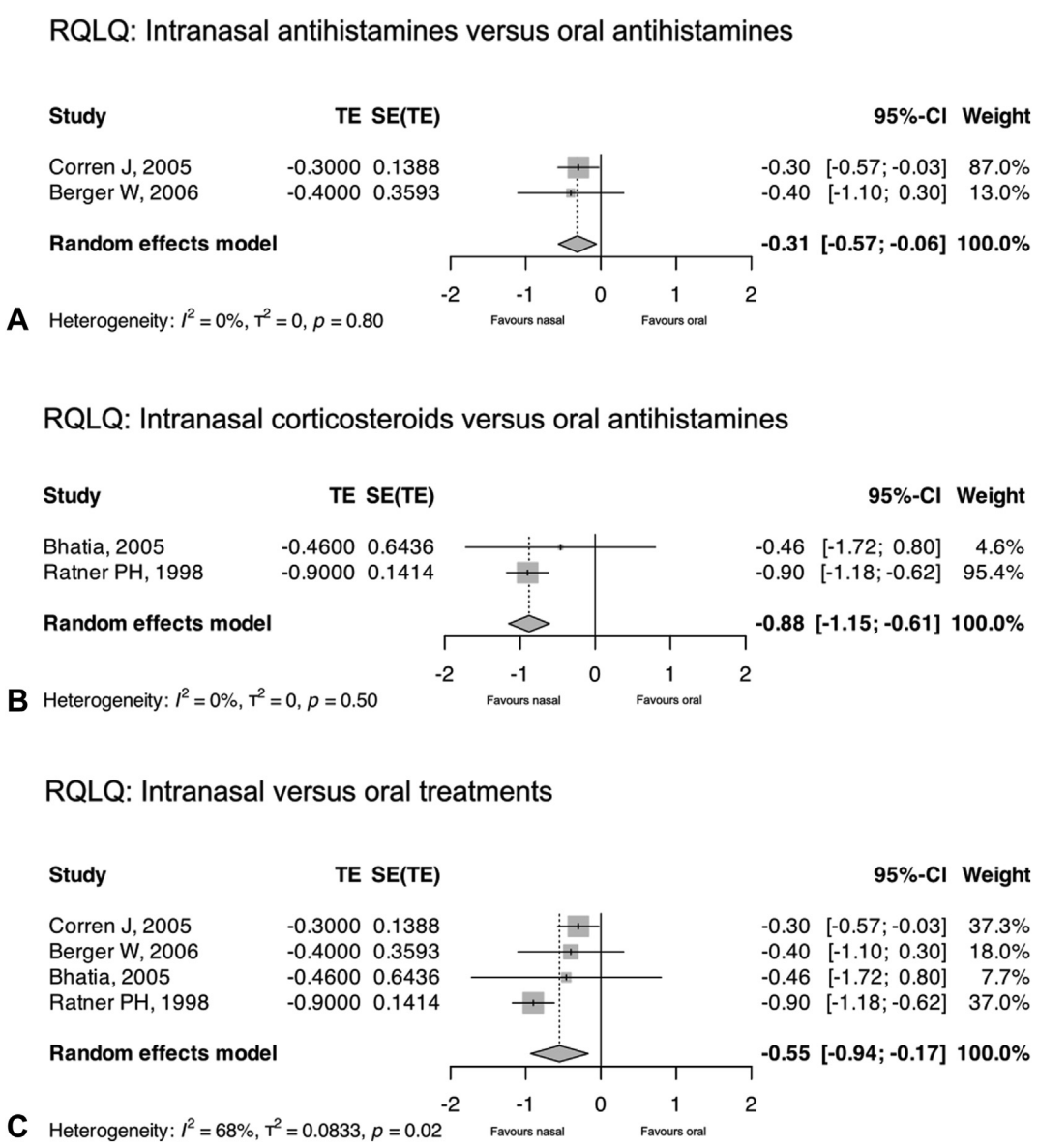

FIGURE 7. Forest plots summarizing meta-analytical results of Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) data on comparison between (**A**) intranasal antihistamines versus oral antihistamines, (**B**) intranasal corticosteroids versus oral antihistamines, and (**C**) intranasal versus oral treatments.

different constructs. Similarly, meta-analysis on the TSS was not conducted because TSS definitions, considered symptoms, and scales varied substantially across the included studies. Fourth, information on spread measures was missing in several studies. In such cases, whenever possible, spread measures were imputed based on reported *P* values. Importantly, we performed sensitivity analysis excluding studies with imputed SDs and obtained consistent results. In addition, individual drugs within a same class may vary in effectiveness (Sousa-Pinto et al, under review). Although we performed sensitivity analyses comparing individual drugs, we were unable to assess the effect of individual drugs comprehensively because of the low number of studies included in each comparison. Similarly, the overall comparison between intranasal and oral treatments could be affected by class differences in effectiveness and safety of medications (and by the number of studies assessing medications of each class). Finally, we used the classification of seasonal and perennial AR despite the existence of a more recent classification according to the duration of symptoms (classifying AR into intermittent or persistent).[47] This was because most RCTs in AR use the seasonal versus perennial classification, and the US Food and Drug Administration issued a 2018 guidance on the development of RCTs for SAR and PAR.[48] As previously stated for PAR, given the similar pathophysiology for intermittent and persistent AR, we believe these results may apply to all patients with AR. However, there is a need for further research, possibly based on real-world data and using modern methods of causal inference and transportability analyses, to inform the effectiveness and safety of interventions better in intermittent and perennial AR.

Nevertheless, this study also has important strengths. First, we performed an extensive bibliographic search including four bibliographic databases and three clinical trial datasets, without applying exclusion criteria based on publication language, date, or status (thus, minimizing the impact of publication bias). Second, we applied the GRADE approach to assess the CoE for each outcome across comparisons and found varying levels of CoE depending on the specific comparison and outcome, in which most comparisons displayed a high CoE. These results may be valuable for informing clinical guidelines, particularly because previous guidelines did not perform a systematic review to assess the comparative effectiveness and safety of intranasal versus oral treatments for AR[1,2] (it is important to note, however, that the CoE in the guideline context is performed across outcomes and reflects the outcomes that have been prioritized by the guideline panel). Third, we performed sensitivity analyses according to the risk of bias, the need for imputation of spread measures, the follow-up period, and individual drugs being compared. Fourth, when sensitivity analysis suggested the existence of a significant effect modification on effectiveness outcomes, we also assessed the credibility of such a modification using the Instrument to Assess the Credibility of Effect Modification Analyses. Finally, we also conducted a complementary approach to assess the probability that for each pair of interventions, differences corresponded to clinically relevant effects. This approach was based on decision thresholds and was adopted to contextualize effect size measures, as suggested by the GRADE working group.[49]

This systematic review may have important clinical implications. These results support the current recommendations in the ARIA guidelines and the US Practice Parameter on the management of AR,[1,3] but they should be considered alongside other sources of evidence to determine the role for nasal and oral medications in the treatment of AR. Importantly, in this systematic review we do not consider patients' preference regarding oral versus intranasal medications or the severity of disease. Most AR patients may have mild disease and may not be accurately represented by participants enrolled in RCTs.[50] As suggested by studies assessing real-world data, oral medications are frequently prescribed by physicians and used over-the-counter by patients with AR.[51-53] This may be related to aspects such as the cost, ease of use of oral versus nasal medications, and efficacy of oral medications in many patients. All of these factors should be considered both when developing guideline recommendations and prescribing treatments for individual patients.

Intranasal treatments are more effective than oral treatments at improving symptoms and quality of life in patients with SAR, with a similar safety profile. This systematic review could be helpful for future guideline developers in formulating recommendations for AR. Importantly, further RCTs or observational studies based on real-world data directly comparing the effectiveness of nasal and oral treatments should use standardized outcomes such as the four-symptoms TNSS, the three-symptoms TOSS, and the RQLQ to ensure comparability.

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