

# Intranasal antihistamines in the treatment of idiopathic non-allergic rhinitis: a systematic review and meta-analysis\*

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## Abstract

**Background:** Idiopathic rhinitis (IR), previously known as vasomotor rhinitis (VMR), is the most common type of non-allergic rhinitis (NAR) which affects around 100 million people worldwide. The treatment of patients with IR is not standardized. Intranasal antihistamines (INAH) are potent drugs in the treatment of allergic rhinitis but are frequently prescribed in the treatment of IR. This systematic review of the literature and meta-analysis aims to assess the effects of INAH on IR.

**Methodology:** A comprehensive review of the literature was conducted on Medline, Embase and Cochrane library. Randomized, controlled trials and non-randomized comparative parallel group trials comparing INAH to placebo or different INAHs were included. The primary outcome was the change in disease specific quality of life questionnaires, total nasal symptom score (TNSS). The secondary outcomes were other reported nasal symptom scores, individual symptom scores and adverse events.

**Results:** Six trials out of 987 assessing a total of 675 participants were deemed relevant for inclusion. Compared to placebo, INAH decreased total nasal symptom scores. One study also reported reduction of symptoms recorded on a visual analogue scale. There was no difference between the INAHs in terms of efficacy. Bitter taste sensation was the most frequently reported adverse event.

**Conclusions:** INAHs seem to have benefit over placebo on nasal symptoms improvement in the treatment of NAR. No superiority between INAHs was identified.

**Key words:** antihistamines, azelastine, nonallergic, olopatadine, rhinitis, topical, vasomotor, idiopathic

## Introduction

Non-allergic rhinitis (NAR) consists of an array of unrelated heterogeneous rhinologic syndromes. At first, NAR was classified in a dichotomous fashion between the non-allergic rhinitis with eosinophilia syndrome (NARES) and the non-NARES<sup>(1)</sup>. However, due to the diminished use of nasal smear cytology and the emergence of other NAR types a more detailed classification was created. The latter accounts for eight different entities where all patients present nasal symptoms of rhinitis with no evidence of allergic, infectious or anatomical diseases<sup>(2)</sup>. Around 200 million people suffer of NAR worldwide. Of those it is estimated that 40 to 50 % have an idiopathic rhinitis (IR) subtype, previously known as vasomotor rhinitis (VMR). IR patients

are patients with NAR symptoms who do not fit in any other subtype (senile rhinitis, gustatory rhinitis, occupational rhinitis, hormonal rhinitis or drug induced rhinitis)<sup>(3,4)</sup>. In most patients IR is characterized by symptoms of nasal hyper-reactivity (NHR) (eg, rhinorrhea, nasal congestion, sneezing, post nasal dripping) which are induced by non-allergic non-infectious triggers as strong odors, changes in temperature, humidity, barotraumatic pressure, alcohol exposure and others<sup>(2–5)</sup>. The pathophysiologic explanation behind IR is still not very well understood. The most accepted pathophysiologic theories are those of autonomic sino-nasal imbalance, nociceptive nerve dysfunction, neurogenic inflammatory reflex and entopy<sup>(5,6)</sup>. Patients diagnosed with IR are often offered different treatment

modalities ranging from nasal topical medication to surgical procedures like the vidian neurectomy. The lack of systematized treatment protocols and the scarcity of high grade evidence regarding the treatment of this pathology has led to a high burden on quality of life and low patient satisfaction overall <sup>(7)</sup>. One of the few topical medication categories with a registered label in the treatment of NAR are intranasal antihistamines (INAH). Although known for their effect on allergic rhinitis, second generation INAH like Azelastine Hydrochloride (HCl) are thought to be beneficial and are frequently prescribed for this non allergic condition. Hence, the aim of this project is to systematically review the literature on the matter and to assess the effects of INAH on IR.

## Materials and methods

### Protocol registration

No registered review protocol similar to ours was identified prior to the beginning of this review. The protocol of this systematic review has been validated and registered in the International prospective register of systematic reviews (PROSPERO) of the National Institute for Health Research (NIHR). Registration number: CRD42020159786.

### Eligibility criteria

Randomized, controlled trials (RCTs) and non-randomized comparative parallel group trials (non-RCTs) comparing INAH to placebo or different INAHs were included. The patients must have had a diagnosis of nonallergic IR after an objective confirmation of negative allergic, infectious and mechanical sino-nasal diseases. The studies included doses, duration and frequencies of the evaluated treatment agent.

Exclusion criteria encompassed articles not written in English language and studies that included patients with other types of rhinitis or other IR treatment modalities. The outcome measures were not used as inclusion or exclusion criteria.

### Information sources and search strategies

A comprehensive review of the literature was conducted on Medline (PubMed), Embase (Ovid) and Cochrane from January 1990 to January 2023 while following the PRISMA statement for systematic reviews and meta-analyses. The search terms used were “vasomotor rhinitis and (therapy or treatment)” and “nonallergic rhinitis and (therapy or treatment)” and idiopathic rhinitis and (therapy or treatment). These terms were used on purpose to widen the search array and try to include articles where IR was still defined as VMR. References of the included studies were searched for additional missing trials.

### Study selection process

The selection of the included papers was independently performed by two reviewing authors (MK and RA). At first records were

screened and chosen by relevancy of the titles and abstracts. Then full texts of the selected articles were reviewed. The above cited eligibility criteria guided the choice of trials to be finally included in the statistical analysis. In case of insufficient data, the corresponding authors were contacted by electronic mail. Disagreements in study selection were solved by the senior authors (NK and WAH).

### Data extraction

The included articles were reviewed by the same reviewing authors for the study type, INAH agent, dosage of the INAH, frequency of administration, duration of treatment, number of patients in each arm and mean age. The primary outcomes were changes in the quality of life (QoL) measures, or in the total nasal symptom score (TNSS). The secondary outcomes were other reported nasal symptom scores and individual nasal symptom scores. Adverse experiences were also reviewed.

### Risk of bias

Studies that underwent meta-analysis were subjected to a risk of bias assessment using the Cochrane risk of bias tool <sup>(8)</sup>. The following types of biases were assessed: selection bias, performance bias, detection bias, attrition bias, reporting bias and others. The risk was then graded for each study as low, high or unclear.

### Statistical analysis

Articles providing full raw statistical data or the mean difference of the examined scores with the standard deviations were included in the meta-analysis. Other articles where statistical data lacked and were not provided by the authors on demand were only included in the qualitative review.

Mean difference (MD) of the TNSS was pooled for the meta-analysis using a random effect method and with a 95% confidence interval (CI). Heterogeneity ( $I^2$ ) between trials was calculated and was considered significant when  $I^2$  exceeded 50% and low when it was equal or inferior than 50%. The statistical analysis and the generation of the forest plot were done on Review Manager version 5.3 <sup>(9)</sup>.

## Results

### Study selection

A total of 987 records were identified after the primary search and after removing duplicates. 893 records were believed irrelevant according to their title or abstract and were excluded. The remaining 94 records were analyzed by their full texts. Subsequently, five articles (six trials) were included for qualitative analysis (Table 1). Of those two studies (three trials) were deemed relevant for a meta-analysis after providing all the needed statistical data. A flow chart detailing the screening and selection process of manuscripts is presented in Figure 1.

Table 1. Overview of the studies included in this review.

INAH vs placebo trials						
Study (design)	Intervention	Comparison	Included patients	Baseline Study Population	Measured Outcomes	Primary outcome scores
Banov et al. <sup>(9)</sup> , 2001	Azelastine HCl (1.1mg/day) 2 sprays/nostril q12 for 21 days	Placebo	Positive diagnosis of VMR, rhinitis duration > 1yr, negative allergy skin tests, negative cytology for eosinophils, normal sinus xray, absence of clinical nasal deformities.		TVRSS; individual symptom scores; dropouts' percentage; patients global effectiveness adverse experiences; clinical evaluation.	
Study 1 (Double blind RCT)				INAH, n= 113; Placebo, n= 110		INAH, mean difference: -1.54 ± 0.14; Placebo, mean difference = -0.84 ± 0.17
Study 2 (Double blind RCT)				INAH, n= 103; Placebo, n= 100		INAH, mean difference: -1.54 ± 0.18; Placebo, mean difference = -0.88 ± 0.18
Gehanno et al. <sup>(11)</sup> , 2001 (Double blind RCT)	Azelastine HCl (0.84mg/day); 1 spray q8 for 15 days	Placebo	Positive diagnosis of VMR, symptoms duration > 1yr, negative phadiatop, normal sinus xray, absence of clinical nasal deformities.	INAH, n=44; Placebo, n=45	Nasal Symptomatology (0-100 scale); rhinoscopy (inflammation, edema, color) (0-100 VAS scale); efficacy assessed by physicians and patients (0-100VAS scale).	Better results for all symptoms on VAS in INAH. Score differences graphically reported favoring INAH (p<0.05)
Smith et al. <sup>(12)</sup> , 2011 (Double blind, crossover study)	Olopatadine HCl 0.6%; 2 sprays in each nostril	Placebo	Positive diagnosis of VMR, negative allergy skin tests, negative specialist allergy review.	INAH, n=22; Placebo, n=22 (crossover)	TNSS; peak inspiratory flow.	INAH, mean difference: -0.95 ± 2.4; Placebo, mean difference = 1.27 ± 2.54
Gawlik et al. <sup>(10)</sup> , 2013 (Prospective, comparative parallel-group study)	Azelastine HCl (137mcg/spray); 2 sprays/ nostril q12 for 10 days	Untreated	Positive diagnosis of perennial NAR/ IR, normal IgE titers, negative allergy skin tests, negative cytology for eosinophils, normal sinus xray, absence of mechanical obstruction.	INAH, n=13; Control, n=10	TVRSS; concentration of substance P in nasal lavage fluid; adverse experiences.	INAH, before treatment score: 7.46 ± 1.64, after treatment score: 5.91 ± 1.20; Controls, before treatment score: 7.4 ± 1.56, after treatment score: 7.1 ± 1.44. Mean difference with SD not reported.
INAH types comparative trials						
Lieberman et al. <sup>(13)</sup> , 2011 (Double blind RCT)	Olopatadine HCl 0.6%; 2 sprays/nostril q12 for 14 days	Azelastine HCl 0.1%; 2 sprays/ nostril q12 for 14 days	Positive diagnosis of VMR, symptoms duration > 2yr, negative allergy skin tests, absence of clinical nasal anomalies.	OLO, n=57; AZE, n=58	TVRSS; treatment satisfaction questionnaire; patient global assessment; safety; adverse events	OLO, mean difference: -5.9 ± 3.0; AZE, mean difference: -6.5 ± 2.2

RCT: randomized controlled trial; IR: Idiopathic rhinitis; VMR: vasomotor rhinitis; NAR: nonallergic rhinitis; INAH: intranasal antihistamine; AZE: Azelastine HCl; OLO: Olopatadine HCl; TVRSS: total vasomotor rhinitis symptom score; TNSS: total nasal symptom score; VAS: visual analogue scale; Mean difference : score after treatment – score before treatment.

**Participants**

Six trials assessed a total of 675 participants with a reported mean age of 40.1 years (10–14). Women accounted for 69.8%

(n=471) of the participants whereas men accounted for 30.2% (n=204). All participants aged over 13-year-old and had a positive diagnosis of VMR/IR.

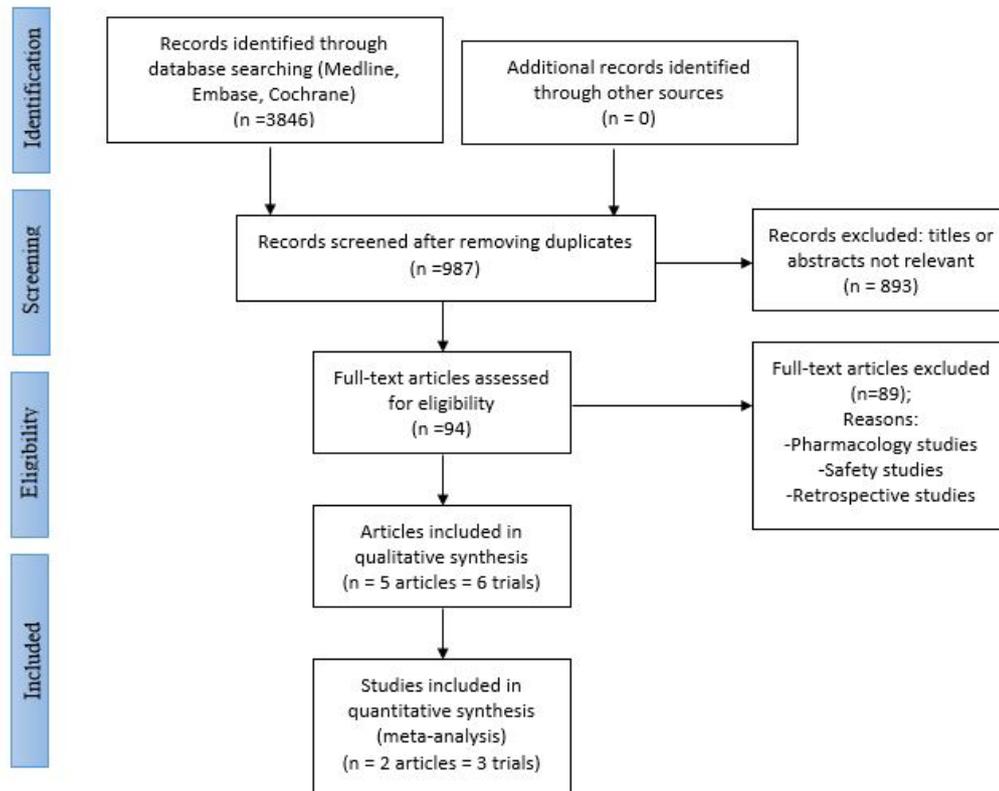


Figure 1. Flow chart detailing study selection process.

### Interventions

Second generation INAHs were used across all studies: Azelastine Hydrochloride (HCl) (137 mcg/spray) <sup>(10–12,14)</sup> or Olopatadine HCl 0.6% (665 mcg/spray) <sup>(13,14)</sup>. Three trials compared Azelastine HCl to placebo <sup>(10,12)</sup> and one trial compared Azelastine HCl to an untreated group <sup>(11)</sup> whereas only one trial compared Olopatadine HCl to placebo <sup>(13)</sup>. A single trial by Lieberman et al was found to be comparing head to head the two INAHs <sup>(14)</sup>. Table 1 details the intervention used in each of the trials and the number of participants in each therapeutic arm.

### Outcomes

#### Primary outcomes

TNSS was the most commonly reported score. None of the articles used QoL measures for the evaluation of the included patients.

INAH vs Placebo : Four studies used TNSS as an objective outcome measure <sup>(10,11,13)</sup>, one of those did not provide standard deviations (SD) <sup>(11)</sup>. The cumulative meta-analysis was therefore based on three studies; two RCTs by Banov et al. and one randomized crossover trial by Smith et al. <sup>(10,13)</sup>. A total of 230 participants were included in the INAH group and 228 in the placebo group. The overall mean difference was of -0.68 with a 95% confidence interval (CI) of (-0.75;-0.61). This difference was significant with overall effect  $Z=19.03$  ( $p<0.000001$ ). Random

effect was used with acceptable non-significant heterogeneity ( $I^2=65\%$ ;  $p=0.06$ ) (Figure 2).

Azelastine HCl vs Olopatadine HCl: both groups showed a significant decrease in the TNSS after 14 days of treatment ( $p<0.001$ ). In between-group comparison showed no statistical difference ( $p=0.354$ ) <sup>(14)</sup>.

#### Secondary outcomes

Other nasal symptom scores: One trial reported statistically significant reduction of symptoms with INAH compared to placebo ( $p<0.05$ ). The parameter was scored using a visual analog scale (from 0 to 100) and therefore the study was not eligible for inclusion in the previous meta-analysis <sup>(12)</sup>. Another trial has also shown a significant decrease of the TNSS favoring INAH but was not included in the meta-analysis lacking to provide standard deviation of the mean TNSS difference <sup>(11)</sup>.

Individual symptom scores: When reported, the individual symptom scores (rhinorrhea, sneezing, nasal congestion, post-nasal dripping) had improved in the INAH group compared to placebo group ( $p<0.05$ ) <sup>(10,11)</sup>. However, the second trial by Banov et al. has shown limited improvement in nasal congestion with a  $p$  value of 0.079. There was no difference in individual symptom improvement between Azelastine HCl and Olopatadine HCl (Table 2) <sup>(14)</sup>. A meta-analysis by individual nasal symptom improvement was not possible because of the lack of mean differences

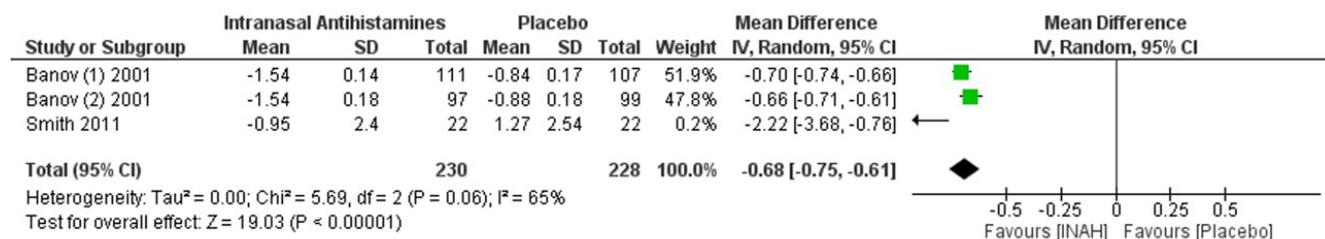


Figure 2. Improvement on total nasal symptom score at endpoint: intranasal antihistamines vs placebo. INAH: intranasal antihistamines; CI: confidence interval; df: degrees of freedom; IV: inverse variance; random: random effects.

Table 2. Statistical significance of individual symptom scores improvement.

	Banov et al. <sup>(9)</sup> (study #1) (AZE vs placebo)	Banov et al. <sup>(9)</sup> (study #2) (AZE vs placebo)	Smith et al. <sup>(12)</sup> (OLO vs placebo)	Gehanno et al. <sup>(11)</sup> (AZE vs placebo)	Gawlik et al. <sup>(10)</sup> (AZE vs control)	Lieberman et al. <sup>(13)</sup> (AZE vs OLO)
Rhinorrhea	p=0.009	p=0.003	n/a	p=0.023	p<0.01	p=0.727*
Sneezing	p=0.030	p=0.049	n/a	n/a	p<0.02	p=0.917*
Nasal congestion	p=0.036	p=0.079*	n/a	p=0.017	p<0.038	p=0.280*
Postnasal Drip	p=0.038	p=0.024	n/a	n/a	p<0.042	p=0.294*

\* No statistically significant difference (p>0.05); AZE: Azelastine HCl; OLO: Olopatadine HCl; n/a: not available; p: p-value.

and standard deviations.

**Adverse experiences**

Bitter taste sensation was a statistically significant reported adverse event. Three of the included studies have reported such an adverse event in patients treated with Azelastine HCl with a combined rate of 17.7% of the participants. Minor nasal bleedings were also reported but there was no statistically significant difference of occurrence between groups <sup>(10,11,14)</sup>.

**Risk of bias of included studies**

The three trials included in the meta-analysis were subjected to bias risk assessment. All trials had low risks in attrition and reporting bias but an unclear risk of selection bias (allocation concealment). One trial (33.3%) had an unclear blinding method that lead to unclear risks in performance and detection bias. Two trials (66.7%) had incomplete information on the random sequence generation and thus an unclear selection bias (Figure 3). Risks of bias in each of the included trials are shown in Figure 4.

**Discussion**

Intranasal antihistamine sprays seem to be beneficial in the treatment of idiopathic rhinitis. In fact, after regrouping the results of 458 participants from three different trials in a meta-analysis, a mean difference of -0.68 was found with a confidence interval of (-0.75; -0.61), denoting a significant improvement of the TNSS in patients treated with INAH. The overall effect Z was 19.03 with a p-value inferior to 0.000001 (Figure 2). Due to

heterogeneity between trials, random rather than fixed effect was used reaching a heterogeneity value I<sup>2</sup> of 65%. I<sup>2</sup> should be preferably inferior to 50% in order to consider an acceptable heterogeneity. However, given that the p-value for heterogeneity was not significant (p=0.06), our reported heterogeneity of 65% was considered acceptable.

Two other trials <sup>(11,12)</sup>, comparing INAH to placebo, were included in the qualitative analysis and have also shown improvement of the symptomatology in their treatment groups. All individual nasal symptom scores had significantly improved when compared to placebo across all reporting trials (Table 2). Consequently, we may conclude that both the quantitative and qualitative analyses go in favor INAH efficacy in patients diagnosed with IR.

Azelastine HCl was given FDA approval for the treatment of patients (>12y.o.) with VMR in November 2000, based on safety studies and the results of the two trials by Banov et al. <sup>(10,15)</sup>. So far, this is the first systematic review, to our knowledge, to regroup all placebo-controlled INAH trials in the treatment of IR. Although the meta-analysis was based on three trials only, it goes, along with the qualitative review, in favor of the efficacy of INAHs in improving rhinitis symptoms of patients with IR. No superior agent, in terms of efficacy, was found in the single RCT by Lieberman et al. comparing Azelastine HCl to Olopatadine HCl. A tendency towards higher patients' satisfaction was reported with Olopatadine HCl.

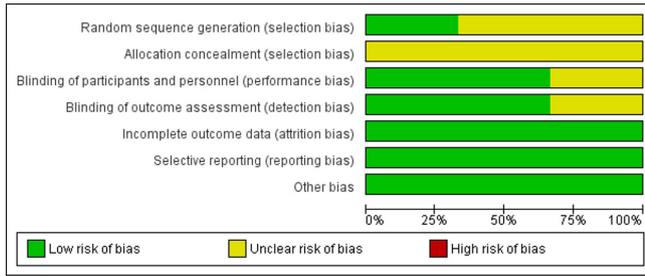


Figure 3. Risk of bias graph. Each risk of bias item shown as a percentage across all studies included in the meta-analysis.

Bitter taste sensation is a known adverse effect of Azelastine HCl, which was reaffirmed in this review. The comparative rate of nasal bleeding between groups suggests that it is consequent to the use of the spray device itself rather than antihistamine induced mucosal dryness mechanism.

Although the mechanism of action of antihistamines in allergy is well established, their effect on non-allergic rhinopathy is still not well understood. Lieberman reviewed possible mechanisms of action of antihistamines in NAR. The antagonism of the different types of histamine receptors was found to have a minor role in the treatment of NAR because histamine itself was rarely incriminated in its pathophysiology<sup>(12,16)</sup>. Moreover, histamine release has a negligible role compared to the autonomic nervous system imbalance effect on vasodilatation. However, it has been claimed that an anti-inflammatory activity of antihistamines against the neurogenic inflammatory reflex seen in IR may be the mainstay behind the improvement of symptoms<sup>(5,15)</sup>. Mediators like substance p (SP), calcitonin gene related peptide and neurokinin A are proinflammatory peptides found in the human nasal mucosa and were thought to be implicated in the neural mechanisms of NAR<sup>(15,17)</sup>. Gawlik et al. have induced the secretion of SP in the nasal mucosa using a non-allergenic challenge with hypertonic saline in patients with NAR and have shown the propensity of topical Azelastine HCl to reduce SP's concentration and alleviate rhinitis symptoms in the same treatment group<sup>(11)</sup>. In 2014, Singh et al., demonstrated in an in-vitro experiment that azelastine induces desensitization of the transient receptor potential vanilloid 1 (TRPV-1), a receptor also incriminated in the mechanism of action of capsaicin<sup>(18)</sup>.

This review encompasses highest available evidence in the literature but has some minor limitations. First, the review was only based on 6 trials with only 3 included in the quantitative analysis. Publication bias could be in cause since our literature search was only based on online database sources for the initial search and for the references of the included studies: Medline (PubMed), Embase (Ovid) and Cochrane. We did not look for further data in meetings programs, trials registry database or pharmaceuticals industries research. In addition, the review was

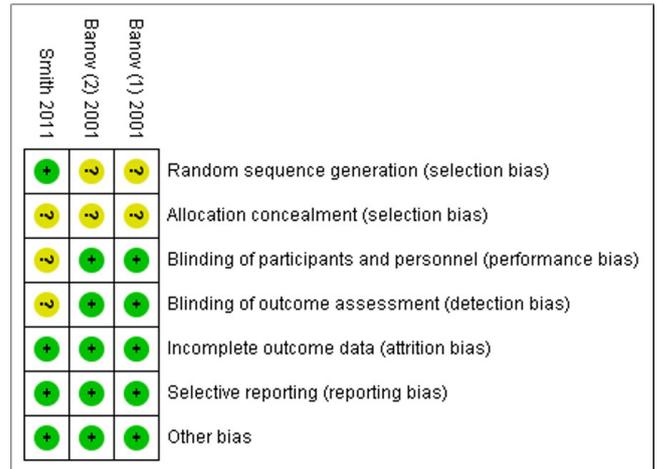


Figure 4. Risk of bias summary. Each risk of bias item for each included study in the meta-analysis.

limited on English language studies. Heterogeneity between studies is another limitation to our review. In fact, a heterogeneity of 65% was noted between the 3 included trials and was barely non-significant p-value of 0.06. When assessing the risk of bias, all trials had low risks in attrition and reporting bias but an unclear risk of selection bias (allocation concealment). In RCTs, allocation concealment is the process of shielding those involved in the trial from knowing the upcoming participant group assignment. Thus, the risk of selection bias is unclear in the 3 included trials. The 2 trials of Banov et al. had also an unclear selection bias due to incomplete information on the random sequence generation<sup>(10)</sup>. The blinding method was not clear in the trial of Smith et al. with subsequent uncertainty regarding the blinding of participants (performance bias) and the blinding of outcome assessment (detection bias)<sup>(13)</sup>. It must also be mentioned that a female to male ratio mismatch (69.8% vs 30.2%) was found in the overall population. Therefore, the concomitant effect of possible hormonal imbalance cannot be precluded. Moreover, patients were included on the basis of old VMR subtype definitions, thus making a diversion from the currently accepted IR phenotype as described by Hellings et al.<sup>(3,4)</sup>. For instance, nasal hyper-reactivity was not objectively assessed by its golden standard test: the cold dry air provocation.

Other treatment options like capsaicin, intranasal corticosteroids (INCS), intranasal anticholinergics (INAC) are frequently prescribed, but the therapeutic arsenal is still under investigation. A recent Cochrane review suggested a favorable response of patients with NAR to INCS but with low certainty evidence<sup>(19)</sup>. A reduction of NAR symptoms was also identified with intranasal capsaicin in a review based on small studies with low quality of evidence<sup>(20)</sup>. INAC sprays like ipratropium bromide were found to act more on rhinorrhea than on other symptoms of NAR in placebo controlled RCTs<sup>(21-23)</sup>.

The clinical extrapolation or relevancy of the favorable results found in this meta-analysis are difficult to judge because of the small yet statistically significant mean difference. Thus, we think that future research should focus on comparing different treatment modalities using high quality RCTs in the perspective of creating treatment guidelines for this rhinologic entity.

## Conclusion

This review identified 5 trials comparing INAH to placebo and one trial comparing Azelastine HCl to Olopatadine HCl in patients with IR. The metanalysis and the qualitative review have shown a statistically significant decrease in the overall perceived symptoms with INAH. The current review of the literature shows that topical intranasal second-generation antihistamines seem effective in the management of IR. No superiority of either agent

was identified.

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## Authorship contribution

NK: Conception, data selection, writing, reviewing. MK: Writing, data selection, reviewing. RA: Writing, data selection, reviewing. SR: Reviewing. WAH: writing, reviewing.

## Conflict of interest

All authors have no conflict of interest to disclose.

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