



# Efficacy of non-sedating H1-receptor antihistamines in adults and adolescents with chronic cough: A systematic review

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## ABSTRACT

**Background:** Nasal symptoms frequently coexist in patients with chronic cough, and non-sedating H1-receptor antihistamines (nsH1RAs) are often prescribed for cough management in several countries. However, recommendations on the use of nsH1RAs vary among chronic cough guidelines. This study aimed to examine the efficacy of nsH1RAs over placebos in adolescents or adults with chronic cough or allergic respiratory conditions that may present as chronic cough.

**Methods:** Electronic databases were searched for studies published until November 2020. Randomized placebo-controlled trials of nsH1RAs reporting cough endpoints in adolescents or adults with chronic cough or cough-associated allergic respiratory conditions (allergic rhinitis, allergic asthma, or atopic cough) were included.

**Results:** A total of 10 placebo-controlled trials were identified. Three studies (one study each involving allergic rhinitis, allergic rhinitis with comorbid asthma, and atopic cough) described baseline and post-treatment cough scores, and all reported significant improvements in subjective cough scores; however, the magnitude of improvement was greater in the 2 studies of patients with atopic cough (relative improvement in cough frequency score:  $-36.6 \pm 8.4\%$ ) or seasonal allergic rhinitis-associated cough (cough frequency score:  $-44.0 \pm 7.3\%$  and cough intensity score:  $-65.7 \pm 8.3\%$ ) than in the 1 study of allergic rhinitis patients with comorbid asthma ( $-4.0 \pm 1.3\%$ ). Meanwhile, the other 7 trials found conflicting results but lacked information on the baseline cough score and did not use validated cough measurement tools; thus, their clinical relevance could not be determined.

**Conclusion:** Despite the widespread use of nsH1RAs in patients with chronic cough, only a few clinical trials examining their benefits on cough outcomes have been conducted. There may be a subgroup of patients, particularly those with seasonal allergic rhinitis-associated cough or atopic cough, whose cough may improve with nsH1RA treatment. However, adequately powered trials

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with validated cough measurement tools are warranted to confirm the role of nsH1RAs in the management of patients with allergic phenotypes of chronic cough.

**Keywords:** Non-sedating H1-receptor antihistamine, Asthma, Allergic rhinitis, Atopic cough, Chronic cough

## INTRODUCTION

Cough is one of the most common reasons for which patients seek medical care.<sup>1-3</sup> The diagnostic approach usually starts from classifying the cough based on duration, followed by identifying cough-triggering conditions.<sup>4</sup> Proper identification and treatment of clinical conditions triggering cough has been recommended as the key initial step in current chronic cough guidelines, although the epidemiology and clinical priorities may differ across age groups or regions.<sup>5-14</sup> In adults with chronic cough (usually defined as > 8 weeks), cough variant asthma, eosinophilic bronchitis, reflux, and nasal diseases are considered as the most common cough-triggering conditions, particularly when the affected patients are non-smokers and have normal chest X-rays and spirometry.<sup>15</sup>

Chronic cough related to upper airway abnormalities is termed as upper airway cough syndrome (UACS), as proposed by the American College of Chest Physicians (ACCP) guidelines in 2006.<sup>16</sup> However, because the symptoms and signs are nonspecific, the diagnosis of UACS is challenging and cannot be made from the medical history and physical examination alone.<sup>16</sup> Thus, a response to treatment targeted to nasal conditions has been suggested as the proof of the diagnosis in the guidelines empiric therapy in the form of a first-generation H1-histamine receptor antihistamine (H1RA) and decongestant combination was suggested as the first-line treatment to screen UACS, even in patients whose specific etiology of cough is not apparent.<sup>16</sup> Although the guideline recommendations for empirical treatment may be clinically useful, they do not confirm the etiological diagnosis of cough because the pharmacologic effects of first-generation H1RAs are not only limited to upper airways but also include central nervous system.<sup>5</sup>

There is an ongoing controversy regarding the causal relationship between nasal diseases and chronic cough.<sup>5</sup> Postnasal drip sensation is a common phenomenon but only a small proportion of those subjects complain about cough.<sup>17</sup> The nasal mucosa is primarily innervated by the trigeminal nerves; furthermore, direct stimulation of nasal afferents with histamine or an irritant has been shown to provoke a sneeze reflex but not to induce a cough response in guinea pigs.<sup>18</sup>

Accordingly, there are different views regarding the use of H1RAs between international and national academic society cough guidelines (Table 1). Unlike the ACCP guidelines,<sup>16</sup> it was not formulated as a recommendation in the guidelines of the British Thoracic Society and European Respiratory Society.<sup>5,10</sup> The guidelines by Australian, Chinese, Japanese, or Korean societies recommended the use of H1RAs, but did not limit it to sedating H1RAs.<sup>7,8,12,14,19</sup> In clinical practice, non-sedating H1RAs (nsH1RAs) are widely prescribed for chronic cough in some countries.<sup>20,21</sup>

The discordance in guidelines is attributed not only to the unclear mechanical linkage between nasal conditions and cough but also to the lack of confirmatory clinical evidence with treatments that are specific to the upper airways and have no central effects, such as nsH1RAs. Furthermore, there is no consensus regarding the effective dose and optimal treatment duration of nsH1RAs in patients with chronic cough, unlike in those with chronic urticaria in whom 2- or 4-fold up dosing may be effective.<sup>22</sup> Given the potential risks associated with the use of sedating H1RAs, such as fatigue, changes in vision, impaired cognitive function, or even injurious falls,<sup>23,24</sup> further evidence is warranted to confirm whether nsH1RAs are truly beneficial and can be recommended instead of sedating

Guideline and academic society	Publication year	Recommendation and/or remarks	Grade
Diagnosis and Management of Cough Executive Summary: ACCP Evidence-Based Clinical Practice Guidelines (American College of Chest Physicians) <sup>4</sup>	2006	<p>1) A patient suspected of having UACS-induced cough who does not respond to empiric antihistamine/decongestant therapy with a <u>first-generation antihistamine</u> should next undergo sinus imaging.</p> <p>2) In patients for whom a specific etiology of chronic cough is not apparent, empiric therapy for UACS in the form of a <u>first-generation antihistamine/decongestant</u> preparation should be prescribed before beginning an extensive diagnostic workup.</p>	<p>1) Quality of evidence: low, Strength of recommendation: moderate</p> <p>2) Quality of evidence: low, Strength of recommendation: weak</p>
Recommendations for the management of cough in adults (British Thoracic Society) <sup>10</sup>	2006	There is a disparity in the reported efficacy of antihistamines. In the USA, the recommended treatment involves a first-line approach with a sedating antihistamine/decongestant combination. The first-generation antihistamines recommended in this document are not available in the UK and there is conflicting evidence as to the efficacy of second generation (less sedating) antihistamines in the treatment of cough.	No recommendation made
CICADA: Cough in Children and Adults: Diagnosis and Assessment. Australian Cough Guidelines summary statement (Lung Foundation Australia) <sup>12</sup>	2010	In children and adults with cough and allergic rhinitis, topical nasal corticosteroids, <u>antihistamines</u> and allergen management are recommended according to current rhinitis management guidelines.	Strength of recommendation: weak
Korean Cough Guideline: Recommendation and Summary Statement <sup>19</sup> (Korean Academy of Tuberculosis and Respiratory Diseases)	2016	<p>1) In UACS, oral <u>anti-histamine</u> is recommended to improve cough.</p> <p>2) If UACS is suspicious, <u>first generation anti-histamine</u> and nasal decongestant can be used empirically.</p>	Quality of evidence: very low, Strength of recommendation: strong

(continued)

Guideline and academic society	Publication year	Recommendation and/or remarks	Grade
Clinical Practice Guidelines for the Diagnosis and Management of Cough (Chinese Thoracic Society Asthma Consortium) <sup>8</sup>	2018	In patients with UACS/PNDS, 1) for nonallergic rhinitis and the common cold, first-line treatment consists of <u>first-generation antihistamines</u> and decongestants, which are efficacious in most patients within several days to two weeks. 2) for allergic rhinitis, intranasal ICS, including budesonide, fluticasone propionate and betamethasone acetate, and <u>oral second-generation antihistamines</u> are used. If second-generation antihistamines are not available, <u>first-generation antihistamines</u> can be used with a similar clinical response, except for the greater drowsiness.	1) Quality of evidence: high, Strength of recommendation: strong 2) Quality of evidence: high, Strength of recommendation: strong
KAAACI Evidence-Based Clinical Practice Guidelines for Chronic Cough in Adults and Children in Korea (Korean Academy of Asthma Allergy and Clinical Immunology) <sup>7</sup>	2018	For adults (age $\geq 15$ years) with nonspecific chronic cough, we recommend the empirical use of <u>H1-antihistamines</u> . This recommendation is supported by the low costs, ease of accessibility, and tolerable safety profiles of H1-antihistamines. However, possible side effects must be discussed with patients.	Quality of evidence: very low, Strength of recommendation: strong
ERS guidelines on the diagnosis and treatment of chronic cough in adults and children (European Respiratory Society) <sup>5</sup>	2020	First-generation antihistamines are thought to be antitussive through their action as centrally penetrant anticholinergics.	No recommendation made
German Respiratory Society guidelines for diagnosis and treatment of adults suffering from acute, subacute and chronic cough (German Respiratory Society) <sup>13</sup>	2020	First generation H1 antihistamines with anticholinergic effect (chlorpheniramine, recommended in the US guideline) and triprolidine in Germany, commercially available as combination preparation with pseudoephedrine only. They also have a central antitussive effect.	No recommendation made

(continued)

Guideline and academic society	Publication year	Recommendation and/or remarks	Grade
Chronic cough in childhood: A systematic review for practical guidance by the Italian Society of Pediatric Allergy and Immunology (Italian Society of Pediatric Allergy and Immunology) <sup>9</sup>	2021	The “allergic salute” and “throat-clearing” type of cough can suggest the presence of postnasal drip, although the evidence of a relationship between postnasal drip and irritation of the larynx is lacking.	No recommendation made
Japanese respiratory society guidelines for the management of cough and sputum <sup>14</sup> (Japanese Respiratory Society)	2021	1) <u>Histamine H1 receptor antagonists</u> are recommended for atopic cough/laryngeal allergy (chronic) 2) Although <u>histamine H1 receptor antagonists</u> have a non-specific antitussive action, they demonstrate a significant effect in most cases with an atopic cough.	Quality of evidence: B for atopic cough and C for chronic laryngeal allergy

**Table 1. (Continued)** Summary of recommendations on the use of H1RAs in recent international and national guidelines for chronic cough in adolescents and adults UACS, upper airway cough syndrome; PNDS, postnasal drip syndrome; ICS, inhaled corticosteroid. Recommended antihistamines are underlined.

H1RAs in adults with chronic cough who are mostly middle-aged or elderly.<sup>25</sup>

On top of the wide gap between clinical practice and evidence, we conducted a systematic review to examine therapeutic effects of nsH1RAs on cough outcomes in adults or adolescents with chronic cough. As we previously found no randomized controlled trials (RCTs) evaluating nsH1RAs in patients with non-specific chronic cough,<sup>7</sup> this systematic review expanded the population to those with allergic respiratory conditions that may present with chronic cough, such as allergic rhinitis, asthma, or atopic cough.

## METHODS

### Search strategy

A systematic literature review was performed to address the following research questions:

- Are nsH1RAs more effective than placebo in improving cough outcomes in adolescents or adults with chronic cough?
- Are nsH1RAs more effective than placebo in improving cough outcomes in adolescents or adults with allergic respiratory diseases that may

present with chronic cough (such as allergic rhinitis, asthma, or atopic cough)?

We searched for RCTs reporting the effects of oral nsH1RAs on cough outcomes in patients with chronic cough, allergic rhinitis, asthma, or atopic cough. We searched the PubMed, Embase, and Cochrane library databases from inception to June 2020, according to the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.<sup>26</sup> The search was updated through November 2020. In addition, we searched the ClinicalTrials.gov registry for any relevant studies. Our search strategy is provided in [Table S1](#). In brief, the search terms were constructed with the combination of target populations (cough, rhinitis, OR asthma) AND intervention (currently available nsH1RAs). Regarding the study population, our search terms included common allergic respiratory conditions for which oral antihistamines were trialed in the literature, using the terms for cough, bronchitis, rhinitis, sinusitis, and asthma.

### Selection criteria

The inclusion criteria were as follows: 1) adolescents or adults with chronic cough, allergic

rhinitis, asthma, atopic cough, or other allergic respiratory conditions (as a population); 2) oral nsH1RAs (as intervention; listed in Table S2);<sup>27</sup> 3) matched placebo (as a comparison); 4) clinical cough outcomes, such as severity, frequency, or cough-specific quality of life (QoL) (as an outcome); and 5) randomized double-blind controlled studies (as the study design). Only randomized placebo-controlled trials were considered for inclusion to control for placebo effects or spontaneous remission of cough.<sup>28</sup> The publication language was restricted to English. We excluded the studies if participants included only children (aged < 12 years). The study protocol was registered as PROSPERO CRD42020198165.

### Data extraction

From all the included studies, we extracted the following outcomes: first author, publication year, study design, country, participant selection criteria, baseline characteristics, disease condition, interventions (active and control), cough outcomes before and after treatment, and other clinical outcomes.

### Risk of bias assessment

Risk of bias was assessed independently by 2 main authors (SWJ and LJH) using the Risk of Bias-2 (RoB-2) assessment tool from the Cochrane Collaboration.<sup>29</sup> Any disagreement between the

reviewers was resolved by discussion to reach a consensus.

### Analysis

From each study, we extracted (or calculated) the means with standard deviations (SDs) or standard error of the mean [SEM] of post-treatment cough outcomes. In addition, the relative improvement in cough score was calculated by dividing the pre- and post-treatment cough score difference by the maximum score of the scale in each trial where the values were available. Random effects meta-analysis was considered *a priori* unless there was heterogeneity in the study population and outcome measurements.

## RESULTS

### Characteristics of the included studies

The PRISMA flow chart for the literature selection is presented in Fig. 1. From a total of 7385 initially retrieved publications, 10 trials involving 1629 participants finally met the eligibility criteria for the systematic review. The baseline characteristics of the included studies are summarized in Table 2. All literature was published between 1988 and 2004, and the results of a study from ClinicalTrials.gov (NCT00295022) were posted in 2018.

Five trials were conducted in the United States, and the others were conducted in the United

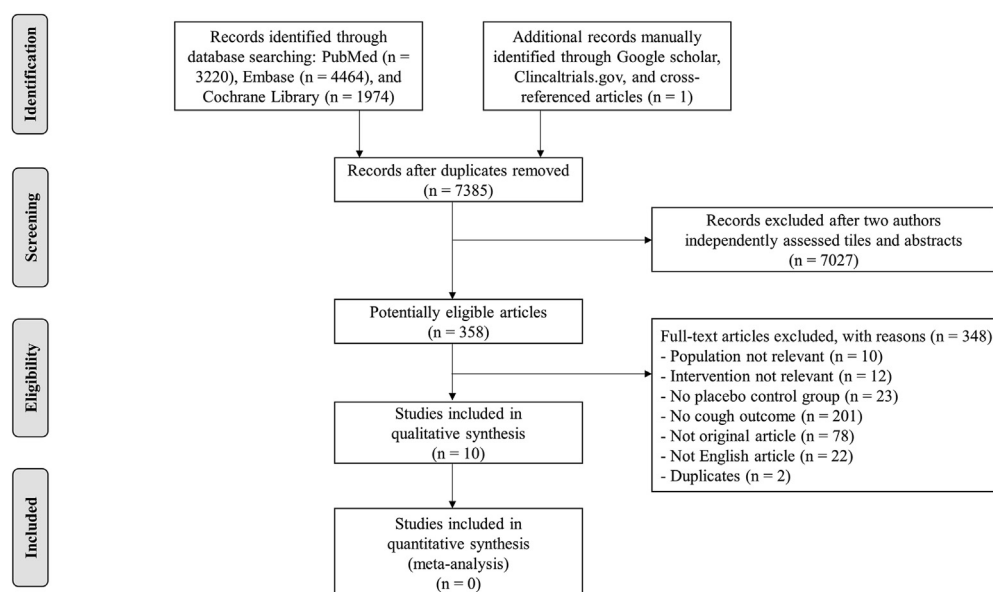


Fig. 1 Flowchart of the search strategy and study selection

Study	Design	Target condition	Patients and region	Intervention	Cough endpoint
<b>Allergic asthma</b>					
Gould 1988 <sup>37</sup>	RDBPCT, parallel group	Extrinsic allergic asthma	n = 24 (women: 20.8%; age: 18-45 years), UK	4.4 mg azelastine bid or matched placebo for 7 weeks	Cough severity score (1-4 scale)
Dirksen 1989 <sup>31</sup>	RDBPCT, crossover	Endogenous or perennial allergic asthma	n = 17 (women: 70.6%; age: 19-63 years), Denmark	10 mg loratadine qd or matched placebo for 8 weeks	Cough score (no scale information)
<b>Allergic rhinitis with asthma</b>					
Grant 1995 <sup>34</sup>	RDBPCT, parallel group	Seasonal allergic rhinitis with mild to moderate asthma	n = 186 (women: 55.9%; age: 12-70 years), US	10 mg cetirizine qd or matched placebo for 6 weeks	Cough score (0-9 scale)
Aaronson 1996 <sup>35</sup>	RDBPCT, parallel group	Perennial allergic rhinitis with mild to moderate asthma	n = 28 (women: 46.4%; age: 13-59 years), US	20 mg cetirizine qd or matched placebo for 26 weeks	Cough score AM and PM (0-9 scale)
Berger 2002 <sup>36</sup>	RDBPCT, parallel group	Seasonal allergic rhinitis with mild asthma	n = 331 (women: 65.9%; age: 15-75 years), US	5 mg desloratadine qd or matched placebo for 4 weeks	Cough score (0-3 scale)
Baena-Cagnani 2003 <sup>32</sup>	RDBPCT, parallel group	Seasonal allergic rhinitis with asthma	n = 613 (women: 64.9%; age: 15-75 years), US	5 mg desloratadine qd or matched placebo for 4 weeks	Cough score (0-3 scale)
<b>Allergic rhinitis without asthma</b>					
Weiler 1988 <sup>30</sup>	RDBPCT, parallel group	Seasonal allergic rhinitis	n = 128 (women: 34.4%; age: 16-60 years), US	2 mg azelastine bid or matched placebo for 4 weeks	Cough score (0-5 scale)
Ciprandi 1995 <sup>38</sup>	RDBPCT, parallel group	Cough associated with allergic rhinoconjunctivitis due to <i>Parietaria Judaica</i>	n = 20 (women: 65.0%; age: 19-65 years), Italy	10 mg loratadine qd or matched placebo for 4 weeks	1) Cough frequency score (0-3 scale) 2) Cough intensity score (0-3 scale)
NCT00295022, 2018	RDBPCT, parallel group	Seasonal allergic rhinitis due to ragweed	n = 262 (women: 61.5%; age: 18)	5 mg levocetirizine qd or matched	Cough score (0-5 scale)

(continued)

Study	Design	Target condition	Patients and region	Intervention	Cough endpoint
			years and older), Canada	placebo for 2 days	
<b>Atopic cough</b>					
Shioya 2004 <sup>33</sup>	RDBPCT, parallel group	Atopic cough	n = 20 (women: 60%; age: 21-71 years), Japan	20 mg epinastine qd or matched placebo for 4 weeks	Cough frequency score (0-50 scale)

**Table 2.** Summary of placebo-controlled trials with non-sedating H1-receptor antihistamines on cough endpoints in patients with allergic rhinitis, asthma, or chronic cough RDBPCT, randomized double-blind placebo-controlled trial

Kingdom, Denmark, Italy, Canada, or Japan. The disease conditions evaluated were allergic asthma, allergic rhinitis with asthma, allergic rhinitis without asthma, or atopic cough. Five studies included adolescents and adults, whereas another 5 consisted of adults only. The details of the inclusion and exclusion criteria are described in Table S3. The number of participants varied from 17 to 613; however, half of the studies included less than 30 patients. The active drugs in these studies were azelastine, loratadine, cetirizine, epinastine, desloratadine, and levocetirizine. The treatment duration ranged from 2 days to 26 weeks. Regarding cough outcomes, only subjective cough scores (such as severity or frequency score from different scales) were utilized.

### Risk of bias

The results of RoB-2 assessments are summarized in Fig. 2. All studies were assessed to have some concerns or high risk of bias except one study registered at ClinicalTrials.gov. Among published studies, only 3 studies<sup>30-32</sup> reported randomization procedures in detail, but none clearly described allocation concealment. Both participants and investigators were blinded in all studies except 1<sup>33</sup> in which the blinding of personnel was considered unclear. Five studies<sup>31,32,34-36</sup> were suspected to have a high risk of bias derived from unbalanced missing cough outcome data between treatment groups that may have affected the conclusions. Two-thirds of the studies<sup>30,31,34,35,37,38</sup> were published

before 2000; thus, an insufficient study protocol hindered further judgement of selective reporting.

### Summary of findings

Two studies were conducted in patients with asthma,<sup>31,37</sup> 4 in allergic rhinitis with asthma,<sup>32,34-36</sup> 3 in allergic rhinitis without asthma,<sup>30,38</sup> 1 in atopic cough,<sup>33</sup> and none in chronic cough. The baseline comparability in cough scores was clearly described in two studies.<sup>33,38</sup> Changes in the mean cough scores were described in 8 studies,<sup>30-35,38</sup> but information on the score distribution (such as the SD or SEM) was only provided in 5 studies,<sup>31-33,38</sup> and statistical significance (such as *p* values) was only briefly addressed in others.<sup>36,37</sup> Due to the differences in study populations and cough endpoints including incomplete reporting of baseline cough scores, a meta-analysis was not conducted, but the findings are presented in a structured way (Figs. 3 and 4).

### Allergic asthma

Both studies had a small sample size (*n* = 17 and 24), and no significant benefits with nsH1RAs in reducing cough in allergic asthma were found.<sup>31,37</sup> The study by Gould et al described that the changes in cough severity score were not significantly different between azelastine and placebo but did not provide actual cough scores.<sup>37</sup> The crossover trial by Dirksen included 17 patients with moderate asthma and reported that the cough score was lower with loratadine than with placebo, but the difference was not statistically significant (mean difference



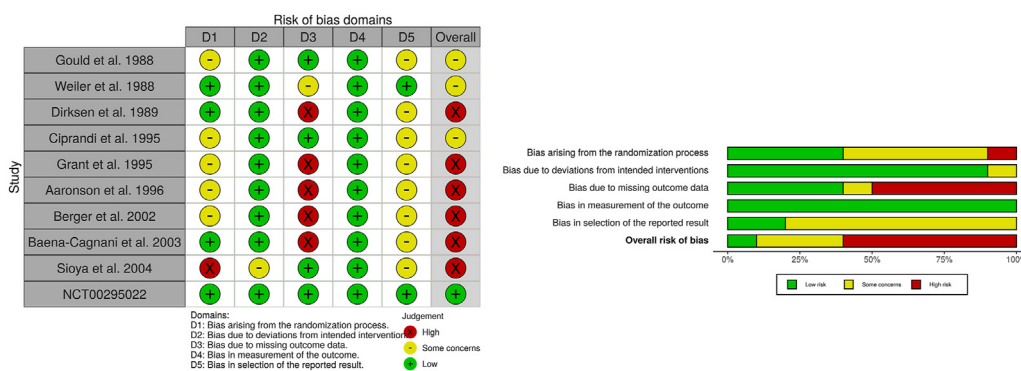


Fig. 2 Risk of bias assessment

[MD] ± SD: 0.49 ± 0.19 vs. 0.83 ± 0.22;  $p > 0.05$ ).<sup>31</sup>

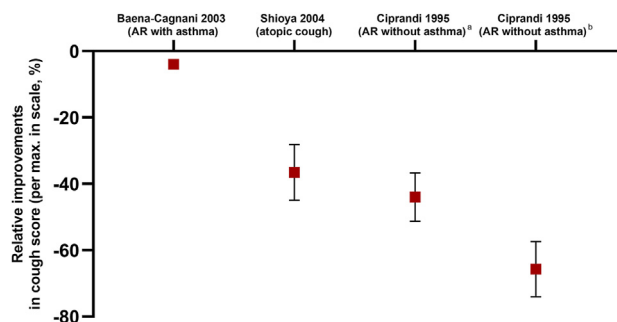
Allergic rhinitis with asthma

There were 4 RCTs involving patients with allergic rhinitis and asthma.<sup>32,34-36</sup> Since the recent use of inhaled corticosteroids was set as one of the exclusion criteria, the severity of asthma in participants was presumed to be mild in all these trials. Three trials reported significant benefits with nsH1RAs over placebo in reducing cough among patients with seasonal allergic rhinitis and

asthma,<sup>32,34,36</sup> and they were multicenter trials and had relatively large sample sizes (range: 186 to 613 patients). Among them, only the study by Baena-Cagnani et al described the mean baseline cough score (1.67; 0-3 scale) and the difference in post-treatment cough score in detail (desloratadine vs. placebo;  $-0.12 \pm 0.04$ ;  $p < 0.05$ ).<sup>32</sup> The other 2 studies did not report the SD or SEM of the scores.<sup>34,36</sup> However, despite the statistical significance of the findings in the study by Baena-Cagnani et al,<sup>32</sup> the relative magnitude of cough improvement was deemed too small to be

Disease	Study information			Chief complaint	Pre-treatment	Post-treatment	
	Active drug and daily dose (first author and year)	Duration (weeks)	Number of participants		Baseline cough	Follow-up cough assessment tool	Cough improvement (nsH1RA vs. placebo)
Allergic asthma	Azelastine 8.8 mg (Gould 1988)	7	24	NR	NR	Cough severity score (1-4 scale)	NS (no information for MD and SD)
	Loratadine 10 mg (Dirksen 1989)	8	17	NR	NR	Cough score (no scale information)	NS (MD -0.3 ± 0.58)
Allergic rhinitis with asthma	Cetirizine 10 mg (Grant 1995)	6	186	Symptomatic seasonal allergic rhinitis	NR	Cough score (0-9 scale)	Significant (MD -0.47; no SD information)
	Cetirizine 20 mg (Aaronson 1996)	26	28	NR	NR	Cough score AM and PM (0-9 scale)	NS (MD AM score -0.004; MD PM score -0.17; no SD information)
	Desloratadine 5 mg (Berger 2002)	4	331	Increased allergic rhinitis and asthma symptoms during allergy season	NR	Cough score (0-3 scale)	Significant (p value only, at week 2; $p = 0.027$ )
	Desloratadine 5 mg (Baena-Cagnani 2003)	4	613	Increased allergic rhinitis and asthma symptoms during allergy season	Cough score: mean 1.67 (0-3 scale)	Cough score (0-3 scale)	Significant (MD -0.12 ± 0.04; $p < 0.05$ )
Allergic rhinitis without asthma	Azelastine 4 mg (Weiler 1988)	4	128	Symptomatic seasonal allergic rhinitis	NR	Cough score (0-5 scale)	NS (MD -0.04; no SD information)
	Loratadine 10 mg (Ciprandi 1995)	4	20	Cough (associated with pollen allergic rhinoconjunctivitis)	1) Cough frequency score: 1.6 ± 0.1 (0-3 scale) 2) Cough intensity score: 1.8 ± 0.1 (0-3 scale)	1) Cough frequency score (0-3 scale) 2) Cough intensity score (0-3 scale)	1) Significant (MD -1.32 ± 0.22; $p < 0.05$ ) 2) Significant (MD -1.97 ± 0.25; $p < 0.01$ )
	Levocetirizine 5 mg (NCT00295022) (Results posted in 2018)	2 days	262	Symptomatic seasonal allergic rhinitis due to ragweed	NR	Cough score (0-5 scale)	NS (MD -0.15 ± 1.26; $p = 0.057$ )
Atopic cough	Epinastine 20 mg (Shioya 2004)	4	20	Chronic cough (atopic cough)	Cough frequency score: 35 ± 8 (0-50 scale)	Cough frequency score (0-50 scale)	Significant (MD -18.3 ± 4.2; $p < 0.01$ )

Fig. 3 Summary of current evidence on the efficacy of nsH1RAs on clinical cough outcomes. The green box indicates a study reporting a statistically significant improvement in the cough endpoint, and the yellow box indicates a study with a nonsignificant improvement. Cough score values are expressed as the mean and standard deviation unless indicated otherwise. Abbreviations: NR, not reported; NS, not significant; MD, mean difference; SD, standard deviation



**Fig. 4** Relative improvements in cough scores in three clinical trials reporting both baseline and post-treatment cough scores.<sup>32,33,38</sup> The squares and vertical lines indicate the mean and standard deviation of relative improvements. The study by Ciprandi et al.<sup>38</sup> reported two types of cough endpoints: (a) the cough frequency score and (b) the cough intensity score.

clinically relevant ( $-4.0 \pm 1.3\%$ ) (Fig. 4). Meanwhile, the negative trial by Aaronson et al evaluated 28 patients with perennial allergic rhinitis and asthma, and 20 mg of cetirizine was not significantly better than placebo (MD -0.004 for AM cough score and  $-0.17$  for PM cough score; all  $p$  values  $> 0.05$ ), and the SD or SEM of the score was not reported.<sup>35</sup>

### Allergic rhinitis without asthma

There were 3 RCTs of allergic rhinitis patients without asthma, where asthma was screened for by medications, symptoms, diagnosis history, or baseline lung function<sup>30,38</sup> (and 1 online post at ClinicalTrials.gov [NCT00295022]). The results were not consistent across the studies but were only positive in the study conducted in patients with seasonal allergic rhinitis with cough as the chief complaint.<sup>38</sup> The study by Ciprandi et al.<sup>38</sup> involving 22 patients with cough associated with allergic rhinoconjunctivitis due to *Parietaria judaica* pollen found significant benefits with loratadine in reducing subjective cough frequency and intensity scores as well as conjunctival and nasal symptom scores (Table S4). The relative improvements in cough were  $-44.0 \pm 7.33\%$  for the cough frequency score and  $-65.67 \pm 8.33\%$  for the cough intensity score (Fig. 4).<sup>38</sup>

Meanwhile, a multicenter study by Weiler et al (128 participants with seasonal allergic rhinitis)<sup>30</sup> and a single-center study (NCT00295022; 262 patients with seasonal allergic rhinitis due to ragweed) did not describe a baseline cough score

but also did not find a significant benefit of nsH1RAs in reducing cough despite improved nasal symptoms (Table S4).

### Atopic cough

One RCT conducted in 20 patients with atopic cough in Japan compared the efficacy of epinastine vs. placebo.<sup>33</sup> Atopic cough was defined according to the criteria of the Japanese Cough Research Society<sup>39</sup> by (1) the presence of chronic nonproductive cough, (2) atopic disposition and/or sputum eosinophilia, (3) no bronchial reversibility, (4) normal bronchial responsiveness, (5) increased cough sensitivity, (6) resistance to bronchodilators, (7) normal chest X-rays, and (8) normal lung functions. The study found that a 4-week treatment with epinastine significantly reduced the cough diary score (scale 0-50) over placebo (MD  $-18.3 \pm 4.2$ ;  $p < 0.01$ ). The relative improvement in cough score was  $-36.6 \pm 8.4\%$  (Fig. 4). The improvement in the cough score was accompanied by an increased cough threshold for capsaicin.

## DISCUSSION

The present systematic review provides the most comprehensive overview of RCTs to date regarding the efficacy of nsH1RAs on cough in adults or adolescents with chronic cough or allergic respiratory conditions that may present with chronic cough. Despite extensive literature search covering studies of several allergic respiratory diseases, only a small number of clinical trials finally met the selection criteria (Fig. 1). Ten RCTs were identified, from patients with allergic rhinitis, asthma, or atopic cough. Even among them, seven studies<sup>30-32,34,35,37</sup> lacked key information, such as a baseline cough score or the validity of their cough scores, to determine the clinical relevance (Fig. 3). Three RCTs that described the baseline and post-treatment cough scores<sup>32,33,38</sup> commonly reported significant improvements in cough scores with nsH1RAs; and 2 trials of non-asthmatic patients with allergic rhinitis or a predisposition (atopic cough)<sup>33,38</sup> suggested a clinical benefit of nsH1RAs for cough in specific allergic phenotypes of chronic cough, with the relative effect sizes of  $-35\%$  to  $-65\%$  (per maximum scale) in subjective cough scores (Fig. 4).

In patients with allergic asthma, both RCTs found that nsH1RAs were not effective in reducing cough.<sup>31,37</sup> These findings are rather expected since nsH1RA is not considered as a main treatment option for patients with classical asthma. Although cough was not specifically addressed in the paper, a meta-analysis by Van Ganse et al published in 1997 concluded that the evidence was insufficient to support the use of nsH1RAs for asthmatics due to limited magnitude of changes in lung function and the use of rescue medication.<sup>40</sup> In 2 RCTs identified in our systematic review,<sup>31,37</sup> nsH1RAs did not significantly improve lung function or most symptoms (including cough), while it only improved histamine airway hyper-responsiveness (Table S4).

Of 4 RCTs in patients with allergic rhinitis and comorbid asthma, 3 trials<sup>32,34,36</sup> reported statistically significant differences in post-treatment cough scores between the nsH1RA and placebo treatment groups. However, such statistical significance is likely attributed to their large sample sizes ( $n = 186$ ,<sup>34</sup>  $331$ ,<sup>36</sup> and  $613$  patients<sup>32</sup>). Moreover, the degree of cough score improvement is deemed too small to be clinically significant, as shown in the study by Baena-Cagnani et al (MD of cough score:  $-0.12 \pm 0.04$  on a 0-3 scale; relative improvement:  $-4.0 \pm 1.3\%$ ; Figs. 3 and 4).<sup>32</sup>

Three RCTs in non-asthmatic patients with allergic rhinitis reported inconsistent findings (Fig. 3).<sup>30,38</sup> Only the study by Ciprandi et al specified cough as the chief complaint and the primary endpoint; thus, this study likely provides more direct evidence to our research question than the others. However, the study population was patients with cough associated with allergic rhinoconjunctivitis due to *Parietaria judaica* pollen,<sup>38</sup> and the external validity should be further examined.

Based on three RCTs reporting both baseline and post-treatment cough scores,<sup>32,33,38</sup> we calculated the relative improvements in the cough score; although this measure is arbitrary, the degree of improvement was greater in non-asthmatic patients compared to asthmatic patients (Fig. 4). As their baseline cough scores were comparable (approximately 60-70% of their maximum scales; Fig. 3), the differences in treatment effects seemed

to be mainly due to the underlying disease, particularly asthma. Importantly, however, those positive studies were conducted before the validation of current cough measurement tools, such as the objective cough frequency or cough-specific QoL questionnaire; thus, the clinical relevance should be further validated.

In addition to the efficacy of nsH1RAs, their optimal dose and treatment duration for reducing cough also remains to be determined. However, with the standard dose (vs. placebo), the improvements in cough scores were progressive from baseline to 4 weeks in the study by Ciprandi et al (where the statistical significance vs. placebo was tested at 4 weeks only)<sup>38</sup> but were already significant beginning at 1 week in the study by Shioya et al.<sup>33</sup> These findings might serve as guidance for clinical practice in patients with these allergic phenotypes.

There are major limitations in interpreting the present systematic review. First, our findings are not conclusive due to the lack of well-designed trials. However, one strength is that we identified the current knowledge status and gaps through an extensive literature search, which we hope will be helpful in clinical decision making and designing future studies. Second, we did not perform a formal statistical test to assess publication bias, as the number of studies was too small. Lastly, 2 positive trials suggesting substantial therapeutic potential were small.<sup>33,38</sup> This should be clarified in adequately powered clinical trials.

In conclusion, this is the most comprehensive systematic review of RCTs to date, evaluating the efficacy of nsH1RAs on cough outcomes among adults or adolescents with chronic cough or allergic respiratory conditions. Despite the widespread use of nsH1RAs in patients with chronic cough, only a few RCTs were identified to address the question. Overall, the effects of nsH1RAs are likely minimal if given to unselected patients with chronic cough. However, positive trials in non-asthmatic patients with seasonal allergic rhinitis or atopic cough suggest that patients with such specific allergic phenotypes of chronic cough might respond to nsH1RA treatment. Further adequately powered trials with validated cough measurement tools are warranted to confirm the

role of nsH1RAs in the management of patients with allergic phenotypes of chronic cough.

### Abbreviations

UACS: upper airway cough syndrome, ACCP: American College of Chest Physicians, H1RAs: H1-receptor antihistamines, nsH1RAs: non-sedating H1-receptor antihistamines, RCTs: randomized controlled trials, PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses, QoL: quality of life, SDs: standard deviations, SEM: standard errors of the mean, MD: mean difference.

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Not applicable.

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### Authors' contributions

WJS conceived of the study. WJS and JHL conducted and drafted this systematic review. JWJ, JA, HKW, SYP, JHL, SYK and YK participated in interpretation of data. HJK interpreted data and critically reviewed the manuscript. All authors read and approved the final manuscript.

### Declaration of competing interest

None to declare.

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### Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.waojou.2021.100568>.

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