

Efficacy and tolerability of second- and third-generation antihistamines in the treatment of acquired cold urticaria: a meta-analysis

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Background: Acquired cold urticaria (ACU) is a form of physical urticaria that has been treated with first-generation antihistamines; there is a paucity of data regarding second- and third-generation antihistamines for the treatment of ACU.

Objective: To perform a systematic review of the literature to determine the efficacy of second- and third-generation antihistamines in the treatment of ACU.

Methods: Data were extracted via a MEDLINE search of the literature between 1950 and May 2009. We included double-blind, randomized, placebo-controlled studies comparing the treatment of patients with ACU with second- and third-generation antihistamine medications vs placebo.

Results: Overall, 98 patients were identified from 4 included studies. Two trials indicated that second- and third-generation antihistamines significantly eliminated the presence of wheals after treatment vs placebo (odds ratio [OR], 8.88; 95% confidence interval [CI], 4.35 to 18.13). Two trials demonstrated a reduction in wheal area after treatment with a second- or third-generation antihistamine compared with placebo (mean difference, -347.99 mm^2 ; 95% CI, -489.43 to -206.54 mm^2). Two trials demonstrated significant elimination of pruritus with second- or third-generation antihistamine treatment vs placebo (OR, 10.44; 95% CI, 4.39 to 24.84). All 4 studies assessed the tolerability of a second- or third-generation antihistamine vs placebo and found an increased rate of adverse events (OR, 3.04; 95% CI, 1.53 to 6.06), although the complaints were mild.

Conclusions: The newer, less-sedating antihistamines seem to be effective in the treatment of ACU in terms of their ability to significantly reduce the presence of wheals and pruritus after cold exposure. These medications are usually well tolerated, with only mild adverse effects.

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INTRODUCTION

Acquired cold urticaria (ACU) is a common form of physical urticaria characterized by the development of urticarial lesions, angioedema, or anaphylaxis on cold exposure. This condition has been observed in patients ranging in age from 3 months to 74 years, and males and females are affected equally.¹ Numerous triggering events have been identified: exposure to cold temperature, evaporation of sweat, swimming in cold water, lowering of body temperature for surgical procedures (such as cardiac bypass), etc.² A diagnosis of ACU is usually made by induction of a wheal and flare response after the application of an ice cube or cold pack to the skin, although more sophisticated methods now allow measurement of the precise temperature required to elicit a response.³ The severity of the reaction varies from patient to patient and depends on the magnitude of the decrease in temperature and the duration of

exposure. For example, those at highest risk for anaphylaxis have been shown to develop wheals after less than 3 minutes of cold exposure during ice cube challenge.^{4,5}

Traditionally, this disease has been treated with first-generation antihistamine medications, in particular the first-generation antihistamine cyproheptadine.¹ The efficacy of cyproheptadine in the treatment of ACU was first demonstrated in a double-blind study by Wanderer et al in 1977.⁶ Later, doxepin, which causes nonspecific and sedating H_1 antagonism and H_2 antagonism, was demonstrated to be effective in reducing symptom development in ACU.⁷ With the development of less-sedating second- and, more recently, third-generation antihistamines, the more-sedating first-generation antihistamines have fallen out of favor for the treatment of histamine-mediated allergic disease in general. Second- and third-generation antihistamines are widely available and tend to be better tolerated because they are more selective for peripheral H_1 receptors than for histaminergic and cholinergic receptors in the central nervous system (Table 1). Third-generation antihistamines are composed of the active metabolite or enantiomer derived from a second-generation antihistamine. Current practice parameters include second-generation antihistamines as an alternative to the traditional regimens of cyproheptadine or doxepin for prophylactic treatment of ACU.⁸ The literature, however, contains only a paucity of data regarding the effectiveness of second- and third-generation antihistamines in the treatment of ACU. To that end, we performed a

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Table 1. Availability of Second- and Third-Generation Antihistamines

Approved in US	Approved Outside of US
Second Generation	
Acrivastine	Acrivastine
Cetirizine	Cetirizine
Loratadine	Ebastine
	Loratadine
	Mizolastine
Third Generation	
Desloratadine	Desloratadine
Fexofenadine	Fexofenadine
Levocetirizine	Levocetirizine

meta-analysis of the medical literature to evaluate the clinical evidence regarding the prophylactic use of second- and third-generation antihistamines in the treatment of ACU.

METHODS

We conducted a systematic search of the MEDLINE medical literature database for articles published between 1950 and May 2009 using the search terms *cold urticaria* and *antihistamine*. A single reviewer (M.W.) evaluated all the potentially relevant studies, and only double-blind, randomized, placebo-controlled studies from either the search or a subsequent review of bibliographies of relevant articles were used in this analysis. Included studies evaluated reduction of wheal area and elimination of wheals and pruritus after cold challenge as end points and reported adverse effects of medication administration. Statistical analyses were performed using Review Manager (RevMan) 5 provided by the Cochrane Collaboration.

RESULTS

We identified 68 potentially relevant articles. Seven clinical trials that compared a second- or third-generation antihista-

mine with placebo in the treatment of ACU were identified, with 4 trials meeting the inclusion criteria. The excluded studies^{9–11} were eliminated because they were individual case reports or were not double-blind (Fig 1).

The 4 double-blind, placebo-controlled, randomized, crossover trials^{12–15} included 98 patients. All the studies had similar population sizes, ranging from 18 to 30 (Table 2). The studies were all performed in Europe (2 in Germany, 1 in Finland, and 1 in France). Patients ranged in age from 15 to 71 years. Female patients significantly outnumbered male patients 69% to 31% (pooled odds ratio [OR], 4.83; 95% confidence interval [CI], 2.77 to 8.43). Each study compared a different second- or third-generation antihistamine with placebo. The antihistamines studied were acrivastine,¹² mizolastine,¹³ ebastine,¹⁴ and desloratadine.¹⁵ The trial of desloratadine compared efficacy at 2 doses: standard (5 mg) and high (20 mg). In addition, 1 study¹² compared acrivastine with placebo and the first-generation antihistamine cyproheptadine.

Two studies^{14,15} compared the ability of second- and third-generation antihistamines to eliminate wheal formation vs placebo after cold challenge (Fig 2). Fifty-two patients were included in the 2 studies that used ebastine¹⁴ and desloratadine (standard and high dose)¹⁵ as treatment. These antihistamines significantly eliminated the presence of wheals compared with placebo (OR, 8.88; 95% CI, 4.35 to 18.13). There was no statistically significant heterogeneity between the studies ($P = .76$).

Two studies^{12,15} compared the ability of second- and third-generation antihistamines to reduce wheal area vs placebo after cold challenge (Fig 3). Acrivastine¹² and desloratadine (standard and high dose)¹⁵ were evaluated in 48 patients. The antihistamines significantly reduced the area of wheals compared with placebo (mean difference, -347.99 mm^2 ; 95% CI, -489.43 to -206.54 mm^2). There was no significant heterogeneity between the studies ($P = .14$). In the study¹² that compared the second-

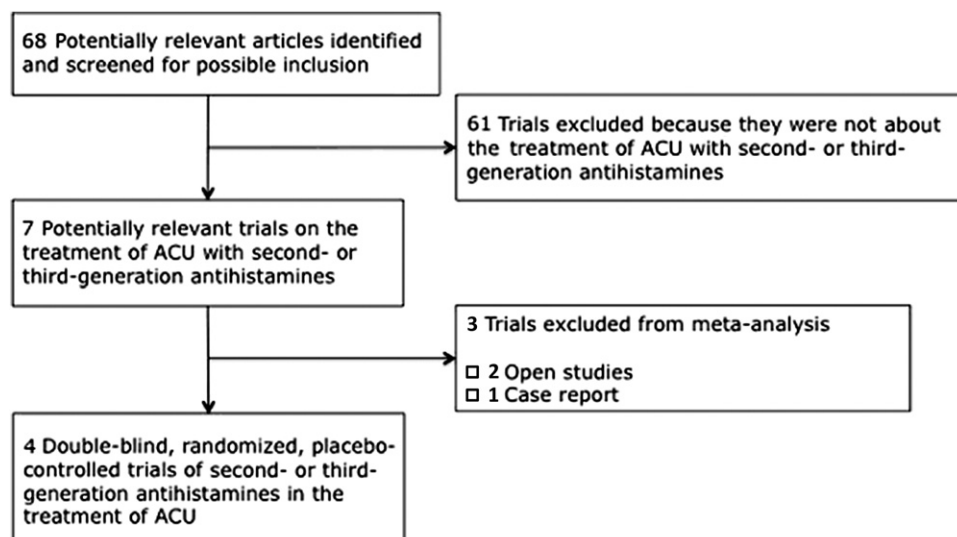


Figure 1. Classification of articles retrieved from the literature for the meta-analysis. ACU indicates acquired cold urticaria.

Table 2. Summary of the 4 Included Trials

Source	Patients, No.	Patient Age, y	Antihistamines	Dose, mg	Daily Frequency	Results
Neittaanmaki, et al, ¹² 1988	18	19–44	Acrivastine	8	3 times	Decreased wheal area and pruritus
			Cyproheptadine	4	3 times	
Dubertret, et al, ¹³ 2003	28	15–60	Mizolastine	10	Once	Decreased wheal and pruritus scores
Magerl et al, ¹⁴ 2007	22	18–70	Ebastine	20	Once	Eliminated the presence of wheals and pruritus
Siebenhaar, et al, ¹⁵ 2009	30	18–71	Desloratadine	5	Once	Decreased wheal area, volume; increased time to symptom development
				20	Once	

generation antihistamine acrivastine with the first-generation antihistamine cyproheptadine and placebo, both the antihistamines were found to be superior to placebo in terms of wheal area after treatment ($P < .01$). Moreover, the mean wheal diameters at the end of treatment were significantly reduced after treatment with acrivastine (365.5 mm²) vs treatment with cyproheptadine (472.2 mm²) ($P < .01$).

Two studies compared the ability of the second-generation antihistamines acrivastine¹² and ebastine¹⁴ to eliminate pruritus vs placebo after cold challenge in 40 patients (Fig 4). The antihistamines significantly reduced pruritus compared with placebo (OR, 10.44; 95% CI, 4.39 to 24.84). There was no significant heterogeneity between the studies ($P = .94$).

In studies that reported conversion to a negative cold challenge test, nearly half (40 of 82) of the patients had complete elimination of wheals after treatment with the second- or third-generation antihistamine. In patients who continued with a positive cold challenge test despite antihistamine therapy, the area of the urticarial wheal was reduced by approximately 50%. Pruritus was eliminated in more than 77% (31 of 40) of patients treated with a second-generation antihistamine.

All 4 studies^{12–15} reported adverse events during the trials in the 98 patients included (Fig 5). Twenty-nine adverse events were reported during antihistamine therapy vs 11 during treatment with placebo (OR, 3.04; 95% CI, 1.53 to 6.06). In general, the complaints were mild, with fatigue or drowsiness being the most common adverse event reported. In the trial¹² that compared acrivastine with cyproheptadine and placebo, a significant increase in adverse events was seen in the cyproheptadine group compared with the acrivastine group ($P < .05$). More adverse events were

reported with standard- vs high-dose desloratadine.¹⁵ Patients taking ebastine reported no adverse events.¹⁴

DISCUSSION

Histamine has been implicated in the development of urticarial lesions in patients with ACU.^{16–18} To that end, antihistamines are considered first-line treatment for urticaria. In particular, current practice parameters suggest that first- and second-generation antihistamines, as well as doxepin, are effective in the prophylactic treatment of ACU.⁸ Previous studies^{7,19} have demonstrated the effectiveness of antihistamines in reducing the response to cold challenge in patients with ACU. The first double-blind controlled trial¹⁹ of an antihistamine medication in the treatment of ACU showed that cyproheptadine prolonged the time needed to generate an urticarial wheal after ice cube challenge. The disadvantages of cyproheptadine, a first-generation antihistamine, are its frequency of dosing (3 times a day) and adverse effects. Because of their ability to gain access to H₁ histamine receptors in the central nervous system, doxepin and first-generation antihistamines, such as cyproheptadine, often cause the unwanted adverse effect of sedation. With the development of second- and third-generation antihistamines, this adverse effect can be avoided or at least reduced compared with first-generation antihistamines, making them more attractive as prophylactic medications. Given the potentially life-threatening reactions of anaphylaxis and laryngeal edema associated with cold exposure in patients with ACU, prophylaxis with a medication capable of mitigating these symptoms is of utmost importance.

This meta-analysis demonstrates the effectiveness of second- and third-generation antihistamines in the treatment of

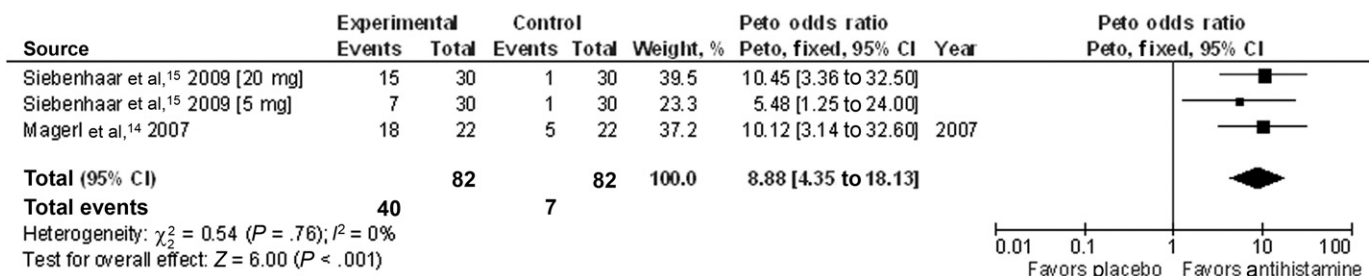


Figure 2. Forrest plot demonstrating the significant ability of second- and third-generation antihistamines to eliminate wheal formation after cold challenge compared with placebo. CI indicates confidence interval.

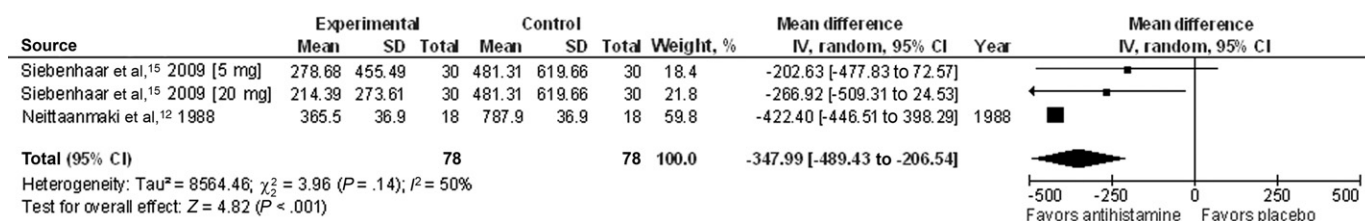


Figure 3. Forrest plot demonstrating the significant ability of second- and third-generation antihistamines to reduce wheal area (in square millimeters) after cold challenge compared with placebo. CI indicates confidence interval.

ACU. These medications significantly reduced the development of pruritus and wheals compared with placebo after cold challenge. In many patients, these medications completely eliminated the development of symptoms after cold challenge. This symptom reduction supports their effectiveness as treatment and use as prophylaxis in patients with ACU. Although studies of only 4 second- or third-generation antihistamines were included in this meta-analysis, the similar mechanism of action in this class of medications suggests effectiveness for all the second- and third-generation antihistamines in the treatment of ACU.

This meta-analysis demonstrates a significant increase in patient adverse effect complaints in those treated with second- or third-generation antihistamines compared with placebo. Generally, these adverse effects were considered mild. In included studies that reported specific adverse effects, the most common complaint was drowsiness or fatigue. No medication is completely benign, so it is not surprising that patients had more adverse effects when taking second- or third-generation antihistamines compared with placebo. Of particular interest in ACU, a disease that often requires prophylactic medication administration in addition to symptomatic administration, is how a specific therapy compares with alternative therapies and not only with placebo. In the 1 study¹² that compared first- and second-generation antihistamines, patients with ACU ($n = 18$) had significantly fewer adverse effect complaints when treated with acrivastine compared with cyproheptadine ($P < .05$).

The antihistamines used in this meta-analysis have been thoroughly studied in larger population trials to evaluate their adverse effect profiles. In previous trials,^{20–22} desloratadine has shown no decrease in wakefulness compared with placebo and has shown significantly reduced somnolence compared with

diphenhydramine. The most common adverse effect in these trials was headache, which was reported in 8% of patients but was not significantly different than placebo. Moreover, there was no significant increase in drowsiness with doses as high as 45 mg/d. Similarly, there were no significant differences in reported adverse effects in patients with ACU treated with a standard 5-mg dose of desloratadine compared with 20 mg; in fact, fewer adverse events were reported during high-dose desloratadine therapy.²³ Ebastine was previously shown to have no significant increase in adverse effects compared with placebo, with headache being the most commonly reported complaint.²⁴ Similarly, no adverse events were reported with ebastine therapy in patients with ACU in this included trial. Acrivastine and mizolastine also demonstrated no significant difference in terms of adverse events compared with placebo in large controlled trials.^{25,26}

ACU has been classified based on 3 clinical patterns that occur with similar frequency.⁵ Type I ACU manifests as localized urticarial lesions or as angioedema after cold exposure. Type II ACU presents with generalized urticaria or angioedema, and type III ACU presents with generalized symptoms and hypotension. Patients with a positive cold challenge reaction after less than 3 minutes of cold exposure have been shown to be at increased risk for type III reactions (57%).^{4,5} Nevertheless, a significant proportion of patients with a positive cold challenge reaction after more than 3 minutes of cold exposure demonstrate type III reactions (24%).¹ Owing to the high risk of potential life-threatening reactions, patients with ACU need to avoid aquatic activities and other cold exposures. To help mitigate these reactions, and for overall patient comfort, prophylactic therapy should be used. The results of this meta-analysis suggest that second- and third-generation antihistamines are effective

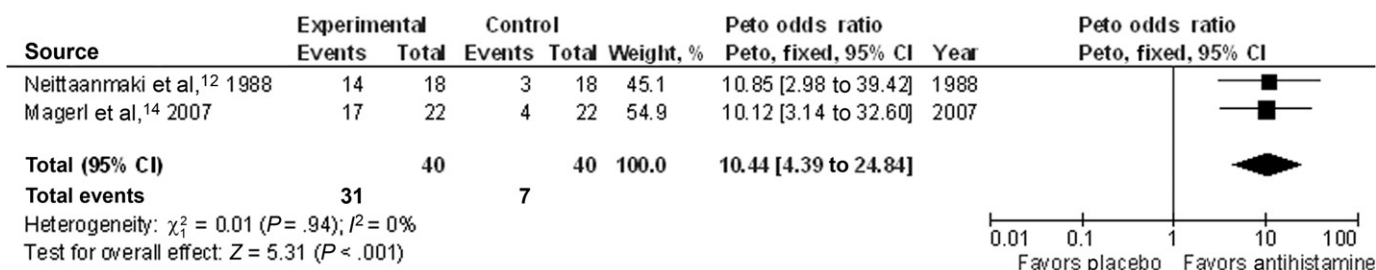


Figure 4. Forrest plot demonstrating the significant ability of second- and third-generation antihistamines to eliminate pruritus during cold challenge compared with placebo. CI indicates confidence interval.

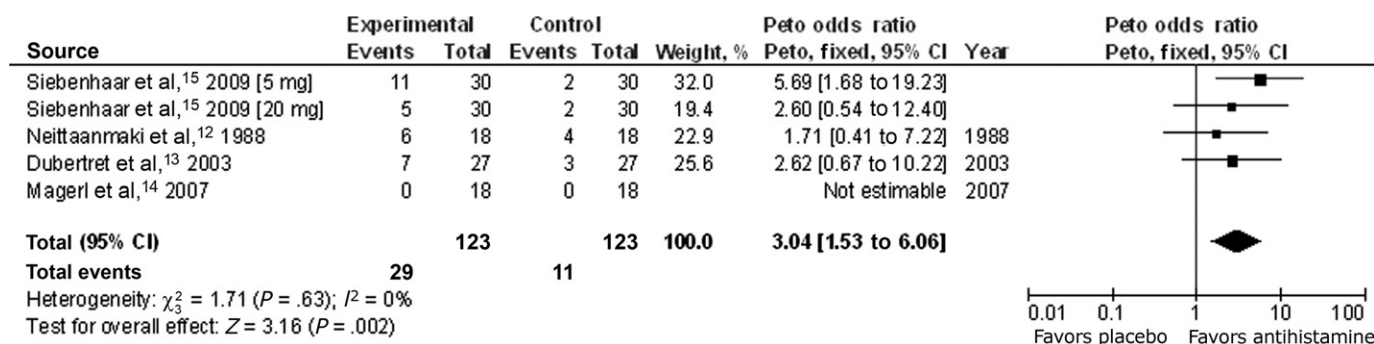


Figure 5. Forrest plot demonstrating a significant increase in adverse event complaints after second- and third-generation antihistamine administration compared with placebo. CI indicates confidence interval.

and well-tolerated treatments that can be safely used as first-line therapy in patients with ACU.

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