

Chronic inducible urticaria: A systematic review of treatment options



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Background: Chronic inducible urticaria (CindU) is a condition characterized by the appearance of recurrent wheals, angioedema, or both as a response to specific and reproducible triggers.

Objective: We sought to systematically assess evidence on the efficacy and safety of treatment options for CindU. Results were used to inform the 2017 update of “The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria.”

Methods: Randomized controlled trials and controlled intervention studies were searched systematically in various databases. Included studies were evaluated with the Cochrane Risk of Bias tool. Where possible, results from single studies were meta-analyzed, applying the Mantel-Haenszel approach by using a random-effects model (Der Simonian–Laird).

Results: We identified 30 studies that included patients with cold urticaria, symptomatic dermatographism, delayed-pressure urticaria, or cholinergic urticaria. No studies on other forms of CindU were eligible. Risk of bias was often rated as unclear or high. Overall, second-generation antihistamines were more effective than placebo, and available data indicate that updosage might be effective. Omalizumab proved effective in patients with symptomatic dermatographism, who did not respond to antihistamines. Detailed results are given for each type of CindU.

Conclusions: The available evidence is limited by small samples, heterogeneous efficacy outcomes, and poor reporting quality in many of the included studies. The findings are congruent with the suggested stepwise approach to treating CindUs. However, the data do not allow for drawing specific conclusions for specific subtypes of CindU. (*J Allergy Clin Immunol* 2018;141:1726-34.)

Key words: Urticaria, angioedema, inducible urticaria, omalizumab, antihistamines, review

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Urticaria is a condition characterized by recurrent wheals, angioedema, or both. Patients experience pruritus, and the condition can severely influence their quality of life. Urticaria is classified as chronic if wheals, angioedema, or both recur for more than 6 weeks. By definition, no specific triggers are associated with the appearance of signs and symptoms for chronic spontaneous urticaria (CSU). In contrast, chronic inducible urticarias (CindUs) are associated with a specific trigger that leads reproducibly to the immediate or delayed appearance of symptoms.¹ Common forms of CindUs are physical urticarias, which are related to the exposure to physical triggers, such as cold, heat, vibration, or pressure. The physical urticarias (ie, symptomatic dermatographism, heat and cold urticarias, delayed-pressure urticaria, solar urticaria, and vibratory angioedema) are distinguished from other inducible urticarias that include cholinergic urticaria, contact urticaria, and aquagenic urticaria.¹ Data on the proportion of physical urticarias among patients with any chronic urticaria range from 7% to 44%,² but up to 36% of patients with CSU have been reported to react concomitantly to physical trigger tests.³ Of the inducible urticarias, symptomatic dermatographism and cholinergic urticaria appear to be the most common forms, but no reliable data exist.¹ However, some of them are extremely rare, such as heat urticaria, with only a few patients having been reported. Therefore it is not easy to perform studies big enough to identify statistically significant differences.

Management of CindU typically involves threshold testing and consecutive avoidance of relevant triggers. Where this is not possible or feasible, symptomatic treatment follows a stepwise

Abbreviations used

AE:	Adverse event
CindU:	Chronic inducible urticaria
CSU:	Chronic spontaneous urticaria
H1-AH:	H1-antihistamine
ITT:	Intention to treat
MD:	Mean difference
RR:	Risk ratio

approach. This approach involves application of antihistamines in up to 4-fold dosage; omalizumab, an anti-IgE antibody approved for the treatment of CSU; or cyclosporine.^{1,4} This basic treatment algorithm resembles the current guideline recommendations for the treatment of CSU.

The goal of the present systematic review was to comprehensively assess the available evidence from randomized controlled trials and controlled interventional studies on the efficacy of medical interventions for the various CindUs. It was used to inform “The EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria” (the 2017 revision and update [under review]).

METHODS

We applied systematic review methods, as recommended by Higgins et al,⁵ and our reporting followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.⁶ An internal protocol was developed *a priori* and followed.

Database searches and study selection

We used the same search strategy as described in the methods report for the 2017 revision and update of the “EAACI/GA²LEN/EDF/WAO guideline for the definition, classification, diagnosis and management of urticaria” (under review). We adapted it to 4 databases (MEDLINE [1946 to March Week 4, 2016; Ovid]; MEDLINE In-Process & Other Non-Indexed Citations [March 31, 2016; Ovid]; EMBASE [1974 to 2016 Week 13; Ovid]; and CENTRAL [Cochrane Central Register of Controlled Trials—Issue 3 of 12; March 2016]) with use of a trial filter (see [Appendix E1](#) in this article’s Online Repository at www.jacionline.org).⁷ We ran an update search on March 13, 2017, and limited the time to 2016/2017.

Our prespecified inclusion and exclusion criteria are shown in [Table 1](#). Two independent reviewers (AN and CD) screened all titles/abstracts for inclusion. All included titles/abstracts were then evaluated in full text independently twice and subsequently extracted twice (CD, RNW, and LE). We used EndNote to manage references.

Data extraction

We used a standardized data extraction sheet (Excel; Microsoft, Redmond, Wash). Data were extracted for the following items: study design and procedure; inclusion criteria; baseline characteristics; proportion of patients reported to be symptom free, wheal free, or with a good/excellent response; mean (change) in time or temperature score (only for cold urticaria); mean (change) wheal response (only for symptomatic dermographism); mean improvement (only for cholinergic urticaria); and mean (change) pressure or weight (only for delayed-pressure urticaria). We also extracted follow-up times and safety outcomes ([Table 1](#)).

Data transformation

The following data transformations were performed. Where dichotomous efficacy data were not reported in the intention-to-treat (ITT) analysis format,

we imputed data by using the nonresponder imputation method. Where SEs or CIs were reported for continuous outcomes, we used standard formulas to calculate SDs.⁵

We used the Engauge Digitizer 4.1 to extract data, which were displayed in image graphs only.

Effect measures and result synthesis

We used Review Manager 5.3.4⁸ to calculate mean differences (MDs) and risk ratios (RRs) with corresponding 95% CIs. For each type of urticaria, a separate Review Manager file was created, and we used subgroups to differentiate time points and dosages. Only pairwise comparisons were calculated. We treated crossover trials as if they were parallel-group trials. For multiple comparisons, including patients from the same trial, we used split groups to avoid counting patients twice when pooling. Data were only pooled if heterogeneity was an I^2 value of 50% or less. The Mantel-Haenszel approach was chosen by using a random-effects model (DerSimonian and Laird).⁹

Risk of bias assessment

The Cochrane Risk of Bias Tool was used to assess sequence generation, allocation concealment, and other sources of bias at the study level.⁵ For blinding, we assessed risk of bias on the outcome level differentiating between patient- and assessor/clinician-reported outcomes. If there was no blinding, the judgement was high risk unless 2 active treatments were compared and the outcome was patient reported (unclear). Regarding incomplete outcome data, only reported or our own ITT analyses were rated as low risk. If no ITT was reported/could not be calculated and a 10% or greater loss to follow-up was reported, the risk of bias for the corresponding outcome was rated as high. Adverse events (AEs) had to be reported in detail per study group to be rated as low. Controlled clinical studies with a comparison group were rated as high risk of bias overall.

RESULTS

The original literature search took place on April 1, 2016. Of the 5627 unique hits, the title and abstract screening led to inclusion of 58 records for further inspection (excluding 1 duplicate). The update search was run on March 13, 2017, leading to 491 hits, 106 of which were duplicates. One new record was included during the title/abstract screening. The full-text screening led to inclusion of this record (abstract only). A total of 30 studies were included. Excluded full text with reasons for exclusion are listed in [Appendix E2](#) in this article’s Online Repository at www.jacionline.org. Characteristics of the included studies are presented in [Appendix E3](#) in this article’s Online Repository at www.jacionline.org.

Cold urticaria

We were able to include 14 studies evaluating H1-antihistamines, doxepin, or cyproheptadine for the treatment of cold urticaria.¹⁰⁻²³ Thirteen studies were crossover trials including 241 patients and 1 study including 30 participants (2-arm parallel design). The studies were published between 1977 and 2016. At least 1 efficacy effect estimate could be calculated for 11 studies.

First generation versus placebo. Three studies evaluated first-generation antihistamines versus placebo.

Wanderer et al²³ compared 4 mg of chlorpheniramine 3 times a day for 7 days with placebo and reported “the minimum time required to induce a coalescent wheal” to be 5 minutes (mean) before and 6 minutes after treatment in both groups ($n = 8$). There were no withdrawals because of AEs.

TABLE I. Eligibility criteria

Inclusion	Exclusion
● Patients with physical urticarias, including ■ symptomatic dermographism (= urticaria factitia, dermographic urticaria) ■ cold urticaria ■ delayed-pressure urticaria ■ solar urticaria ■ heat urticaria ■ vibratory angioedema ● Patients with other inducible urticarias ■ cholinergic urticaria ■ contact urticaria ■ aquagenic urticaria ● At least 80% of study participants had to have a diagnosis of at least 1 type of CIndU ● Any systemic intervention, including off-label drugs ● Comparisons with another included drug and/or placebo ● Combinations of topical and systemic treatments ● Dose-comparison studies ● Studies reporting at least 1 efficacy outcome for at least 2 study groups at the same time point ● Studies report a length of follow-up between 3 d and 4 wk ● RCTs (crossover, parallel, cluster, factorial, pragmatic) ● CCTs (defined here as a clinical study that includes a comparison group)	● Other diagnoses, such as CSU only ● Uncontrolled observational studies ● Publications that do not report any numeric outcome data ● Comparisons of first-generation antihistamines vs different first-generation antihistamines or second-generation antihistamines vs second-generation antihistamines (if in same dose [eg, both 1-fold])

CCTs, Controlled intervention studies; RCT, randomized controlled trial.

St-Pierre et al²¹ compared 1 mg of ketotifen twice daily for 7 days with placebo and found it to be more effective based on patients' effect rating as "excellent/good" (RR, 4.50; 95% CI, 1.25-16.25; n = 11). No safety outcomes were reported.

Neittaanmaki et al¹⁹ compared hydroxyzine versus placebo and found no difference when looking at the outcome "very effective" (RR, 5.00; 95% CI, 0.27-94.34; n = 12). Tiredness was reported by more patients in the active treatment group (n = 8) than in the placebo group (n = 1).

Second-generation H1-antihistamines versus placebo. In 8 studies the effect of second-generation H1-antihistamines (H1-AHs; 1- to 4-fold dose) were compared with placebo.^{10-15,17,18,20} Four studies reported the proportion of patients who were symptom free after 7 days of treatment (based on provocation). Antihistamines were more effective than placebo (RR, 4.33; 95% CI, 2.11-8.85).

Metz et al¹⁷ also reported the outcome "wheal free" after provocation. After 1 week, rupadatin was 2-fold more effective than placebo (RR, 11.00; 95% CI, 1.56-77.76; n = 21); however, the CI was very wide.

Three further studies reported other outcomes. Gimenez-Arnau et al¹² found that "the highest temperature capable to induce a wheal" significantly decreased with 20 mg of rupadatin once daily versus placebo after 7 days (MD, -7.50; 95% CI, -11.21 to -3.79; n = 21). No difference was found in the study by Levnadier et al¹⁵ for "delay in cold-induced wheal reaction" between 10 mg of mizolastine and placebo (RR, 2.50; 95% CI, 0.89-7.03; n = 28). Neittaanmaki et al¹⁸ described that 8 mg of acrivastine 2 times daily led to a smaller "mean area of wheal induction" after 5 days of treatment (acrivastine group, 356.5 mm²; placebo group, 787.9 mm²; n = 18).

Safety. Three of the studies reported in Fig 1 stated that there were no withdrawals because of AEs.^{11,14,17} Four studies reported

the "number of patients with at least one AE" (RR, 1.60; 95% CI, 0.96-2.65; Fig 2). Three studies do not report either of these outcomes.^{12,15,20}

Second-generation versus second-generation different dose. Four studies evaluated second-generation H1-AHs in different doses reporting the outcome "symptom free." There were no differences when comparing 1-2 fold or 2-fold versus 1-fold, or 4-fold versus 2-fold. Only 4-fold versus 1-fold dose showed a significant difference (Fig 3).

Two of these studies also reported "patients with at least one AE" for which no difference could be identified (Fig 4) and withdrawal because of AE (1 study, 0 events in both groups, n = 15 per group).

First generation versus second generation. Villas Martinez et al²² performed a 3-arm study comparing 20 mg of loratadine daily, 1 mg of ketotifen twice daily, and 10 mg of cetirizine once daily and found no difference regarding patients being "asymptomatic" after 14 days of treatment (RR, 0.86; 95% CI, 0.30-2.49), "patients with at least one AE" (RR, 0.37; 95% CI, 0.10-1.39), and "drowsiness" (RR, 0.32; 95% CI, 0.06-1.80; n = 7).

Other treatments. Doxepine versus placebo or first-generation antihistamines. Pooled data from 2 studies¹⁹ showed that 10 mg of doxepine 3 times daily for 1 week is more effective than placebo when treating cold urticaria (RR, 14.90; 95% CI, 2.13-104.08; I² = 0%; n = 44). Neittaanmaki et al¹⁹ found no difference between 10 mg of doxepine 3 times daily and hydroxyzine after 1 week of treatment (RR, 0.33; 95% CI, 0.08-1.33; n = 12). Numbers of AEs or withdrawals were not reported.

Cyproheptadine versus placebo. Wanderer et al²³ compared 4 mg of cyproheptadine 3 times daily for 7 days with placebo and reported "the minimum time required to induce a

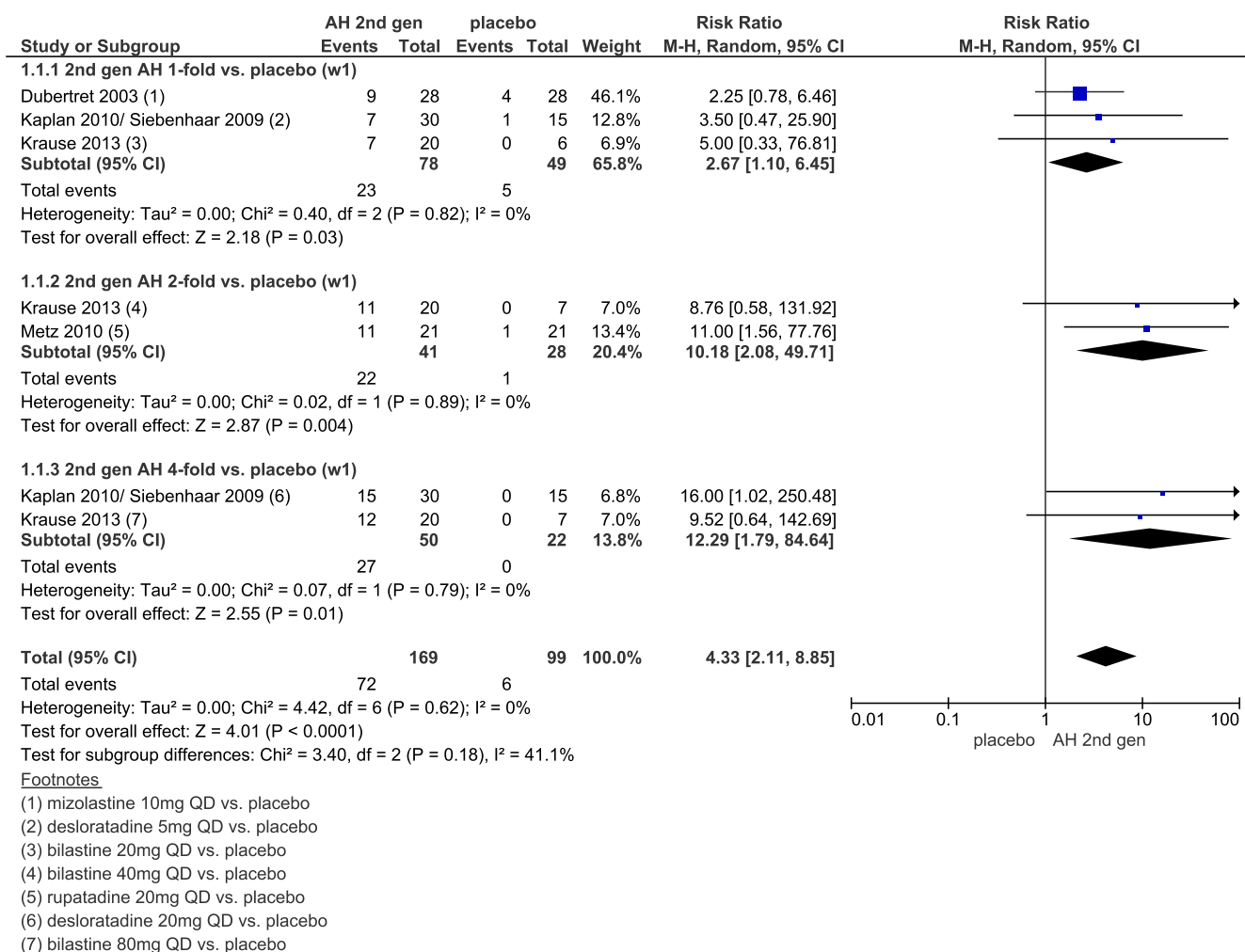


FIG 1. Forest plot for cold urticaria studies comparing second-generation antihistamines with placebo reporting the outcome “symptom free.” *gen*, Generation; *M-H*, Mantel-Haenszel approach; *QD*, once daily.

coalescent wheal” to be 6 minutes (mean) in the placebo group and “no wheal within 15 minutes” in the cyproheptadine group ($n = 8$).

Neittaanmakie et al¹⁹ compared 4 mg of cyproheptadine with placebo and found no difference when looking at the outcome “very effective” (RR, 7.00; 95% CI, 0.40-122.44; $n = 12$).

Risk of bias. The majority of studies reported their methods and outcomes poorly. Many of the risk of bias items could not be assessed because of insufficient reporting (Table II).¹⁰⁻³⁹

Symptomatic dermographism

Seven studies reported in 6 publications assessed interventions for symptomatic dermographism in 102 patients in total.²⁴⁻²⁹

First generation versus placebo. Boyle et al²⁴ evaluated 8 mg of acrivastine 3 times daily versus placebo. More patients “improved” when treated with acrivastine for 5 days (RR, 2.78; 95% CI, 1.31-5.91; $n = 12$), but it is unclear to what extent. Safety data were not available.

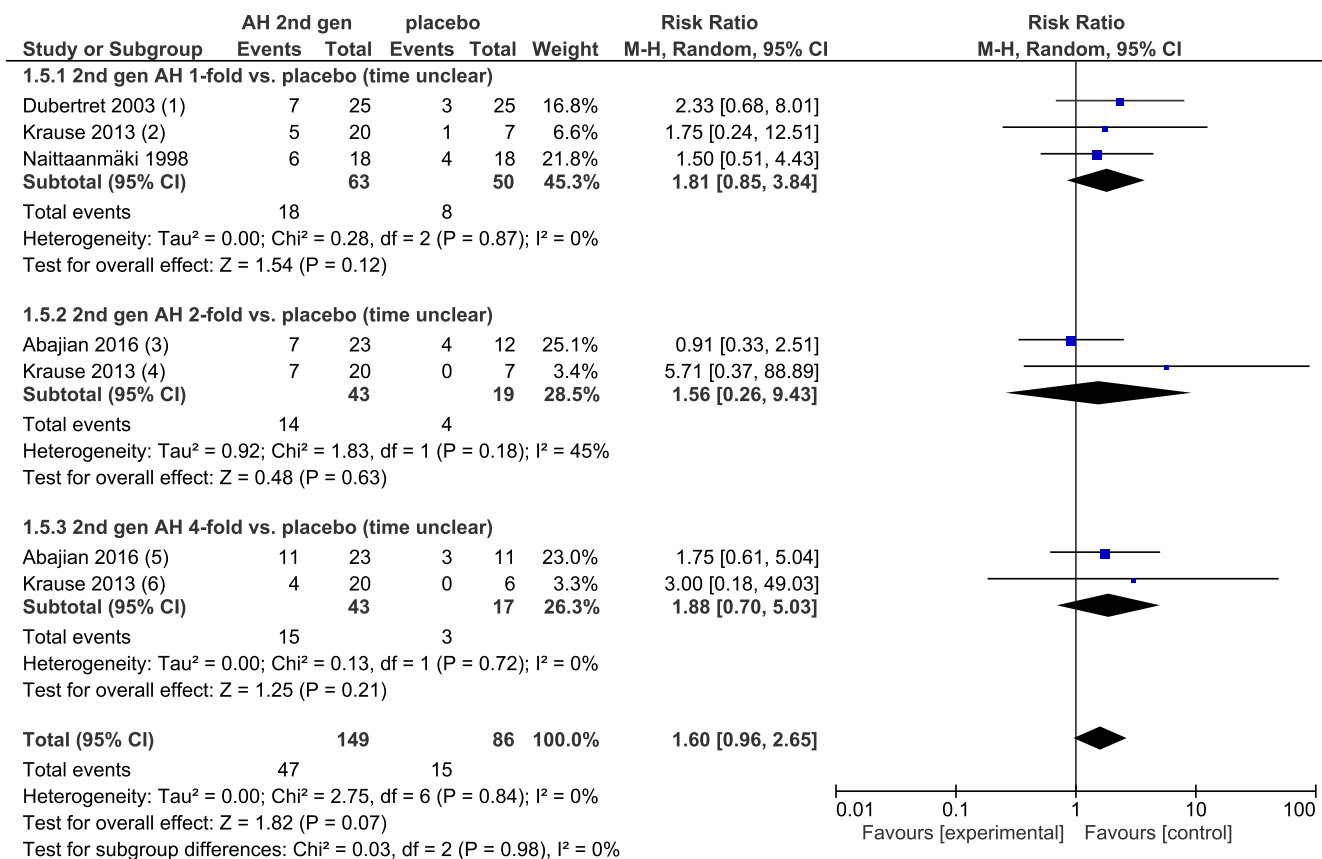
Second-generation H1-AHs versus placebo. Sharpe and Shuster²⁹ compared 10 mg of cetirizine once daily with placebo. The mean change in “patient-reported severity” after 7 days

was 3.9 in the placebo and 1.7 in the active treatment groups. The MD in “subjective wheal assessment” was also lower in the cetirizine group (MD, -17.50; 95% CI, -32.88 to -2.12; $n = 19$). Safety data were not reported in the predefined format.

Second-generation H1-AHs versus second-generation H1-AHs plus other treatment. Kumar et al²⁶ conducted a clinically controlled trial and looked at 10 mg of cetirizine once daily ($n = 9$) in comparison with cetirizine plus 2 mg of betamethasone ($n = 7$). There was no difference when looking at “complete remission” (RR, 1.44; 95% CI, 0.88-2.35) or 90% or greater relief (RR, 1.25; 95% CI, 0.84-1.86) after 4 weeks. There were no withdrawals because of AEs in either group.

First-generation H1-AHs versus second-generation H1-AHs. Krause and Shuster²⁵ compared 10 mg of astemizol 3 times daily with 4 mg of chlorpheniramine 3 times daily in 16 patients. The mean wheal threshold when treated with chlorpheniramine was 43.8 ± 5.3 g/mm² and 45.1 ± 3.4 g/mm² when treated with astemizol after 4 weeks (n unclear). There was no difference in patients with at least 1 AE (RR, 1.46; 95% CI, 0.53-4.00) or in withdrawal because of AEs (RR, 0.33; 95% CI, 0.02-7.14).

Other treatments. Five milligrams of nifedipine 3 times daily or 10 mg 3 times daily versus placebo.



Footnotes

- (1) mizolastine 10mg QD vs. placebo
 (2) bilastine 20mg QD vs. placebo
 (3) rupatadine 20mg QD vs. placebo
 (4) bilastine 40mg QD vs. placebo
 (5) rupatadine 40mg QD vs. placebo
 (6) bilastine 80mg QD vs. placebo

FIG 2. Forest plot of cold urticaria studies comparing second-generation H1-AHs with placebo reporting the outcome “patients with at least one AE.” *gen*, Generation; *M-H*, Mantel-Haenszel approach; *QD*, once daily.

Lawlor et al²⁷ report 2 studies comparing nifedipine with placebo. After 2 weeks, there was no difference (MD, 0.24; 95% CI, -0.54 to 2.04; $n = 18$; $I^2 = 0\%$). Few withdrawals because of AEs were reported (2/13 patients overall for 5 mg of nifedipine vs placebo; RR, 3.00; 95% CI, 0.14-64.26; for 10 mg of nifedipine vs placebo).

Omalizumab versus placebo. Metz et al²⁸ recruited 61 antihistamine-resistant patients and treated them with either 150 mg of omalizumab, 300 mg of omalizumab, or placebo. There was a difference between omalizumab and placebo (RR, 4.36; 95% CI, 1.13-16.79; $n = 55$, per-protocol as number per group unclear, $I^2 = 0\%$). There were “few AEs in both groups,” but no numeric data were provided.

Risk of bias. Risk of bias was unclear to high across all studies (Table II).

Delayed-pressure urticaria

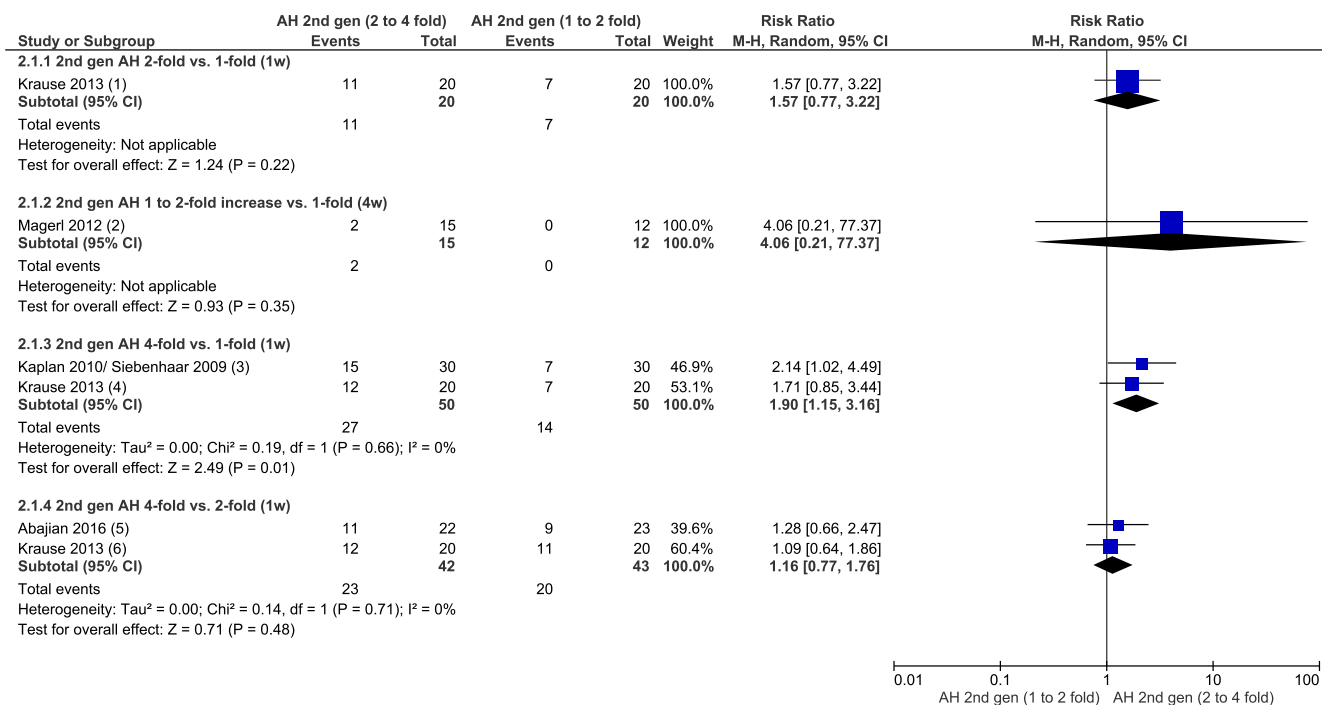
Five studies³⁰⁻³⁴ including 91 patients assessed second-generation antihistamines alone or in combination or colchicine for the treatment of delayed-pressure urticaria.

Second-generation H1-AHs versus placebo. In 2 almost identical studies,^{30,31} the effect of 10 mg of cetirizine 3 times daily was compared with placebo ($n = 11$ per study). After 1 week, the final mean “wheal area” was 806 and 891 mm² in the cetirizine groups and 1722 and 1751 mm² in the respective placebo groups. AEs were not reported.

Nettis et al³³ also compared 5 mg of desloratadine with placebo. The final mean “wheal size” did not differ between the groups (MD, -4.80; 95% CI, -7.87 to 1.73; in square millimeters, $n = 11$ per group). No patients withdrew because of AEs or reported any AEs.

Second-generation H1-AHs versus second-generation H1-AHs plus other treatment. The above-mentioned study included a third arm treating patients with 5 mg of desloratadine plus 10 mg of montelukast ($n = 12$) for 2 weeks. The combination treatment led to a significantly smaller final wheal area (MD, -6.20; 95% CI, -9.18 to -3.22; in square millimeters).

Nettis et al³⁴ compared 10 mg of loratadine plus 10 mg of montelukast versus loratadine alone. The combined treatment was

**Footnotes**

- (1) bilastine 40mg QD vs. bilastine 20mg QD
(2) desloratadine 5mg for 2w then 10mg for 2w vs. desloratadine 5mg for 4w
(3) desloratadine 20mg QD vs. desloratadine 5mg QD
(4) bilastine 80mg QD vs. bilastine 20mg QD
(5) rupatadine 40mg QD vs. rupatadine 20mg QD
(6) bilastine 80mg QD vs. bilastine 40mg QD

FIG 3. Forest plot of cold urticaria studies comparing second-generation H1-AHs in different doses reporting the outcome “symptom free.” gen, Generation; M-H, Mantel-Haenszel approach; QD, once daily.

more effective than loratadine alone when looking at “complete suppression” after 2 weeks (7 kg of weight suspended on the shoulder; RR, 4.00; 95% CI, 1.11-14.35). There were no withdrawals because of AEs.

Other treatments. Lawlor et al³² compared 0.5 mg of colchicine twice daily with placebo. The final MD in “total number of wheals” was 2.75 ± 28.18 (n = 13), an increase in the colchicine group. No withdrawals because of AEs were reported.

Risk of bias. Risk of bias was rated unclear in most studies (Table II).

Cholinergic urticaria

Four studies including 316 patients assessed antihistamines for the treatment of cholinergic urticaria.^{35-38,41}

First-generation H1-AHs versus second-generation H1-AHs versus placebo. Kobza Black et al³⁶ used 20 mg of hydroxyzine 3 times daily versus placebo and found that the mean “degree of improvement” (self-assessed; scale: minimal = 0, maximal = 3) was 1.58 (n = 10) for hydroxyzine and 0.74 (n = 9) for placebo after 5 days of treatment. They reported few AEs evenly distributed in the groups.

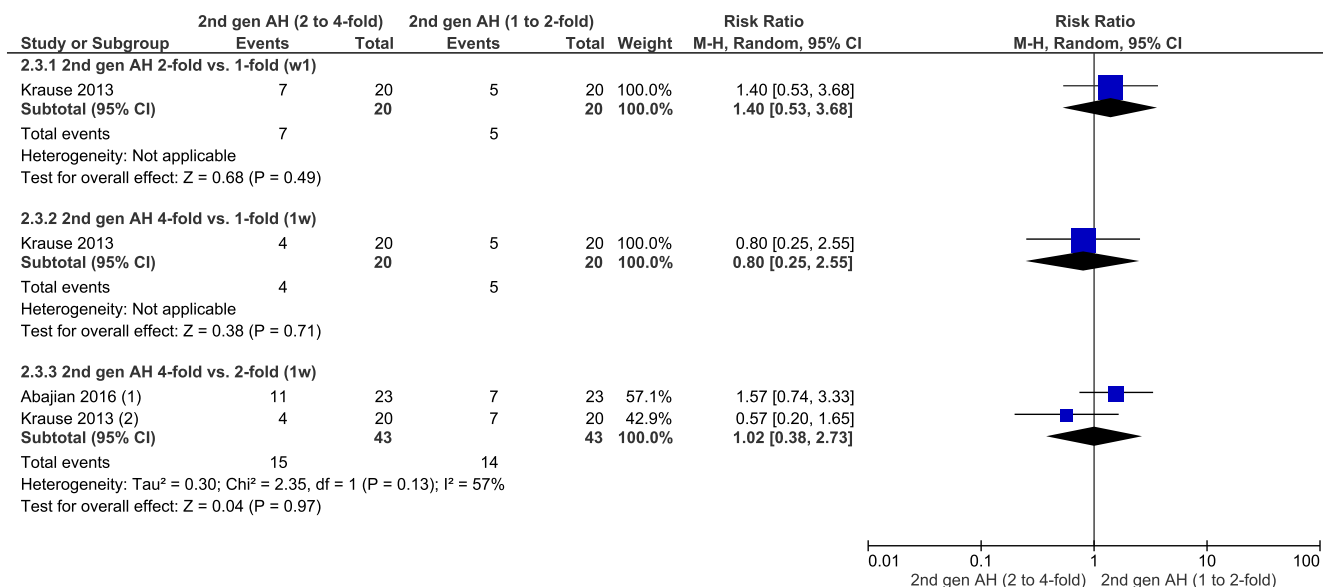
Second-generation H1-AHs (different doses) versus placebo. The above-mentioned study also included a third group treated with 8 mg of acrivastine 3 times daily. Kobza Black et al³⁶ found that the mean “degree of improvement” was 1.24 (n = 19)

for acrivastine and 0.74 (n = 9) for placebo after 5 days of treatment.

Zuberbier et al³⁸ evaluated 20 mg of cetirizine once daily versus placebo. The “mean symptom score” of the last 2 weeks of treatment showed a difference between groups (MD, -0.68; 95% CI, -1.21 to -0.15; n = 11.) There were no AEs and no withdrawals because of AEs.

Zuberbier et al³⁷ evaluated 10 or 20 mg of cetirizine once daily versus placebo and found a difference in the percentage of days with no or mild symptoms during treatment in the higher-dose group versus placebo but not compared with the lower-dose group (RR, 24.00; 95% CI, 8.43-39.57 and RR, 17.00; 95% CI, -0.68 to 34.68, respectively; n = 24). There was no difference between the 20-mg and 10-mg groups (RR, 7.00; 95% CI, -5.76 to 19.76). No difference was found regarding AEs (20 mg vs placebo: RR, 5.00; 95% CI, 0.25-98.96; 10 mg vs placebo: RR, 7.00; 95% CI, 0.38-128.61).

First-generation H1-AHs in combination. Alsamarai et al³⁵ recruited a total of 251 patients and compared 3 groups: 4 mg of chlorpheniramine maleate (half hour before exercise) plus 5 mg of chlorthalidone plus 2.5 mg of clindium bromide 3 times daily versus 4 mg of chlorpheniramine maleate 3 times daily plus 25 mg of maprotiline HCL once daily versus 4 mg of chlorpheniramine maleate 3 times daily plus 20 mg of cimetidine 3 times daily. Pairwise comparisons of all 3 groups showed that adding maprotiline was more effective than adding chlorthalidone and clindium bromide (RR, 0.32; 95% CI, 0.21-0.48),



Footnotes

- (1) rupatadine 40mg QD vs. rupatadine 20mg QD
(2) bilastine 80mg QD vs. bilastine 40mg QD

FIG 4. Forest plot of cold urticaria studies comparing second-generations H1-AHs in different doses reporting the outcome “patients with at least one AE.” *gen*, Generation; *M-H*, Mantel-Haenszel approach; *QD*, once daily.

as was adding cimetidine (RR, 0.28; 95% CI, 0.19-0.42) when evaluating “complete symptom control.” No difference was found between adding on cimetidine and maprotiline (RR, 1.13; 95% CI, 0.94-1.37).

Risk of bias. Risk of bias was unclear to high across these 4 studies (Table II).

DISCUSSION

Our systematic review included 30 studies, most of which were crossover trials including very few patients. Studies examined included patients with cold urticaria, cholinergic urticaria, symptomatic dermatographism, and delayed-pressure urticaria. No randomized or clinically controlled studies on other forms of CindUs (heat, solar, contact, or aquagenic urticaria or vibratory angioedema) could be identified. Overall, the risk of bias in the included studies was often rated as unclear or high, limiting the internal validity of the study results.

For cold urticaria, 9 studies indicate that second-generation antihistamines are more effective than placebo. A partial dose-response relationship when comparing different doses of second-generations antihistamines with placebo and the superiority of a 4-fold dose compared with a 1-fold dose indicate that up dosing might be effective. Not much evidence for other treatments, such as doxepine or cyproheptadine, could be identified. In a recent study, Metz et al³⁹ assessed omalizumab and reported it to be effective for the treatment of cold urticaria. The reporting of safety data in many studies was scarce, making an evaluation of treatment options difficult.

The 4 studies assessing antihistamines alone or in combination for the treatment of cholinergic urticaria were small and of unclear to high risk of bias. Although 2-fold second-generation

antihistamines resulted in a higher efficacy compared with placebo, the robustness of this finding is limited by the risk of bias.

There is little evidence regarding the treatment of symptomatic dermatographism. Most studies were small, and each treatment was only assessed once. However, the superiority of second-generations antihistamines compared with placebo was also found for this type of CindU. In one larger trial omalizumab proved effective in patients who were refractory to antihistamines.

It remains unclear whether second-generation antihistamines alone are effective when treating delayed-pressure urticaria. There might be an indication that adding montelukast could be useful; however, sufficient evidence is lacking. Our findings are supported by a recent review by Maurer et al⁴² of the effects of omalizumab in patients with CindUs, which also found omalizumab to be effective in the included trials. However, Maurer et al performed no assessment of the quality of the evidence or effect size calculations.

Limitations

Study reporting was often poor, making assessment of efficacy and safety problematic. The lack of sample size calculations and small samples in most of the included studies limit the interpretation, particularly of statistically nonsignificant results. Moreover, the assessment of a heterogeneous range of efficacy outcomes in the different studies compromises the comparability of results.

Conclusions

Overall, the available evidence was limited by small sample sizes, heterogeneous efficacy outcomes, and a poor reporting quality in many of the included studies. CindUs remain

TABLE II. Risk of bias

	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias
Cold urticaria							
Abajian et al, 2016 ¹⁰	?	?	+	?	+	+	?
Dubertret, et al 2003 ¹¹	?	?	?	?	?	?	?
Gimenez-Arbau et al, 2009 ¹²	?	?	?	?	?	—	?
Kaplan et al, 2010 ¹³ /Siebenhaar et al, 2009 ²⁰	?	?	?	?	?	?	?
Krause et al, 2013 ¹⁴	?	?	+	?	+	—	?
Levnadier et al, 1997 ¹⁵	?	?	?	?	?	?	?
Magerl et al, 2012 ¹⁶	+	+	+	?	+	—	?
Metz et al, 2010 ¹⁷	?	?	?	?	+	?	?
Neittaanmaki et al, 1998 ¹⁸	?	?	?	?	?	?	?
Neittaanmaki et al, 1984 (RCT1) ¹⁹	?	?	?	?	?	?	?
Neittaanmaki et al, 1984 (RCT2) ¹⁹	?	?	?	?	?	?	?
St-Pierre et al, 1985 ²¹	?	?	?	?	?	?	?
Villas Martinez et al, 1992 ²²	?	?	?	?	?	?	?
Wanderer et al, 1977 ²³	+	?	+	?	?	?	?
Symptomatic dermographism							
Boyle et al, 1989 ²⁴	?	?	+	?	—	—	?
Krause and Shuster, 1985 ²⁵	?	?	+	?	?	?	—
Kumar et al, 2002 ²⁶	—	—	—	—	—	—	—
Lawlor et al, 1988 (RCT1) ²⁷	?	?	+	?	—	—	?
Lawlor et al, 1988 (RCT2) ²⁷	?	?	+	?	+	—	?
Metz et al, 2016 ^{28*}	?	?	?	?	—	?	—
Sharpe and Shuster, 1993 ²⁹	?	?	?	?	?	?	—
Delayed-pressure urticaria							
Kontou-Fili et al, 1990 ³¹	?	?	?	?	?	—	?
Kontou-Fili et al, 1991 ³⁰	?	?	?	?	?	?	?
Lawlor et al, 1989 ³²	?	?	+	?	?	?	?
Nettis et al, 2003 ³⁴	?	?	?	?	+	?	?
Nettis et al, 2006 ³³	?	?	+	+	?	—	?
Cholinergic urticaria							
Alsamarai and Hasan, 2012 ³⁵	?	?	+	—	—	?	—
Kobza Black et al, 1988 ³⁶	?	?	+	?	?	—	+
Zuberbier et al, 1995 ³⁷	?	?	?	?	?	—	?
Zuberbier et al, 1996 ³⁸	+	?	?	?	—	—	?

+, Low risk of bias; ?, unclear risk of bias; —, high risk of bias.

*Based on abstract and now available as full text published after cutoff of literature search.⁴⁰

understudied, and further studies on antihistamines at standard and higher than standard doses are needed by using standardized outcomes. However, the findings suggest that the basic treatment algorithm, as suggested by international guidelines, might be effective in the treatment of CindUs. This includes a stepwise approach with second-generations H1-AHs in increasing (up to 4-fold) dose as first- and second-line treatment choice. Omalizumab as a suggested third-line treatment might be an effective treatment option in patients unresponsive to antihistamines. No data on the efficacy of cyclosporine as an alternative treatment option for CindUs were identified. The data do not allow for drawing specific conclusions for specific subtypes of CindUs.

Key messages

- A systematic review identified 30 RCTs on treating chronic inducible urticaria.
- Findings are congruent with the stepwise treatment approach suggested in international guidelines.
- No conclusions can be drawn about subtypes.

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Appendix 1: Example search strategy

Database: Ovid MEDLINE(R) 1946

1. exp Urticaria/
2. "urticaria*".ab,kf,ti.
3. hives.ab,kf,ti.
4. w?eals.ab,kf,ti.
5. "dermatographi*".ab,kf,ti.
6. ("factiti*" adj3 urticaria*).ab,kf,ti.
7. ((cold or heat or pressure or solar) adj3 urticaria*).ab,kf,ti.
8. (vibratory adj3 angio?edema).ab,kf,ti.
9. ((cholinergic or contact) adj3 urticaria*).ab,kf,ti.
10. ((aquagenic or (water adj3 induc*)) adj3 urticaria*).ab,kf,ti.
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12. Randomized Controlled Trials as Topic/
13. randomized controlled trial/
14. Random Allocation/
15. Double-Blind Method/
16. Single Blind Method/
17. clinical trial/
18. clinical trial, phase I.pt.
19. clinical trial, phase II.pt.
20. clinical trial, phase III.pt.
21. clinical trial, phase IV.pt.
22. controlled clinical trial.pt.
23. randomized controlled trial.pt.
24. multicenter study.pt.
25. clinical trial.pt.
26. exp Clinical Trials as topic/
27. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
28. (clinical adj trial\$).tw.
29. ((singl\$ or doubl\$ or treb\$ or tribl\$) adj (blind\$3 or mask\$3)).tw.
30. Placebos/
31. placebo\$.tw.
32. randomly allocated.tw.
33. (allocated adj2 random\$).tw.
34. 28 or 29 or 30 or 31 or 32 or 33
35. 27 or 34
36. case report.tw.
37. letter/
38. historical article/
39. 36 or 37 or 38
40. 35 not 39
41. 11 and 40

Appendix 2: Excluded Studies

First Author	Year	Reason for exclusion
F. Aubin, M. Avenel-Audran, M. Jeanmougin, H. Adamski, J.-L. Peyron, M.-C. Marguery, F. Leonard, M. Puyraveau, M. Viguier and P. Societe Francaise de	2016	no comparison group, no CCT
C. B. Bentley-Phillips, R. A. Eady and M. W. Greaves	1978	no CCT/RCT
P. Brodska and P. Schmid-Grendelmeier	2012	no CCT/RCT
J. P. Cap, H. J. Schwanitz and B. M. Czarnetzki	1985	no values for 2nd arm
E. Di Leo, E. Nettis, N. Cassano, C. Foti, P. Delle Donne, G. A. Vena and A. Vacca	2009	no control group/ cross-over RCT, no CCT
J. S. Dover, A. K. Black, A. M. Ward and M. W. Greaves	1988	no CCT/RCT
M. Geller	2016	no CCT/RCT
G. Hu, Y. Zhu, Z. Y. Wang and N. H. Ran	1999	no relevant comparison
L. Juhlin	2004	no CCT/RCT
D. Kalogeromitros, D. Kempuraj, A. Katsarou-Katsari, S. Gregoriou, M. Makris, W. Boucher and T. C. Theoharides	2005	no relevant comparison
D. Kalogeromitros, D. Kempuraj, A. Katsarou-Katsari, M. Makris, S. Gregoriou, D. Papaliadis and T. C. Theoharides	2006	not inducible urticaria
H. D. Komarow, A. R. Eisch, M. Young, C. Nelson and D. D. Metcalfe	2015	no CCT/RCT
K. Krause, A. Spohr, M. K. Church, T. Zuberbier and M. Maurer	2012	no numerical data
K. Krause, A. Spohr, M. K. Church, T. Zuberbier and M. Maurer	2013	duplicate
F. Lawlor and A. K. Black	2004	no CCT/RCT
F. Lawlor, A. K. Black, R. D. Murdoch and M. W. Greaves	1989	topical treatment
R. A. Logan, T. J. O'Brien and M. W. Greaves	1989	no comparison group, no CCT
M. Magerl, J. Schmolke, M. Metz, T. Zuberbier, F. Siebenhaar and M. Maurer	2009	no relevant time point of evaluation
M. Magerl, J. Schmolke, F. Siebenhaar, T. Zuberbier, M. Metz and M. Maurer	2007	medication only 1 time 10h before test/ not 1-2 weeks after
W. Marsch	1992	no CCT/RCT
C. N. Matthews, J. D. Kirby, J. James and R. P. Warin	1973	1st vs 1st - no relevant comparison; no data for diazepam group
M. Metz, E. Scholz, I. Izquierdo, M. Ferran, A. Torrents, A. Gime Nez-Arnau and M. Maurer	2009	Efficacy data already included Metz 2010
K. Oh Sang, H. Ji Hwan, S. Dae Hun, Y. Jai Il and E. Hee Chul	1997	terfenadine is no longer used
A. D. Ormerod, R. Baker, J. Watt and M. I. White	1986	terfenadine is no longer used
P. D. Pigatto, M. Fumagalli, A. Bigardi, G. Altomare and A. F. Finzi	1990	terfenadine is no longer used
E. Seropian, I. B. Iamandescu and V. Filip	1984	1st vs 1st gen AH - no relevant comparison

J. P. St Pierre, A. A. Wanderer and E. F. Ellis	1974	no numerical data
C. Tosoni, F. Lodi-Rizzini, L. Bettoni, P. Toniati, C. Zane, R. Capezzera, M. Venturini and P. Calzavara-Pinton	2003	no CCT /RCT
G. A. Vena, N. Cassano, V. D'Argento and M. Milani	2006	topical treatment
E. Wong	1987	no data for plc arm

Appendix 3: Study Characteristics

Study Characteristics									Baseline data	
Author Year	Intervention	Randomized or assigned patients	Study design	Inclusion criteria disease	Inclusion criteria age	Special patient population	Washout	Concomitant treatment	Age	Female gender %
COLD URTICARIA										
Abajian 2016 NCT01605487	rupatadine 20mg QD for 7d	23 or 24	cross-over RCT MC	confirmed diagnosis of cold urticaria of at least 6 months' duration	NDA	no	2w between periods, 7d for H1-antihistamines or anti- leukotrienes, 28d for oral or 3m for depot corticosteroids and 28d for immunosuppressants / immunomodulators	NDA	45 (19-68)	75
	rupatadine 40mg QD for 7d									
	placebo QD for 7d									
Dubertret 2003	mizolastine 10mg QD for 7d	28	cross-over RCT MC	cold urticaria ≥ 6m, confirmed by ice-cube test & cold stimulation test	15-60	no	14d between treatment periods washout prior to study: 6w astemizol, 4w sys. Corticosteroids, 6m delayed corticosteroids, 4w ketotifen, antidepressants; 7d AHs, inhaled steroids, NSAIDS, ACC, H2, sedatives, anticholinergics	NDA	data only available for each treatment sequence m to p: 36±13; 77% p to m: 34±13; 71%	
	placebo for 7d									
Gimenez-Arnau 2009 (conference abstract)	rupatadine 20mg QD for 7d	21	cross-over RCT	cold urticaria patients	NDA		yes, duration unclear	NDA	41.1±13.9	76
	placebo									
Kaplan 2010; Siebenhaar 2009 NCT 00600847	desloratadine 5mg QD for 7d	30 (33)	cross-over RCT SC	cold urticaria ≥ 6w, positive provocation test 10 mins at 4°C	18-75	2 patients with dermographism	14d between treatment periods before study: 7d for AH and leukotrine antagonists, 14d corticosteroids, 21d systemic /depot corticosteroids	NDA	50 (18-71)	66
	desloratadine 20mg QD for 7d									
	placebo for 7d									
Krause 2013 NCT 01271075	PBO for 7d	20	cross-over RCT, MC	cold contact urticaria at least 6w prior to screening; positive cold provocation test at 4°C within 10 min	NDA		14d washout between treatments washout 14-28d prior to study: 2w for AH, antidiuretics, antipsychotics, corticosteroids, aluminium & magnesium -containing antacids, ketoconazole, erythromycin, mast cell stabilizers; 24h before study and during study no citrusfruits	NDA	45 (22-68)	65
	bilastine 20mg QD for 7d									
	bilastine 40mg QD for 7d									
	bilastine 80mg QD for 7d									

Study Characteristics									Baseline data	
Author Year	Intervention	Randomized or assigned patients	Study design	Inclusion criteria disease	Inclusion criteria age	Special patient population	Washout	Concomitant treatment	Age	Female gender %
Levnadier 1997 (abstract only)	mizolastine 10mg 7d	28	cross-over RCT	NDA					35±17	NDA
	placebo 7d									
Magerl 2012 NCT 01444196	desloratadine 5mg QD for 6w	15	parallel RCT	cold urticaria for at least 6m, 2C	NDA		1w AH or LA, 4w syst. corticosteroids	NDA		
	desloratadine 5mg QD for 2w, 10mg QD for 2w then 20mg QD for 2w	15								
Metz 2010	rupatadine 20mg QD for 7d	21	cross-over RCT	cold urticaria ≥ 6w, confirmed by positive ice cube test,	NDA	no	2w between treatment periods; washout prior to study: 7d for AHs or leukotrine antagonists, 14d for oral corticosteroids, 21d for depot & long- term systemic corticosteroids	NDA	41.1 ±13.9	76
	Placebo QD for 7d		MC							
Neittaanmäki 1988	acrivastine 8mg TID for 5d	18	cross-over RCT	idiopathic cold urticaria, positive ice cube test	NDA		1w prior to study, 2d between treatments	N/A	31,1 (19-44)	56%
	cyproheptadine 4mg TID for 5d									
	placebo TID for 5d									
Neittaanmäki 1984 RCT 1 (2 studies in 1 publication)	PBO for 2w	10	crossover RCT SC	cold urticaria inpatients	NDA		unclear	NDA	14-42	40
	doxepine 10mg TID for 2w									
	cinnarizine 10mg TID for 2w									
Neittaanmäki 1984 RCT 2 (2 studies in 1 publication)	doxepine 10mg TID for 1w	12	crossover RCT SC	cold urticaria inpatients	NDA		unclear	NDA	15-43	50
	hydroxyzine 10mg TID for 1 w									
	PBO TID for 1 w									
	cyproheptine 4mg for 1w									
St-Pierre 1985	placebo	11	cross-over RCT	pts. w/ history of local or generalized whealing after exposure to cold or coalenscent wheal after ice test	NDA		7d washout inbetween	NDA	6-58	63
	ketotifen 1mg BID for 7d									

Study Characteristics									Baseline data	
Author Year	Intervention	Randomized or assigned patients	Study design	Inclusion criteria disease	Inclusion criteria age	Special patient population	Washout	Concomitant treatment	Age	Female gender %
Villas Martinez 1992	ketotifen 1mg BID for 14d	7	cross-over RCT	clinical history/physical evidence of cold- induced wheals and/or angiodema, neg. evidence of underlying disease, positive provocation test at 0- 4°C	19-72	no	7d washout between treatments no data for other medications	4 patients had concomitant physical urticaria of other types	31.7±18	71
	loratadine 10mg QD for 14d									
	cetirizine 10mg QD for 14d									
Wanderer 1977	cyproheptadine 4mg TID for 7d	8	cross-over RCT	clinical history of primary cold urticaria, no evidence of secondary cold urticaria, induction of coalescent response within 10 minutes of cold test	NDA				7-60	63
	chlorpheniramine 4mg TID for 7d									
	placebo TID for 7d									
SYMP. DERMOGRAPHISM										
Boyle 1989	acrivastine 8mg TID for 4d + once on d5	12	cross-over RCT SC	positive dermographism test,	NDA		3 day break before study entry and 2 day break between treatments	no other treatment for SD or those that likely cause sedation were permitted	34.2 (15-50)	50
	terfenadine 60mg TID for 4d + once on d5									
	placebo									
Krause 1985	astemizole 10mg TID for 4w	16	parallel group RCT SC	daily attacks for > 2 months otherwise healthy	≥ 16	no	3d prior to study,	NDA	34 (18-67)	100
	chlorpheniramine 4mg TID for 4w									
Kumar 2002	cetirizine HCl 10mg QD for 4w	9	parallel group CCT, SC	chronic dermographic urticaria for ≥ 6m	NDA	no	NDA	NDA	31.12 (18- 53) n=25	48
	betamethasone 2mg + cetirizine HCl 10mg QD for 4w	7								
Lawlor 1988(1)	Study 1: Nifedipin	13	cross-over	history of itchy whealing	16-60	NDA (1 patient	no antihistaminics 3d prior to first	1 pts salbutamol	NDA	46

Study Characteristics									Baseline data	
Author Year	Intervention	Randomized or assigned patients	Study design	Inclusion criteria disease	Inclusion criteria age	Special patient population	Washout	Concomitant treatment	Age	Female gender %
	5mg TID for 2w		RCT	response to friction and positive response to dermatographic assessment		suffered from concurrent cholinergic urticaria)	visit, no washout in between	(drop out)		
	Placebo TID for 2w									
Lawlor 1988 (2)	Study 2:Nifedipin 10 mg TID for 2w	8	cross-over RCT	pruritus and whealing; positive whealing response to dermographometer of 3,5x10^5	N/A	NDA (1 patient w/ cold urticaria)	1w	not allowed	18-46	63
	Placebo TID for 2w									
Metz 2016 (abstract only) NCT02169115	placebo	61	parallel RCT	antihistamine resistant patients	NDA				18-75	NDA
	omalizumab 150mg every 4 weeks (3 injections in total)									
	omalizumab 300mg every 4 weeks over 12w (3 injections in total)									
Sharpe 1993	cetirizine 10mg for 7d at night	21	cross-over RCT	≥ 2m duration	N/A		3d prior to study	N/A	39 (18-65)	62
	placebo									
DELAYED PRESSURE URTICARIA										
Kontou-Fili 1990	cetirizine 10mg every 8h (=TID) for 1w	11	cross-over RCT	delayed pressure urticaria	NDA	no	2w between treatments	NDA	45 (23-69)	55
	PBO every 8h for 1w		SC							
Kontou-Fili 1991	cetirizine 10mg every 8h for 1w	11	cross-over RCT	delayed pressure urticaria	NDA	no	2w between treatments	NDA	45 (23-69)	55
	PBO every 8h for 1w		SC							
Lawlor 1989	colchicine 0.5mg BID for 1w	13	cross-over RCT SC	delayed pressure urticaria based on a history of delayed sweeling following	NDA	3 pts. with attacks of angioedema, 1 pt. with mild cold urticaria	1w between treatments before sudy: 3d for AH	no	42 (28-54)	62

Study Characteristics									Baseline data	
Author Year	Intervention	Randomized or assigned patients	Study design	Inclusion criteria disease	Inclusion criteria age	Special patient population	Washout	Concomitant treatment	Age	Female gender %
	PBO BID for 1w			application of pressure to the skin and the development of papular responses hours after pressure testing using a calibrated dermatographometer						
Nettis 2003 (Letter)	loratadine 10mg (regime unclear) for 15d	10	parallel group RCT,	delayed pressure urticaria, diagnosis confirmed by challenge test (7kg weight was suspended from the pts. shoulder for 15min, readings of the test area were done at 0.5, 3, 6, 8 and 24h)	NDA	60% of pts. with concurrent chronic idiopathic urticaria and/or dermatographism	1m for sys. corticosteroids	NDA	45.5±15.17	75
	montelukast 10mg + loratadine 10mg (regime unclear) for 15d	10	SC							
Nettis 2006	desloratadine 5mg + PBO for 2w	12	parallel group RCT,	delayed pressure urticaria, diagnosis confirmed by challenge test with dermatographometer (pressure of 100 g mm², applied perpendicularly to different sites on the back for 5, 15, 33, 70 and 100s; appearance of a papule after 6h was interpreted as a positive reaction and DPU was diagnosed if these occurred at the 5, 15, 33 or 70 s application sites)	NDA	53% of pts. had concurrent chronic idiopathic urticaria	1w run-in before study: 1m for sys. corticosteroids	"Medications that could interfere with the clinical evaluations and systemic or topical medication for urticaria [...] were not allowed during the trial."	38.7±13.9	36 n=11
	desloratadine 5mg + montelukast 10mg for 2w	12							34.7±14.1	33
	PBO for 2w	12							34.8±8.6	55 n=11
CHOLINERGIC URTICARIA										
Alsamarai 2012	Chlorpheniramine maleate 4mg (1/2h before exercise) + chlorthalidone	92	parallel RCT NDA	cholinergic urticaria of any duration, diagnosed by physician	16 - 29	no	5d for fexofenadine, 3d for loratadine, desloratadine, cetirizine, hydroxyzine, diphenhydramine, cyproheptadine etc., 2d for H2, 7d for H1 and H1	n.s.	21±5	15

Study Characteristics									Baseline data	
Author Year	Intervention	Randomized or assigned patients	Study design	Inclusion criteria disease	Inclusion criteria age	Special patient population	Washout	Concomitant treatment	Age	Female gender %
	5mg + clindium bromide 2.5mg TID for 6w	77					receptor antagonists, 4d for leukotrine anatgonists, 28d for corticosteroids, 30d tricyclic antidepressants,		23±4	
	Chlorpheniramine maleate 4mg TID + maprotiline HCL 25mg QD for 6w									
	Chlorpheniramin maleate 4mg TID + cimetidine 20mg TID for 6w									
Kobza Black 1988	acrivastine 8mg TID for 5d	10	cross-over RCT	clinical diagnosis of CU, positive exercise challenge test	NDA	no	3days prior to study, 2days between treatments	other drugs relevant to CU or liekly causing sedation were not permitted	30.3 (19-67)	40
	hydroxyzine HCl 20mg TID for 5d									
	placebo									
Zuberbier 1996	cetirizine 20mg QD for 3w	13	cross-over RCT, MC	at least 1 attack of cholinergic urticaria per week, > 1m duration of disease, gloabl score of 3 on provocation at the time of screening	18-65	no	before study: 2m for sys. corticosteroids, 6w for astemizole, 2w for ketotifen, top. steroids, 4d for other AH, 2d for anticholinergics within study: 1w washout --> no real washout, cross-over medication was already used (not evaluated)	rescue medication: 20 tablets of cetirizine 20mg - -> used by 2 pts.	26.5±4.9	54
	PBO QD for 3w									
Zuberbier 1995	cetirizine 10mg QD for 3w	25	cross-over RCT, MC	cholinergic urticaria for at least 1m, disease had to be verified by the provocation tests commonly used for the diagnosis in each specific clinic, such as physical exercise	18-65	no	before study: 60d for astemizole, 15d for ketotifen, 7d for corticosteroids, 4d for common H1-antagonists, 2d for anticholinergics, beta- sympathomimetics, beta-blockers within study: 3w PBO (single-blind)	NDA	26.06±7.30	58
	cetirizine 20mg QD for 3w									
	PBO QD for 3w (washout phase between verum application)									