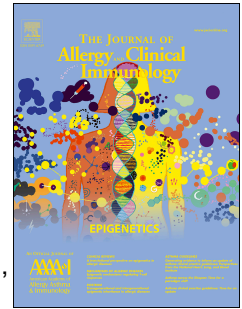


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Treatments of Cold Urticaria: A Systematic Review

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Treatments of Cold Urticaria: A Systematic ReviewKanokvalai Kulthanan, MD,¹Saowalak Hunnangkul, PhD,²Papapit Tuchinda, MD,¹Leena Chularojanamontri, MD,¹Puncharas Weerasubpong, MD,¹Chanika Subchookul, MD,¹Marcus Maurer, MD.³¹ Department of Dermatology, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand² Office of Research and Development, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand³ Department of Dermatology and Allergy, Charité – Universitätsmedizin Berlin, Berlin, Germany**Corresponding Author:**

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Abstract

Background: Several treatment options for cold urticaria (ColdU) have been studied and reported, but systematic reviews and meta-analyses are limited.

Objectives: To meta-analyze and review the efficacy and safety of ColdU treatments.

Methods: We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations. Suitable reports were identified by searching PubMed, Scopus, and Web of Science. Our systematic review included 16 studies, 9 of which met the eligibility criteria for the meta-analysis. We analyzed the effects of treatments on the critical temperature thresholds (CTTs) and critical stimulation time thresholds (CSTTs), as well as on the rates of complete response and adverse events.

Results: Our pooled meta-analyses showed that non-sedating, second-generation H₁-antihistamines (nsAHs) are effective in the treatment of ColdU, and that the up dosing of nsAHs significantly reduced CTTs relative to their own standard doses and placebos. In 4 studies involving CSTT, the up dosing of nsAHs also showed significantly better CSTTs than their own standard doses or placebos. Omalizumab resulted in a marked reduction of CTTs in H₁-AH-resistant patients. Of 118 adverse events in 8 studies, standard-dose nsAHs, up dosed nsAHs, and omalizumab produced lower numbers of adverse events than first-generation AHs.

Conclusions: Our study showed that higher dosages of nsAHs were more effective than their own standard dosages in controlling ColdU symptoms. Increasing the dosages was not significantly associated with higher adverse event rates. Omalizumab at 150 and 300 mg every 4 weeks was shown to be effective for ColdU patients refractory to AHs.

Capsule summary:

Modern, second-generation H₁-antihistamines at standard and up to fourfold dosages, as well as 150- and 300-mg dosages of omalizumab, are safe and effective in the treatment of cold urticaria.

Key Messages:

- Modern, second-generation H₁-antihistamines should be the first-line treatment of cold urticaria and, if needed, at up to fourfold the standard dose.
- Omalizumab should be considered for the treatment of antihistamine-resistant patients.

Key words: Cold urticaria, meta-analysis, systematic review, treatment, efficacy, safety, antihistamines, omalizumab

Abbreviations:

AH: antihistamine

ColdU: cold urticaria

CSTT: critical stimulation time threshold

CSU: chronic spontaneous urticaria

CTT: critical temperature threshold

MD: mean difference

nsAH: non-sedating, second-generation H₁-antihistamine

87 RCT: randomized controlled trial

INTRODUCTION

Cold urticaria (ColdU), a subtype of physical urticaria, is characterized by the development of wheals and/or angioedema in response to cold exposure and rewarming of the skin.¹⁻³ The signs and symptoms of ColdU are held to be related to the activation and degranulation of skin mast cells, which release histamine and other pro-inflammatory mediators, resulting in vasodilation and extravasation.⁴ Several studies have suggested that mast cell degranulation in ColdU involves immunoglobulin E and an unknown cutaneous autoallergen that becomes accessible upon cold stimulation.⁵

Due to the absence of validated activity scores and quality of life instruments for ColdU, the clinical problems include the challenge of assessing patients for their disease activity and response to treatment. Cold provocation tests are performed by the application of a cold stimulus (ice cubes, cool packs, cold water baths, or *TempTest*) to the forearm for 5 minutes; the arms are assessed after 10 minutes.^{2, 3} Positive reactions are indicated by the development of wheals within minutes of skin rewarming. The AACI/GA²LEN/EDF/UNEV consensus recommends that critical stimulation time threshold (CSST) and critical temperature threshold (CTT) measurements should be performed to assess objective disease severity and activity as well as drug effectiveness.³ The CSST is the shortest duration of cold exposure needed to induce a wheal response, while the CTT is the highest temperature required to induce a wheal response. *TempTest* is the only validated instrument that provides continuous temperature gradients from 4°C to 44°C, and it can be used to determine both CSST and CTT.^{3, 6, 7}

Because the pathogenesis of ColdU is currently unclear and causal treatment is, therefore, not possible, the avoidance of cold and the prevention of ColdU signs and symptoms are the two most common management approaches. In 2010, Weinstein et al.⁸

conducted a meta-analysis to investigate the efficacy and tolerability of second and third generation antihistamines (AHs) in ColdU treatment. However, they included only 4 randomized-controlled trials with 4 AHs (acrivastine, mizolastine, ebastine, and desloratadine). The subjective wheal and pruritus elimination, not the objective CTT and CSTT measurements, were used to determine drug effectiveness.

Nowadays, several novel AHs and a new biological agent, omalizumab, are available, and the results of their use have been published.⁹⁻¹⁴ The current systematic review and meta-analysis aims to determine the efficacy of AHs and omalizumab across all previously published studies using objective outcomes, including CTT and CSTT. These objective measures better reflect disease activity and changes to the treatment of ColdU patients than subjective evaluation, unless there is complete resolution.

METHODS

Protocol and registration

This review adhered to the PRISMA recommendations (Fig 1). A systematic search was conducted using PubMed, Scopus, and Web of Science (without date limitations) using the terms “cold urticaria”, “acquired cold urticaria”, “cold induced urticaria”, and “cold contact urticaria”.

Eligibility criteria for systematic review

To be eligible for systematic review, a study needed to (i) be an RCT or non-RCT; (ii) involve patients with ColdU; (iii) have patients who received medications at any dosage; (iv) involve comparisons with another drug and/or a placebo; and (v) report any of the following outcomes—CTT: the highest temperature to generate a wheal response after cold provocation

(the more pronounced the CTT reduction, the better the treatment); CSTT: the shortest exposure time to cold that is sufficient to induce a positive reaction (the more pronounced the CSTT prolongation, the better the response to treatment)³; the complete responder rate (a complete response was defined as no wheals being present after cold provocation); and adverse events. The eligible studies did not need to report all of the aforementioned outcomes, but had to report at least one.

Eligibility criteria for meta-analysis

The studies identified by the systematic review were further evaluated for their eligibility for the meta-analysis. To be included, studies had to have one arm of patients who did not receive active treatment (e.g., a placebo group).

Literature review process and bias assessment

Review articles, case reports, case series, in vitro studies, and comments and replies were excluded. Two independent reviewers (PW and SH) evaluated all of the potentially relevant studies, and disagreements were resolved with a third researcher (KK). The quality and risk of bias of the included RCT studies were assessed with the Cochrane Collaboration's tool, and for non-RCTs, with the Methodological Index for Non-Randomized Studies (Table D).¹⁵

Quantitative meta-analysis

Our objective was to investigate the efficacy and safety of ColdU treatments. The outcomes were the CTT, CSTT, rate of complete responders, and the rate of adverse events. The CTT and CSTT were reported as mean differences (MD) compared to the placebos. In those cases where numeric outcomes of the CTT and CSTT improvements were unavailable, we compared the pre- and post-treatment values using the Wilcoxon signed-rank test. The complete responder and adverse event rates were reported as odds ratios (OR) with

corresponding 95% confidence intervals (CI).

Review Manager 5.3 software from the Cochrane Collaboration (London, United Kingdom) was used for all statistical analyses. Adjusted point estimates and standard errors or raw data to calculate the point estimates were extracted from individual studies and combined by the generic inverse variance method of DerSimonian and Laird which assigned a study's weight inversely to its variance.¹⁶ The mean CTT and CSTT and SD of participants were extracted from each study to calculate the mean difference (MD). Pooled MD was then calculated by combining MDs of each study using random-effects model. If a study provided only the median, its median was used as the estimate for the mean. We estimated SD from IQR using the formula $SD = IQR/1.35$ as suggested by the Cochrane handbook of systematic review and meta-analysis.¹⁷ Given the high likelihood of between study variance due to different background populations and methodologies, random-effect model was chosen over fixed-effect model. The existence of heterogeneity was assessed using Cochran's Q statistic and the I^2 statistic to quantify the total variation across the studies that is due to heterogeneity rather than chance.¹⁸ A value of I^2 of 0% to 25% indicates insignificant heterogeneity, 26% to 50% low heterogeneity, 51% to 75% moderate heterogeneity, and 76% to 100% high heterogeneity.¹⁸ Visualization of funnel plots was used to assess the presence of publication bias. Trim-and-fill sensitivity analysis¹⁹ was performed to adjust for publication bias using Comprehensive Meta Analysis version 3 software (Biostat, Englewood, NJ, USA). For all results, a two-sided p -value of $\leq .05$ was considered as denoting statistical significance.

RESULTS

Systematic review: insights into the efficacy and safety of ColdU treatments

Sixteen studies^{9-14, 20-29} were included in our systematic review (Fig 1; Tables II and III), comprising 14 RCTs^{9-14, 20-26, 29} (13 double-blind and 1 single-blind); 1 open-label, prospective study²⁸; and 1 retrospective study²⁷. Among the 320 ColdU patients, gender data were reported by 14 of the studies (85 males and 183 females) for 7 countries (Germany, Finland, France, Spain, United Kingdom, the United States, and Thailand). As to medications, H1-AHs (different types and doses), omalizumab, doxycycline, and prednisone were administered to 257, 31, 26, and 6 ColdU patients, respectively. Non-sedating AHs (nsAHs) were the most studied treatment (9 out of 16 studies).^{9, 10, 12-14, 20, 21, 24, 26} Treatment benefits were reported by all of the studies except one, a glucocorticoid study. Of the nsAH studies, none compared the efficacy of different antihistamines. Four out of 9 studies investigated the effects of standard vs higher-than-standard doses of nsAHs.

Efficacy as assessed by rates of complete responders, clinical improvement, CTTs, CSTTs (Tables II and III)

Bilastine: A crossover study by Krause et al. showed that bilastine at 20, 40, and 80 mg for 7 consecutive days with 14-day washout periods led to a complete response in a dose-dependent manner and showed significant differences from a placebo. All bilastine dosages caused statistically significant reductions in pruritus and median CTT reductions from pretreatment levels, compared to the placebo group. Bilastine 80 mg resulted in significantly better CTT reductions than bilastine 20 mg and 40 mg.¹²

Desloratadine: Magerl et al. studied 2 groups of ColdU patients. Group A received a constant dose of desloratadine 5 mg/day for 6 weeks. Group B started with 5 mg desloratadine and escalated to 10 and then 20 mg, for 2 weeks each.¹¹ Using TempTest 3.0 provocation at 4°C, no patients in group A showed complete wheal suppression, with a mean CTT reduction of 2.3°C compared to pretreatment. As to group B, 13.3% (10 mg/day) and

23.1% (20 mg/day) showed complete wheal suppression with a significant mean CTT reduction (5 mg, -2.3°C; 10 mg, -6.8°C; and 20 mg, -9.3°C) compared to the pretreatment level. Desloratadine 20 mg resulted in a significantly better CTT reduction than dosages of 5 mg and 10 mg.¹¹ Siebenhaar et al. reported that 23.3% and 50% of 30 ColdU patients receiving 5 mg and 20 mg desloratadine, respectively, had complete remission as assessed by cold provocation with TempTest 2.0/2.1 at 4°C. For pruritus intensity, the only significant difference was seen between the 20 mg desloratadine and the placebo group.⁹ Desloratadine 20 mg significantly reduced the CTT and improved the CSTT better than its standard dosage and a placebo.⁹ In both studies, higher-than-standard dosages of desloratadine yielded higher complete response rates than its standard dose.^{9, 11}

Rupatadine: Abajian et al. showed that 30% and 50% of ColdU patients had no wheal formation by cold provocation with TempTest 3.0 at 4°C after treatment with twofold (20 mg) and fourfold (40 mg) standard rupatadine dosages for 7 days, respectively.¹³ Two-thirds of the patients in the 20 mg rupatadine group had no pruritus, compared to 14% of the placebo group. Rupatadine 20 mg and 40 mg reduced the CTT by 4°C and 10°C, respectively, and prolonged the CSTT to 3 and 5 minutes, respectively, all of which were significantly better than the results for a placebo. However, there was no significant difference in CTT reduction and CSTT prolongation between 20 mg and 40 mg rupatadine.¹³ Metz et al. found that 52% of patients were complete responders when receiving 20 mg (twofold) rupatadine for 7 days, compared to only 5% of the placebo group, using TempTest 3.0. The burning sensation was absent in 86% and 0% of the patients treated with rupatadine 20 mg/day and a placebo, respectively. Rupatadine 20 mg/day significantly reduced the CTT, by 8°C, while the placebo did not. The CSTT was significantly increased by a median of 1.9 minutes, compared with zero minutes with the placebo. This study did not compare different dosages of rupatadine.¹⁰

Other AHs: Magerl et al. showed that 82% of ColdU patients treated with ebastine 20 mg had complete wheal suppression after a cold challenge with a 4°C cold pack. The number of patients experiencing moderate to severe pruritus and a burning sensation was reduced.²⁰ Neittaanmaki et al. reported that acrivastine 8 mg three times daily for 5 days was significantly more effective than cyproheptadine 4 mg three times daily and a placebo. Both drugs significantly reduced pruritus compared to the placebo.²⁴ Another study by Neittaanmaki et al. demonstrated significant wheal reductions of 53%, 61%, and 56%, and significant pruritus reductions of 67%, 72%, and 71%, in ColdU patients receiving cyproheptadine, doxepin, and hydroxyzine, respectively, compared to baseline.²⁵ They also showed in the subgroup open study that doxepin 25 mg three times daily led to a 78% reduction of wheal size, post ice-cube testing. The duration of the wheal response was shortened by 74% during the first 12 hours of doxepin.²⁵ Wanderer et al. showed that cyproheptadine 4 mg three times daily for 7 days was effective in completely suppressing wheal formation in ColdU patients, and was superior to chlorpheniramine 12 mg/day and a placebo in reducing ColdU symptoms. The CTTs were significantly increased compared to chlorpheniramine and the placebo.²⁶ Villas Martinez et al. showed that 85.7%, 28.6%, 80%, and 80% of ColdU patients treated with loratadine, cetirizine, cyproheptadine, and ketotifen, respectively, became asymptomatic after treatment, and that those drugs significantly increased the mean CSTTs compared to the baseline values.²³ In children with ColdU, Visitsunthorn et al. showed that the effectiveness (clinical score improvement assessed by patients and parents) of ketotifen ($88 \pm 6\%$) was high and comparable to that of cyproheptadine ($85 \pm 6\%$).²² St-Pierre et al. also showed that ketotifen significantly increased the mean CSTT from baseline compared to a placebo.²⁹ Dubertret et al. noted a significant reduction of pruritus intensity and prolongation of CSTT after ice-cube testing in patients receiving mizolastine vs a placebo.²¹

Other drugs: Black et al. showed that both prednisone 20 mg for 3 to 5 days and prednisone 25 mg single dose showed no significant reductions in erythema and edema following a cold challenge assessed by patients.²⁸ Gorczyza et al. showed that 19% of ColdU patients treated with doxycycline 200 mg/day (n = 2) or doxycycline 200 mg/day with an H₁-AH (n = 24) had complete wheal suppression following cold provocation with a TempTest 3.0 at 4°C. Doxycycline 200 mg/day did not significantly reduce CTTs.²⁷ Metz et al. showed that omalizumab 150 mg and 300 mg every 4 weeks for 3 consecutive months in ColdU patients refractory to AHs led to 40% and 44% negative cold provocations with TempTest 4.0, respectively, compared to 0% for the placebo group. Omalizumab rapidly reduced CTT within 4 weeks. The study also showed significantly higher reductions in CTTs in response to omalizumab 150 mg and 300 mg compared to a placebo. Patients with low and high baseline CTTs showed similar responses, and there were no significant differences between the 150 and 300 mg groups.¹⁴

Safety

The adverse event rates in patients with standard vs higher doses of modern nsAHs were not significantly different, and adverse events from nsAHs were rare, mild, and transient. Somnolence was the most common, followed by dizziness, headache, gastric pain, and fatigue. The adverse event rates were higher with patients receiving sedating AHs. Ten out of 18 patients receiving cyproheptadine experienced drowsiness throughout the treatment period.²⁴ In ColdU patients receiving first-generation AHs (cinnarizine, cyproheptadine, hydroxyzine, and doxepin), the most common adverse event reported was tiredness.²⁵ A significantly higher number of patients with sedation were found among patients using cyproheptadine rather than a placebo.²⁶ Patients treated with omalizumab 150 or 300 mg showed similar adverse event rates to patients receiving a placebo, and without serious adverse events.¹⁴

Meta-analysis of the studies

Nine studies^{9, 10, 12-14, 20, 21, 24, 26} (205 ColdU patients) met the eligibility criteria for the meta-analysis.

Treatment efficacy as assessed by CTT measurements

Treatment efficacy was assessed by CTT measurements before and after treatment in 5 studies, of which 4 used nsAHs while the fifth used omalizumab (Fig 2A).^{9, 10, 12-14} An analysis was made of the differences in the treatment efficacies of standard versus higher-than-standard doses of nsAHs (bilastine, desloratadine, and rupatadine) as well as of the different dosages of omalizumab. The pooled analysis of the updosed nsAHs in 4 studies showed significantly better reductions in CTTs than with their own standard dosages (MD -7.2°C vs -5.8°C, compared to the placebos, $p = .02$). No studies of first-generation AHs reported CTT results.

Treatment efficacy as assessed by CSTT measurements

Fig 2B compares the effects of AHs on CSTTs in 4 studies^{9, 10, 13, 26}, with longer CSTTs indicative of a better efficacy. The updosing of nsAHs led to significantly increased CSTTs compared to placebos and demonstrated a tendency towards increased CSTTs relative to their own standard dosages (MD 1.7 vs 1.2 minutes, $p = .4$). There was a moderate degree of heterogeneity between the studies. (I^2 69%, p -value = .004). First-generation AHs also increased CSTTs compared to placebos. It should be noted that there was only one study of first-generation AHs, and it used higher-than-standard dosages of cyproheptadine and chlorpheniramine (4 mg three times daily, each), and with only 8 patients for each drug.

Treatment efficacy as assessed by responder analyses

The drug efficacy to inhibit wheal formation after cold provocation was investigated by 8 studies (Fig 3).^{9, 10, 12-14, 20, 21, 26} The pooled analysis showed that AHs (cyproheptadine, ebastine, mizolastine, bilastine, desloratadine, and rupatadine) and omalizumab significantly inhibited wheal formation compared with placebos (overall OR 13.1; 95% CI, 7.2 to 23.8). Higher-than-standard nsAH doses showed a higher rate of elimination of the wheal response (OR 26.6; 95% CI, 10.2 to 69.7) relative to their own standard doses (OR 7.9; 95% CI, 3.6 to 17.2), but without a statistically significant difference ($p = .06$). First-generation AHs led to higher rates of wheal inhibition compared to placebos. Again, the only first-generation AH study available, and included in our analysis, used higher-than-standard doses of cyproheptadine and chlorpheniramine (4 mg three times daily, each), and with only 8 patients for each drug.

When comparing within the same population, bilastine 40 and 80 mg had a similar efficacy in suppressing the wheal responses (OR 23.2; 95% CI, 2.6 to 208.6; and OR 28.5; 95% CI, 3.2 to 257.4, respectively). Both dosages were superior to bilastine 20 mg (OR 10.2; 95% CI, 1.1 to 93.3). There was no significant heterogeneity between the studies ($I^2 0\%$, $p = 1.0$).

Adverse events

Fig 4A illustrates all of the adverse events reported by 8 studies^{9, 10, 12-14, 20, 21, 24} Of the 118 events, 66, 14, and 38 were reported during AH, omalizumab, and placebo treatment, respectively. At least one possible adverse event was reported most and least commonly among patients receiving sedating AHs and omalizumab, respectively, with standard- and higher-than-standard-dose nsAHs in between. There was no significant difference between the standard-dose and updosed nsAHs ($p = .8$), or between omalizumab 150 and 300 mg ($p > .05$). The adverse events were mild, with sedation or somnolence being the most common.

There was no significant heterogeneity between the studies (I^2 0%, $p = .6$). A meta-regression analysis of the AH treatment duration (Fig 4B) showed that it was not a significant predictor for the occurrence of adverse events (coefficient = -0.2, 95% CI, -0.6 to 0.5, $p = .9$).

Evaluation for publication bias

Two funnel plots were relatively symmetric and did not suggest the presence of a publication bias (Fig 5B, 5D). The other two funnel plots for the analysis of CTT (Fig 5A) and complete response rate (Fig 5C) were fairly asymmetric. The funnel plots were further analyzed by the Egger regression test, which showed non-significant p -values for the first two aforementioned meta-analyses ($p = .4$ and $.4$ for CSTT and AEs, respectively), and significant p -values for the meta-analyses of CTT and the complete response rate ($p = .001$ and $.004$, respectively).

Sensitivity analysis for publication bias

To address the concern of a publication bias in the analysis of CTT and the complete response rate, a trim-and-fill sensitivity analysis was additionally performed (Fig 5E, 5F).¹⁹ The sensitivity analysis identified and added 3 theoretically missing studies to the meta-analysis of CTT, and 6 to the complete response rate. The new pooled CTT and complete response rate decreased slightly to -1.0 and 9.2, respectively, but remained statistically significant (95% CI -0.5 to -1.5; and 95% CI 5.6 to 15.1, respectively).

DISCUSSION

The most important results of our study are that non-sedating H_1 -AHs are consistently effective in ColdU treatment, that higher-than-standard doses are more effective than standard doses, and that updosed nsAHs do not increase the risk of adverse events.

In our systematic review, nsAHs were studied by 8 independent studies, all of which found them to be effective. Their efficacies were demonstrated by significant CTT reductions, CSTT prolongation, and/or responder rates. In the 6 nsAHs studies in the meta-analysis, standard doses reduced CTTs by 4°C on average and were 8 times more likely than placebos to completely inhibit cold-induced whealing.

Higher-than-standard doses of nsAHs were reported to be more effective than their own standard doses in all of the 4 studies we reviewed and meta-analyzed. Two studies of rupatadine were performed only with higher-than-standard-dose nsAHs, and they were also included in the analysis. Higher-than-standard nsAH doses reduced CTTs by 7.5°C on average and were 23 times more likely to bring a complete response.

Importantly, standard-dose and higher-than-standard-dose nsAHs showed similar safety profiles, with adverse events reported to be rare, mild, and transient in both groups. The risk of developing one of those events was not statistically different between the groups.

The current international guidelines for urticaria recommend the use of nsAHs and discourage the use of sedating AHs in the treatment of chronic spontaneous urticaria (CSU). The evidence supporting those recommendations is currently limited. Here, we provide more data that show that nsAHs are as effective as, and less harmful than, sedating AHs. Traditionally, ColdU has been treated with first-generation AHs. Previous double-blind controlled trials of first-generation AHs showed that cyproheptadine had a significant suppressive action on experimental ColdU and prolonged the time needed to generate wheal formation after an ice-cube test, while a placebo and chlorpheniramine were ineffective.^{25, 26} Because first-generation AHs often cause more adverse effects (especially sedation), modern nsAHs are recommended for use as the first-line, symptomatic treatment of ColdU.³

Metz et al. reported that omalizumab had a high efficacy in reducing CTTs and a high

complete-responder rate.¹⁴ Since this study was performed in AH-resistant patients, omalizumab can be considered to be the most effective treatment of ColdU to date. In contrast to CSU, for which omalizumab 300 mg monthly has been reported to be more effective than 150 mg,³⁰⁻³² omalizumab 150 mg and 300 mg had the same level of effectiveness for ColdU.¹⁴ These results were similar to the findings of a study of the efficacy of omalizumab in symptomatic dermatographic patients, namely, that omalizumab 150 and 300 mg monthly were equally effective.^{33, 34} It should be noted that the use of omalizumab in ColdU patients, who do not also have CSU, is currently off-label.

The advantages of our study include the relatively sizeable number of studies included as well as our focus on the analyses of objective measures of disease activity.

Limitations

As this systematic review and meta-analysis has some limitations, its results should be interpreted with caution. Firstly, the precision of our pooled analysis is rather imprecise due to the relatively high heterogeneity of the included studies. Another limitation is the presence of a publication bias in favor of positive studies in the meta-analysis of CSTT and adverse event rates of patients after treatment. Nevertheless, this publication bias should not affect the conclusion of the meta-analysis as the pooled CSTT remained statistically significant after adding the theoretically missing studies, based on our trim-and-fill sensitivity analysis. Moreover, a true comparison of different classes of treatments (e.g., sedating vs non-sedating AHs, or omalizumab vs AHs) is not possible because there were not enough trials. Another reason is that the patient populations were different between the AH trials, and between the AH and omalizumab trials (which recruited recalcitrant ColdU patients). Well-designed, head-to-head RCTs are needed to compare the efficacy of different nsAHs, and of

omalizumab vs AHs, in the same ColdU patient population. The use of standardized provocation testing, threshold testing, readouts, and outcome parameters should be encouraged to be performed in clinical practice and in all clinical trials for ColdU patients.

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Figure legends

FIG 1. Flow diagram of literature review in this meta-analysis study. Nine studies meeting the inclusion criteria were included. In the different studies, various disease activity assessments were used to assess the effects of treatment of ColdU. *Five studies^{9, 10, 12-14} used the critical temperature threshold (CTT). † Four studies^{9, 10, 13, 26} used the critical stimulation time threshold (CSTT). ‡ Eight studies^{9, 10, 12-14, 20, 21, 26} assessed the response of treatment by the wheal elimination rate. § For analysis of treatment safety, 8 studies^{9, 10, 12-14, 20, 21, 24} were included.

FIG 2A: The mean differences of CTT after treatment with standard dosage and up-dosed H₁-antihistamines (AHs), and omalizumab in cold urticaria patients. Five studies^{9, 10, 12-14} were included in the analysis. Abajian et al. did not study the efficacy (CTT) of the standard dose of rupatadine (10 mg).

FIG 2B: The mean differences of CSTT after treatment with various H₁-AHs. Four studies^{9, 10, 12-14} were included in the meta-analysis.

FIG 3: The rate of complete response. Forest plot demonstrating the ability of H₁-AHs and omalizumab to prevent wheal formation in response to cold provocation testing.

FIG 4A: The rate of patients with one or more possible adverse events after AHs and omalizumab treatment.

FIG 4B: A meta-regression analysis of the AH treatment duration showed that the treatment duration was not a significant predictor for the occurrence of adverse events (coefficient = -0.2, 95% CI, -0.6 to 0.5, $p = .9$).

FIG 5: Funnel plots of studies evaluating (5A) the mean difference of CTT; (5B) the mean difference of CSTT; (5C) the complete response rate; (5D) the adverse event rate of patients after treatment; (5E) trim-and-fill analysis of the mean difference of CTT (filled-dots represent imputed studies, and empty-dots represent observed studies); and (5F) trim-and-fill analysis of the complete response rate (filled-dots represent imputed studies, and empty-dots represent observed studies). Figures 5A and 5C show asymmetric patterns of funnel plots, which suggests that publication bias and lack of negative data could be relevant factors. Figures 5B and 5D show symmetric funnel plots for the CSTT outcome and adverse event rate, suggesting that there is a relatively low probability of publication bias.

TABLE I. Quality and risk of bias assessment of included articles in systematic review

A. Randomized controlled trials

Study, year ^{Ref}	Random sequence generation (selection bias)	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Metz, 2017 ¹⁴	+	+	+	+	+	+
Abajian, 2016 ¹³	+	+	+	+	+	+
Krause, 2013 ¹²	+	+	+	+	+	+
Magerl, 2012 ¹¹	+	+	+	+	+	+
Metz, 2010 ¹⁰	+	+	+	+	+	+
Siebenhaar, 2009 ⁹	+	+	+	+	+	+
Magerl, 2007 ²⁰	+	+	+	+	+	+
Dubertret, 2003 ²¹	+	+	+	+	+	+
Visitsunthorn, 1995 ²²	+	+	+	+	+	+
Villas Martinez, 1992 ²³	+	+	+	-	+	+
Neittaanmäki, 1988 ²¹	+	+	+	+	+	+
St-Pierre, 1985 ²⁹	+	+	+	+	-	+
Neittaanmäki, 1984* (1 st and 2 nd trials) ²⁴	+	+	+	+	+	+
Wanderer, 1977 ²⁶	+	+	+	+	+	+

B. Non-randomized controlled trials

Study, year	Criteria								Additional criteria in the case of comparative study					
	A stated aim of the study	Inclusion of consecutive patients	Prospective collection of data	End point appropriate to the study aim	Unbiased evaluation of end points	Follow-up period appropriate	Loss to follow-up not exceeding 5%	Prospective calculation of the study size	A control group having the criterion standard intervention	Contemporary groups	Baseline equivalence of groups	Prospective calculation of the sample size	Statistical analyses adapted to the study design	Total
Gorczyza, 2017 ²⁷	2	1	0	2	0	1	2	0	-	-	-	-	-	8
Neittaanmäki, 1984* (3 rd trial) ²⁵	2	1	2	2	0	2	2	0	-	-	-	-	-	11
Black, 1981 ²⁸	1	1	2	2	0	1	2	0	-	-	-	-	-	9

Note. *, Neittaanmäki had 2 randomized controlled trials and one open-label study; +, low risk of bias; ±, unclear; -, high risk of bias; 0, not reported; 1, reported but inadequate; 2, reported and adequate

TABLE II. Study characteristics of included articles in systematic review

Study, year	Treatment	N	Dosage (mg/day)	Treatment duration	Washout period	Devices	Outcome measurement	Definition of response	Complete response N (%)	Drop out N (%)	Main outcomes
Randomized control trials											
Metz, 2017 ¹⁴	Omalizumab	31	150 mg every 4 weeks (N=10)	8 weeks (3 injections)	N/A *	TempTest 4.0	- CTT	Complete response: negative provocation test result for the lowest temperature (4°C) Partial response: improvement of at least 4°C in the CTT	4/10 (40.0)	0 (0.0)	- Omalizumab was similarly effective in both doses, 150 mg and 300 mg, with no statistical differences between the 2 treatment groups.
			300 mg every 4 weeks (N=9)						4/9 (44.4)		
	Placebo		N/A (N=12)						0.0		
Abajian, 2016 ¹³ (crossover)	Rupatadine	24	20	1 week	2 weeks	TempTest 3.0	- CTT - CSTT	Complete responders: no evidence of whealing response at 4°C Partial responders: reduction of CTT $\geq$ 4°C Non-responders: reduction in CTT < 4°C	7/23 (30.4)	1 (4.2)	- Rupatadine 20 mg and 40 mg daily significantly improved CTT and CSTT and reduced wheal formation more than of placebo without an increase in sedation or other AEs. - No significant difference between each rupatadine dosages
			40						11/22 (50.0)		
	Placebo		N/A						N/A		
Krause, 2013 ¹² (crossover)	Bilastine	20	20	1 week	2 weeks	- TempTest 3.0 - microdialysis	- CTT - Symptoms severity [‡] (itch, burning sensation) - Histamine and cytokines level (only performed with 20 mg and 80 mg dosage compare to baseline)	Complete response: no whealing response at a provocation temperature of 4°C	7/20 (35.0)	0 (0.0)	- Bilastine 20 mg daily was highly effective in reducing CTT, symptoms of ACU and pruritus. - Up-dosing to 80 mg daily significantly increased efficacy on CTT but no significant difference between doses on complete response rate and pruritus score. - No evidence in increasing of sedation upon dose escalation - Microdialysis levels of histamine, IL-6, IL-8 significantly decreased following up-dosing with 80 mg bilastine.
			40						11/20 (55.0)		
			80						12/20 (60.0)		
	Placebo		N/A						1/20 (5.0)		
Magerl, 2012 ¹¹ (parallel)	Desloratadine	27	10	2 weeks	2 weeks	TempTest 3.0	- CTT	Complete remission: no wheal at 4°C Strong effect: reduction in CTT of > 6°C Weak effect: reduction in CTT of 4-6°C Negligible: reduction in CTT of 2°C or less	2/15 (13.3)	0 (0.0)	- A complete responder rate was significantly greater in the dose escalation group. - The mean CTT reduction with desloratadine 20 mg was significantly greater than with the standard dose.
			20						3/13 (23.1)		
	Desloratadine		5						0		
Metz, 2010 ¹⁰ (crossover)	Rupatadine	21	20	1 week	2 weeks	TempTest 3.0	- CTT - CSTT - Symptoms severity [‡] (itch, burning sensation, subjective complaints)	Complete protection: no induction of urticaria when challenged with TempTest 3.0 at 4°C	11/21 (52.4)	0 (0.0)	- Rupatadine 20 mg daily markedly improved CTT, CSTT and symptoms compared with placebo.
	Placebo		N/A						1/21 (4.8)		
Siebenhaar, 2009 ⁹ (crossover)	Desloratadine	33	5	1 week	2 weeks	TempTest 2.0/2.1	- CTT - CSTT - Symptoms severity [‡] (itch, burning sensation, general subjective severity)	Complete protection: did not develop a wheal response after cold provocation (4°C, 5 minutes)	7/30 (23.3)	3/33 (9.1)	- 5 mg and 20 mg desloratadine significantly reduced wheal volume and improved CTT and CSTT results compared with placebo. - Up-dosing of desloratadine at 20 mg/day significantly reduced wheal area, CTT and CSTT compared with desloratadine at standard dosage but well-tolerated.
			20						15/30 (50.0)		
	Placebo		N/A						1/30 (3.3)		
Magerl, 2007 ²⁰ (crossover)	Ebastine	22	20	Single dose	1 week	4°C cold pack (evaluated at 10 $\pm$ 2 hours after drug intake)	- Presence of wheal and erythema - Symptom severity [‡] (pruritus, burning)	Complete response: no wheal after cold challenge with 4°C cold pack	17/22 (77.3)	0 (0.0)	- Ebastine 20 mg daily significantly reduced the number of patients who experienced wheals, pruritus, and burning without AEs.
	Placebo		N/A						5/22 (22.7)		
Dubertret, 2003 ²¹ (crossover)	Mizolastine	28	10	1 week	2 weeks	Ice-cube test	- CSTT - Wheal score [¶] - Pruritus intensity [□]	Responders: CSTT > 15 minutes	N/A (36.0)	3/28 (10.7)	- Mizolastine significantly improved the CSTT, reduced wheal reaction and pruritus intensity with a few minor AEs.
	Placebo		N/A						N/A (14.0)		

Study, year	Treatment	N	Dosage (mg/day)	Treatment duration	Washout period	Devices	Outcome measurement	Definition of response	Complete response N (%)	Drop out N (%)	Main outcomes
Visitsunthorn, 1995 ²² (crossover)	Cyproheptadine ----- Ketotifen	6	0.25 mg/kg/day ----- < 35 kg: 0.5 mg bid ≥ 35 kg: 1 mg bid	4 weeks	2 weeks	Ice-cube test	- Ice-cube score [†] - Clinical improvement and side effect score [□]	N/A	N/A	0 (0.0)	- Ketotifen was as effective as cyproheptadine in treatment of ACU in Thai children with lower side effect.
Villas Martinez, 1992 ²³ (cross over)	Loratadine ----- Ceterizine ----- Cyproheptadine ----- Ketotifen	7	10 mg/day ----- 10 mg/day ----- 4 mg tid ----- 10 mg bid	2 weeks	1 week	Ice-cube test	- Clinical symptoms - CSTT - Wheal area (mm ²)	Complete response: asymptomatic	6/7 (85.7) ----- 2/7 (28.6) ----- 4/5 (80.0) ----- 4/5 (80.0)	2 (28.6)	- Both loratadine and cetirizine showed suppression of symptoms with rare AEs. - Improvement in CSTT was statistically significant for all drugs compare with baseline. - The histamine-induced wheal area was significantly reduced by all antihistamines.
Neittaaniemi, 1988 ²⁴ (crossover)	Acrivastine ----- Cyproheptadine ----- Placebo	18	8 mg tid ----- 4 mg tid ----- N/A	5 days	2 days	Ice-cube test	- Wheal area (mm ²) - Symptoms severity [‡] (itching)	N/A	N/A	0 (0.0)	- Acrivastine was significantly more effective than cyproheptadine in reducing wheal areas. - Cyproheptadine significantly caused drowsiness more than acrivastine or placebo, the last two did not significantly differ from each other.
St-Pierre, 1985 ²⁹ (crossover)	Ketotifen ----- Placebo	11	1 mg bid ----- N/A	1 week	1 week	Ice-cube test	- CSTT	N/A	N/A	0 (0.0)	- Ketotifen might be useful in the treatment of ACU, and also in patients whom resistant to standard antihistamines.
Neittaaniemi, 1984 ²⁵ (crossover)	1 st trial Doxepin ----- Cinnarizine ----- Placebo	10	10 mg tid ----- 10 mg tid ----- N/A	2 weeks	1 week	No device used	- Questionnaire on effectiveness of treatment [†]	N/A	N/A	1 (10.0)	- Doxepin was more effective than cinnarizine in the treatment of ACU, with fewer AEs.
	2 nd trial Doxepin ----- Cyproheptadine ----- Hydroxyzine ----- Placebo	12	10 mg tid ----- 4 mg tid ----- 10 mg tid ----- N/A	1 week	1 week	Ice-cube test	- Questionnaire on effectiveness of treatment [†] - Wheal response and itching [§]	N/A	N/A	1 (8.3)	- More than half of patient considered doxepin the most effective treatment for ACU with only dryness of mouth as an AE.
	3 rd trial Doxepin (open-labelled study)	10	25 mg at 10 pm and 8 am the following morning, then every 8 hours	12 hours and 38 hours	N/A	Ice-cube test (evaluated on 1 st and 2 nd morning, 2 hours after drug intake)	- CSTT - Wheal response and itching [§]	N/A	N/A	0 (0.0)	- Doxepin effectively suppressed the wheal and itching responses and shortened the duration of the wheal response in ice-cube test.
Wanderer, 1977 ²⁶ (crossover)	Chlorpheniramine ----- Cyproheptadine ----- Placebo	8	4 mg tid ----- 4 mg tid ----- N/A	1 week	1 week	Ice-water slurry	- CSTT	Complete response: no wheal reaction after cold test	N/A ----- 5/8 (62.5) ----- N/A	0 (0.0)	- Cyproheptadine significantly suppressed symptoms of ACU, while placebo and chlorpheniramine proved ineffective. - The usual AEs (mild sedation, increased appetite) of cyproheptadine was considered significant as compare to placebo or chlorpheniramine.
Retrospective study											
Gorczyza, 2017 ²⁷	Doxycycline ----- Doxycycline + H ₁ -antihistamine	2 ----- 24	200 ----- 20 or 25 (N=3)	7-28 days	N/A	- TempTest 3.0 (N=24) - Ice-cube test (N=1) - 15°C hand bath (N=1)	- CTT	Complete responder: no evidence of whealing response at 4°C Partial responders: reduction in CTT ≥ 4°C compared with baseline Non-responders: CTT reduction < 4°C compared to baseline	5/26 (19.2) overall	0 (0.0)	- Doxycycline did not significantly reduce CTT of patients with chronic cold urticaria.
Open labeled prospective study											
Black, 1981 ²⁸	Prednisone	6	20 (N=3) ----- 20 or 25 (N=3)	3-5 days	N/A	- 10°C cold water - 10°C cryoprobe (N=2)	- Grading of clinical response [#] - Histamine content of venous blood and forearm skin - Minimum time for whealing	N/A	N/A	0 (0.0)	- Prednisolone inhibited histamine release evoked by cold exposure to the skin of ACU patients. - No correlation between suppression of histamine release and clinical improvement in erythema and edema, though pruritus was improved.

*: N/A, data was not available in the study

Abbreviation: CTT, critical temperature threshold; CSTT, critical stimulation time threshold; VAS, visual analogue scale; AEs, adverse events

†: The estimation of CSTT on 40 mg rupatadine was lost for one patient due to a technical error

‡: Symptoms Severity Score (4-point scale): Itching/pruritus (0 =no itching, 1 = mild itching, 2 = moderate itching, 3 = very strong or severe itching), burning sensation (0 = none, 1 = mild, 2 = moderate, 3 = severe)

μ: Wheal score: 0 = no wheal, 1 = numerous small, noncoalescent wheals, 2 = a large, regular, slightly edematous, coalescent wheal, 3 = a large and moderately edematous wheal, 4 = a large, regular, and significantly edematous wheal without pseudopodia, 5 = a large, very edematous wheal with pseudopodia

□: Pruritus intensity; patients evaluated the intensity of pruritus using 100-mm horizontal visual analogue scale (0 = no pruritus to 100 = intolerable pruritus)

□: Clinical improvement score: recorded as percent of improvement (0-100%), side effect score: 0 = no side effect, 1 = mild side effect, 2 = moderate side effect, 3 = severe side effect

‡: Questionnaire on effectiveness of treatment: effects (very effective, some effect, no effect), side effects (tiredness, dryness of mouth, vertigo, nausea, headache, irritability, and other possible side effects)

§: Wheal response (0-8), itching response (0-2)

#: Grading of clinical response: edema (0-3), erythema (0-3), pruritus or pain (0-3)

! : Ice-cube score: 0 =none, 1 = red, very little edema, 2 = some wheal, slight raise, 3 = definite wheal, 4 = large wheal, 1/8 inch height

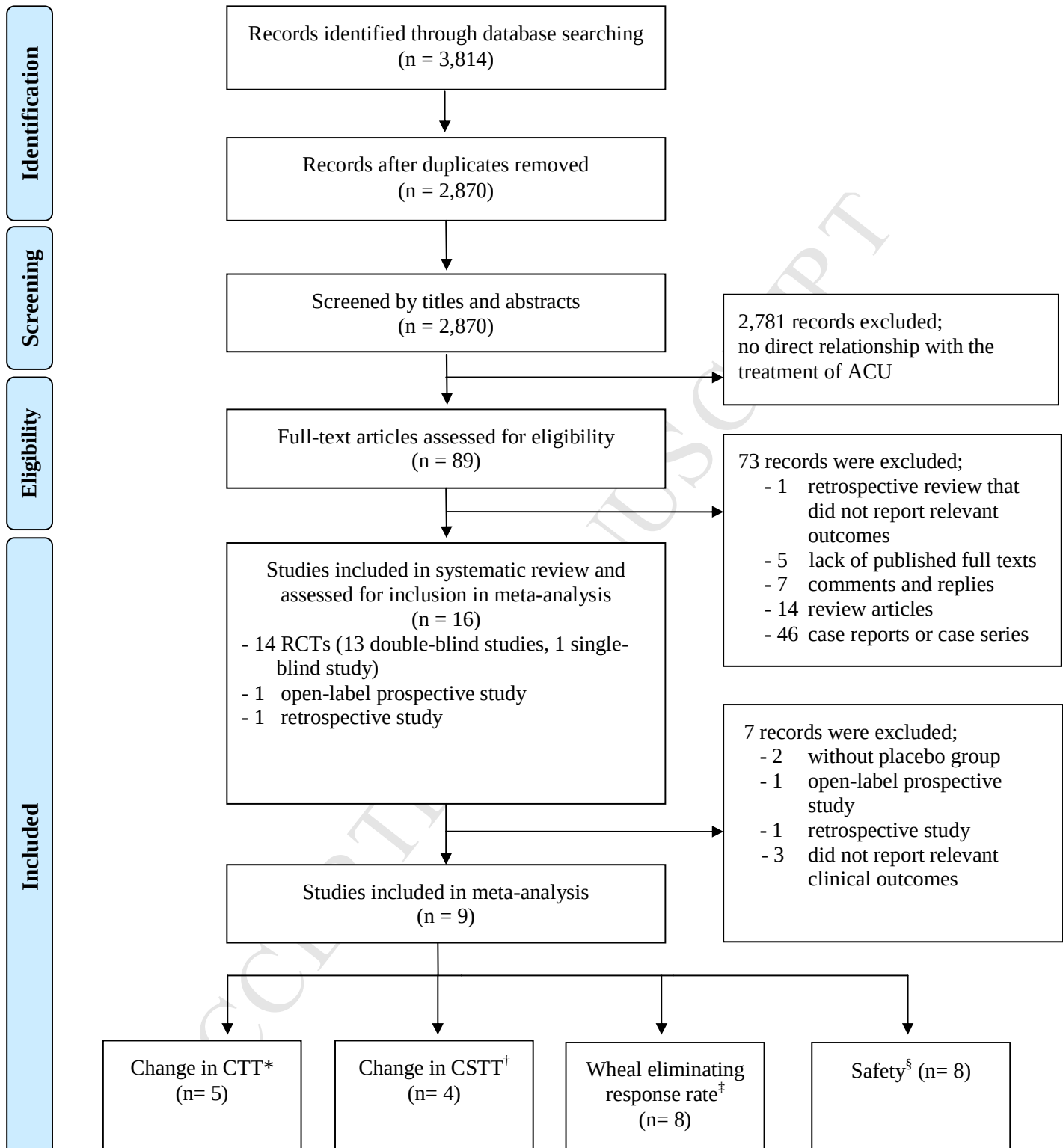
TABLE III. Response to treatments (CTT, CSTT, wheal, and pruritus suppression) of included articles in systematic review

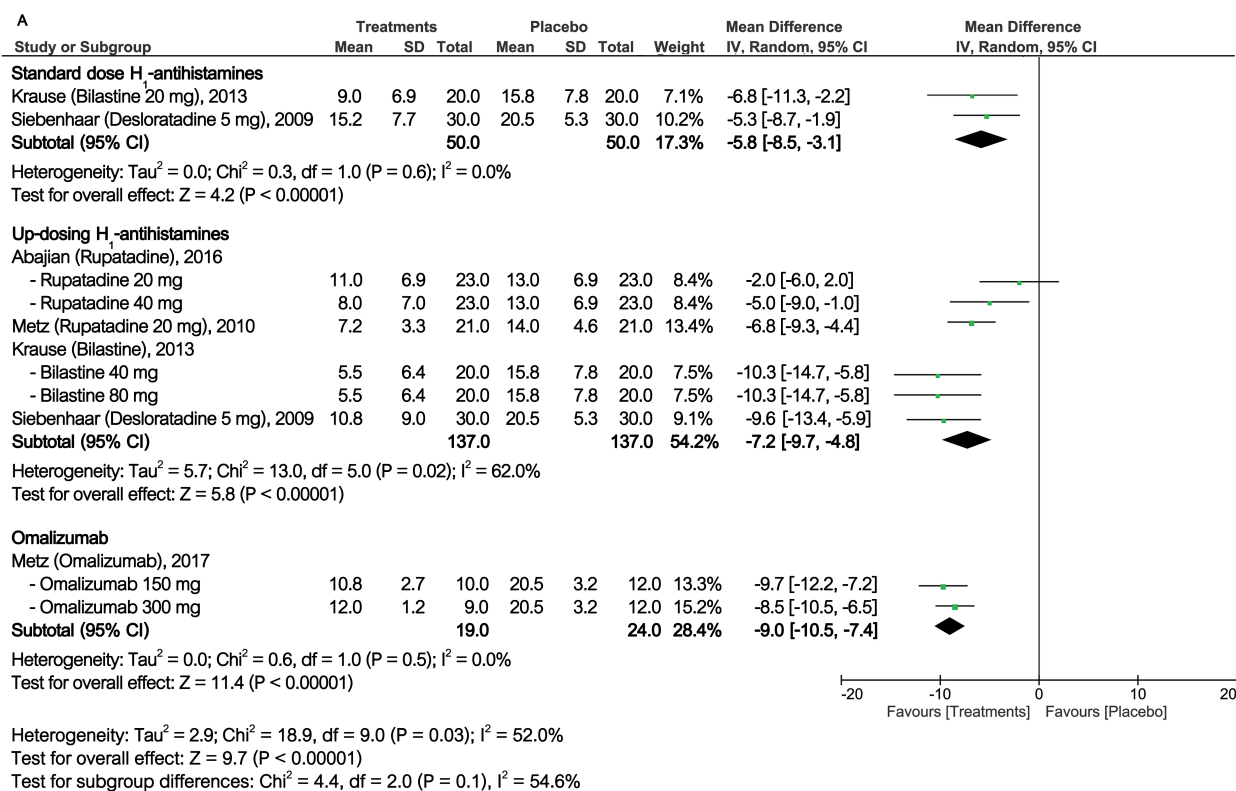
Study, year	N	Drugs	Inclusion criteria	Baseline CTT (mean ± SD; °C)	Post-treatment CTT (mean ± SD; °C)	CTT Improvement (mean ± SD; °C)	Baseline CSTT (mean ± SD; min)	Post-treatment CSTT (mean ± SD; min)	CSTT Improvement (mean ± SD; min)	Complete responder rate (after cold provocation ¹⁾ , N (%)	Rate of wheal suppression in real life, N (%)	Pruritus suppression, N (%)
Metz, 2017 ^{14,λ}	31	Omalizumab 150 mg	ColdU patients refractory to AHs treatment	21.4 ± 5.1	10.8 ± 2.7 [§]	-10.6 ± 2.4 (p=0.001)	N/A	N/A	N/A	4/10 (40.0)	N/A	N/A
		Omalizumab 300 mg		22.4 ± 4.3	12.0 ± 1.2 [§]	-10.4 ± 3.1 (p=0.01)				4/9 (44.4)		
		Placebo		20.8 ± 4.3	20.5 ± 3.2 [§]	-0.3 ± 1.1°C				0/12 (0.0)		
Abajian, 2016 ^{13,λ}	24	Rupatadine 20 mg	ColdU patients	N/A	median 10.0 (range <4.0 to 24.0, p<0.001)	N/A	N/A	median 3.0 (range 1.0 to 5.0, p<0.001)	N/A	7/23 (30.4)	N/A	N/A
		Rupatadine 40 mg			median 4.0 (range <4.0 to 24.0, p<0.001)			median 5.0 (range 1.0 to 5.0, p<0.001)		11/22 (50.0)		
		Placebo			median 14.0 (range <4.0 to 24.0)			median 1.5 (range 1.0 to 5.0)		N/A		
Krause, 2013 ^{12,λ}	20	Bilastine 20 mg	ColdU patients with positive cold provocation test	median 19.0 (range 10.0 to 27.0)	median 6.0 (range 13.0 to <4.0, p<0.0001)	median -9.0 [§] (p<0.05) [¥]	N/A	N/A	N/A	7/20 (35.0) p=0.04	N/A	13/20 (65.0) p=0.003
		Bilastine 40 mg			median <4.0 (range 11.0 to <4.0, p<0.0001)	median -12.0 [§] (p<0.05) [¥]				11/20 (55.0) p=0.001		12/20 (60.0) p=0.007
		Bilastine 80 mg			median <4.0 (range 5.5 to <4.0, p<0.0001)	median -13.0 [§] (p<0.05) [¥]				12/20 (60.0) p=0.0004		10/20 (50.0) p=0.04
		Placebo			median 18.0 (range 0.0 to 27.0)	median -1.0 [§] (p=0.2) [¥]				1/20 (5.0)		3/20 (15.0)
Magerl, 2012 ¹¹	27	Desloratadine 5 mg	ColdU patients	19.3 ± 6.2	17.0 ± 6.2	-2.3 ± 1.7 [§] (p=0.2) [¥]	N/A	N/A	N/A	0/27 (0.0)	N/A	N/A
		Desloratadine 10 mg		20.3 ± 3.1	13.5 ± 7.0	-6.8 ± 1.5 [§] (p<0.0001) [¥]				2/15 (13.3) (p=0.008) [‡]		
		Desloratadine 20 mg		20.3 ± 3.1	11.0 ± 6.5	-9.3 ± 1.4 [§] (p<0.0001) [¥]				3/13 (23.1) (p=0.008) [‡]		
Metz, 2010 ^{10,λ}	21	Rupatadine 20 mg	ColdU patients with positive ice-cube test	median 14.0 (range 8.0 to 24.0)	median 6.0 (range 2.7 to 24.0)	median -8.0 (p<0.001)	median 2.5 (range 0.2-3.5)	median 4.1 (range 1.0 to 6.2)	median 1.9 (p=0.04)	11/21 (52.4)	N/A	N/A (66.7) (p<0.01)
		Placebo			median 14.0 (range 6.0 to 22.0)	median 0.0		median 2.5 (range 0.3 to 4.0)	median 0.0	1/21 (4.8)		N/A (14.3)
Siebenhaar, 2009 ^{9,λ}	33	Desloratadine 5 mg	ColdU patients	21.8 ± 4.9 [§]	15.2 ± 7.7 (p<0.001)	-6.6 ± 1.6 [§] (p=0.0001) [¥]	1.2 ± 1.2	2.4 ± 2.2 (p<0.001)	1.2 ± 0.4 [§] (p=0.008)	7/30 (23.3) (p<0.05)	N/A	N/A
		Desloratadine 20 mg			10.8 ± 9.0 (p<0.001)	-11.0 ± 1.8 [§] (p<0.0001) [¥]		3.9 ± 2.3 (p<0.001)	2.7 ± 0.5 [§] (p<0.001)	15/30 (50.0) (p<0.001)		
		Placebo			20.5 ± 5.3	-1.3 ± 1.3 [§] (p=0.3) [¥]		1.2 ± 1.2	0.0	1/30 (3.3)		
Magerl, 2007 ^{20,λ}	22	Ebastine 20 mg	ColdU patients	N/A	N/A	N/A	N/A	N/A	N/A	18/22 (81.8) (p<0.001)	N/A	17/22 (77.3) (p<0.001)
		Placebo								5/22 (22.7)		4/22 (18.2)

ACCEPTED MANUSCRIPT													
Study, year	N	Drugs	Inclusion criteria	Baseline CTT (mean ± SD; °C)	Post-treatment CTT (mean ± SD; °C)	CTT Improvement (mean ± SD; °C)	Baseline CSTT (mean ± SD; min)	Post-treatment CSTT (mean ± SD; min)	CSTT Improvement (mean ± SD; min)	Complete responder rate (after cold provocation ¹⁹), N (%)	Rate of wheal suppression in real life, N (%)	Pruritus suppression, N (%)	
Dubertret, 2003 ^{21,1}	28	Mizolastine 10 mg	ColdU patients with positive ice-cube test	N/A	N/A	N/A	N/A	N/A	N/A	N/A (36.0)	N/A	N/A (63.6)	
		Placebo								N/A (14.0)		N/A (21.7)	
Visitsunthorn, 1995 ²²	6	Cyproheptadine Ketotifen	ColdU children	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	
Villas Martinez, 1992 ²³	7	Loratadine 10 mg	ColdU patients with positive ice-cube test	N/A	N/A	N/A	4.6 ± 1.9	11.1 ± 5.5 (<i>p</i> <0.05) *	N/A	N/A	6/7 (85.7)	N/A	
		Ceterizine 10 mg						13.4 ± 6.0 (<i>p</i> <0.01) *			2/7 (28.6)		
		Cyproheptadine 4 mg tid						14.2 ± 5.8 (<i>p</i> <0.05) *			4/5 (80.0)		
		Ketotifen 10 mg bid						10.4 ± 4.5 (<i>p</i> <0.05) *			4/5 (80.0)		
Neittaanmäki, 1988 ^{24,1}	18	Acrivastine 8 mg tid	ColdU patients with positive ice-cube test	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	
		Cyproheptadine 4 mg tid											
		Placebo											
St-Pierre, 1985 ²⁹	11	Ketotifen 1 mg bid	ColdU patients with positive ice-cube test	N/A	N/A	N/A	6.4 [§]	11.7	83.0% increase from baseline	N/A	N/A	N/A	
		Placebo						N/A					N/A
Neittaanmäki, 1984 ²⁵	1 st trial	Doxepin 10 mg tid	ColdU patients with positive ice-cube test	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	
		Cinnarizine 10 mg tid											
		Placebo											
	2 nd trial	Doxepin 10 mg tid								N/A	% difference -61.0, (<i>p</i> <0.005) *	% difference -67.0, (<i>p</i> <0.05) *	
		Cyproheptadine 4 mg tid									% difference -53.0, (<i>p</i> <0.001) *	% difference -72.0, (<i>p</i> <0.005) *	
		Hydroxyzine 10 mg tid									% difference -56.0, (<i>p</i> <0.001) *	% difference -71.0 (<i>p</i> <0.01) *	
		Placebo									% difference +3.0, (<i>p</i> >0.05) *	% difference +31.0 (<i>p</i> >0.05) *	
	3 rd trial	10	Doxepin 25 mg at 10 pm and 8 am then every 8 hours							4/10 (40.0)	N/A	N/A	
Wanderer, 1977 ^{26,1}	8	Cyproheptadine 4 mg tid	ColdU patients	N/A	N/A	N/A	5.0	> 15.0	>10.0 (<i>p</i> <0.01)	5/8 (62.5)	8/8 (100.0)	N/A	
		Chlorpheniramine 4 mg tid					5.0	6.0		N/A	5/8 (62.5)		
		Placebo					5.0	6.0		N/A	5/8 (62.5)		

ACCEPTED MANUSCRIPT												
Study, year	N	Drugs	Inclusion criteria	Baseline CTT (mean ± SD; °C)	Post-treatment CTT (mean ± SD; °C)	CTT Improvement (mean ± SD; °C)	Baseline CSTT (mean ± SD; min)	Post-treatment CSTT (mean ± SD; min)	CSTT Improvement (mean ± SD; min)	Complete responder rate (after cold provocation ¹⁹), N (%)	Rate of wheal suppression in real life, N (%)	Pruritus suppression, N (%)
Gorczyza, 2017 ²⁷	2	Doxycycline 200 mg	ColdU patients with positive cold provocation test	14.0 ± 6.0	12.0 ± 8.0 (p=0.5) *	-2.0 ± 2.0 [§] (p=0.3) [‡]	N/A	N/A	N/A	5/26 (19.2)	N/A	N/A
	24	Doxycycline 200 mg + H ₁ -antihistamine										
Black, 1981 ²⁸	3	Prednisone 20 mg	ColdU patients	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	3/6 (50.0)
	3	Prednisone 20 or 25 mg										

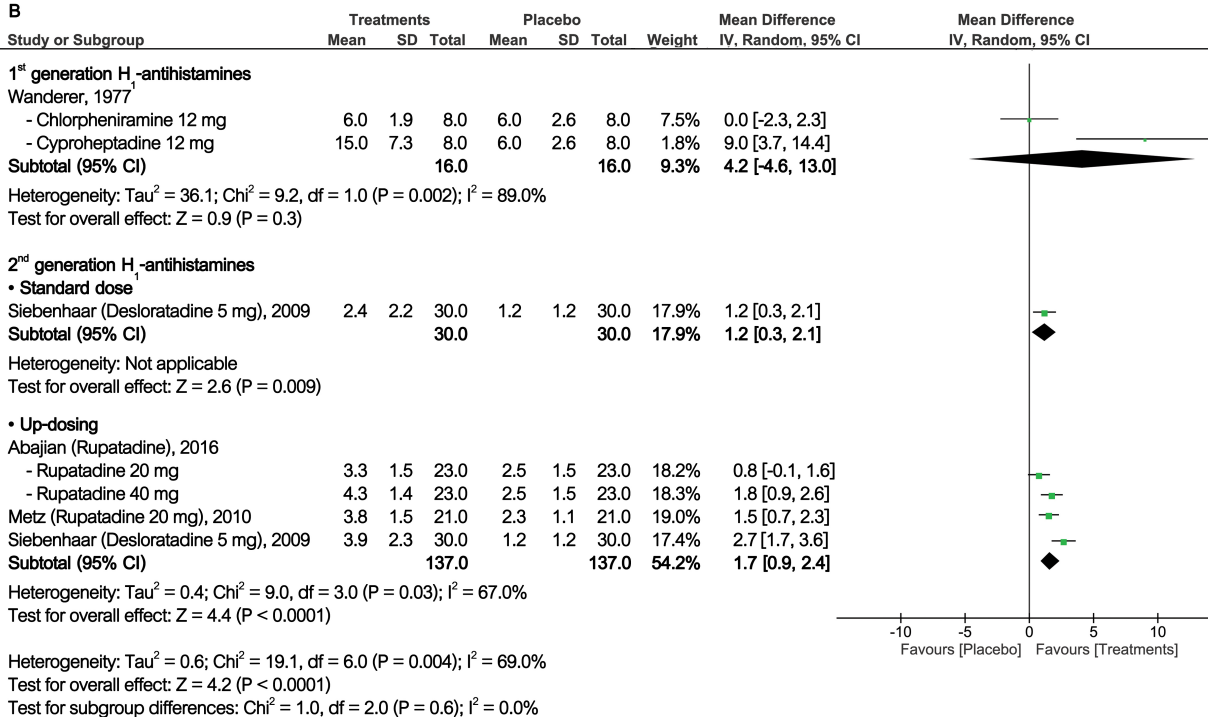
N/A; data not available, NS; not significant
 All *p*-values compare treatments to placebo except for * *p*-value; compare to baseline value, [‡] *p*-value; compare dose escalating group to the constant dose group, [‡] *p*-value; compare pre-treatment and post-treatment group
[^]Included studies in meta-analysis, [§] Data retrieved from calculation, ¹⁹ Cold provocation by Temptest and ice-cube test



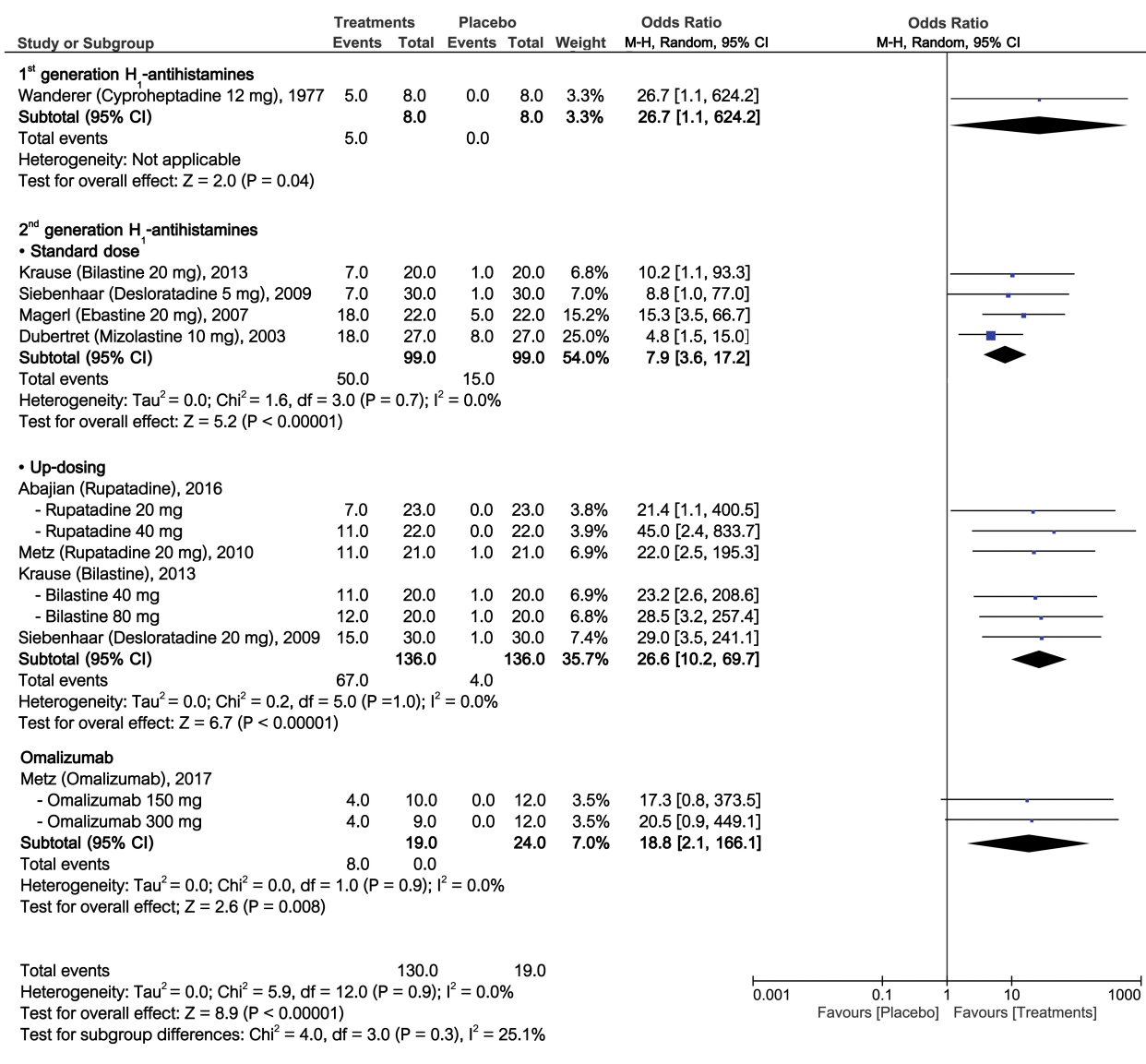


Solid squares and their horizontal lines represent effect estimates and 95% CI of each study. Upper and lower angles of the diamond represent pooled effect estimates. Lateral angles of the diamond represent 95% CI of the pooled effect estimates.

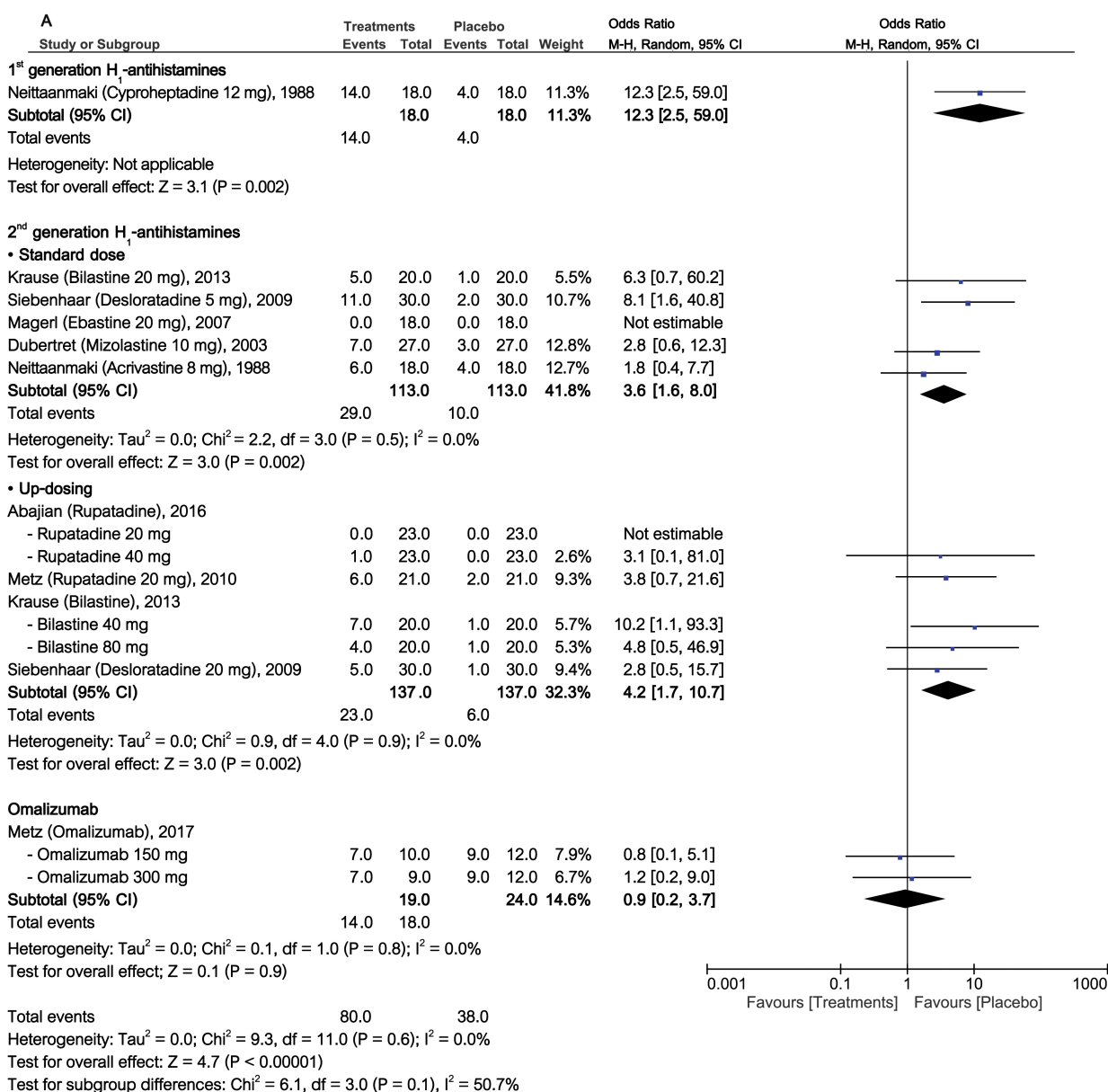
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B

