Updosing non-sedating antihistamines in patients with chronic spontaneous urticaria: a systematic review and meta-analysis

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Summary

There is a lack of large, randomized, double-blind studies that address antihistamine updosing for chronic spontaneous urticaria (CSU). The objective of this systematic review is to explore and analyse available data to provide clinical evidence for the efficacy of antihistamine updosing. We searched the literature in Medline, Scopus, Google Scholar, Embase, Web of Science and Cochrane databases using the keywords ‘chronic, urticaria, antihistamines’ to identify studies published between January 1990 and November 2014. We assessed quality using the Jadad score that evaluates quality of randomization, double-blinding and losses to follow-up. We identified 1042 articles and 15 articles were included in the final evaluation. We performed two meta-analyses, one that included studies that analysed treatment response among groups receiving different antihistamine dosages vs. placebo, and another that analysed antihistamine updosing in those patients who did not respond to standard dosages. Only five articles obtained a high quality level score. We did not find significant differences in response rates or number of weals in those patients who received a standard dosage vs. a high dosage. We found a significant improvement only in the pruritus variable of the Urticaria Activity Score scale. The estimated relative risk for improvement by increasing the antihistamine dosage was 2.27 [95% confidence interval (CI) 1.68–3.06]; however, there was significant heterogeneity. The proportion of non-respondent patients with CSU who responded to antihistamine updosing was 63.2% (95% CI 57–69.6). We found that updosing antihistamines significantly improved control of pruritus but not weal number. However, the relative weakness of the studies and the significant heterogeneity among them made it difficult to reach a final conclusion.

What’s already known about this topic?

• Antihistamines represent the first-line therapy for chronic spontaneous urticaria (CSU).
• In spite of their efficacy, CSU remains uncontrolled in a high percentage of patients receiving regular doses of antihistamines.
• Guidelines for the management of CSU recommend updosing antihistamines up to fourfold as a second-line therapy.
Chronic spontaneous urticaria (CSU) is a highly debilitating disease that has a substantial impact on quality of life and an estimated prevalence of 0.6%. There has been an immense change in how CSU is viewed following the availability of better clinical scoring tools and treatment options that have clarified a stepwise management approach. Current guidelines agree that antihistamines are the first-line therapy, and this treatment is supported by a high level of evidence. However, because of the frequent failure to gain a complete response using licensed dosages, all of the guidelines recommend that the second treatment step should consist of increasing second-generation antihistamine dosages. Nevertheless, and despite some reliable clinical studies, this recommendation is mainly based on expert opinions, and a strong clinical consensus has not yet been reached.

There have been conflicting results from several published studies. Moreover, there is a lack of well-conducted meta-analyses demonstrating the likelihood of completely controlling CSU with antihistamines at dosages higher than the licensed dosage. However, because of the safety profiles of most second-generation antihistamines, the recommendation to use these drugs above their licensed dosages as a second-line therapy is widely accepted. In addition to the problem of recommending an off-label indication, which is not allowed in some countries, the availability of newer effective treatments, such as omalizumab and other emerging biologics, makes it very important to offer clear and rigorous data on the use of high-dosage antihistamines rather than much more expensive second-line alternatives as a second-line therapy.

To shed light on this issue, we performed a systematic review and meta-analysis to evaluate the efficacy of using second-generation antihistamines at high dosages to control CSU. We also calculated the percentage of patients who were non-responsive to standard dosages of second-generation antihistamines and would be likely to experience an improvement by increasing the antihistamine dosage.

Materials and methods

Protocol and registration

The protocol for the meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement. The meta-analysis was registered in the international prospective register of systematic reviews and received the registration number CRD42015015747. The protocol is publicly available at the PROSPERO website (http://www.crd.york.ac.uk/PROSPERO). A literature search was performed using the keywords ‘chronic, urticaria, antihistamines’ in Medline, Scopus, Google Scholar, Embase, Web of Science and Cochrane databases to identify studies published between January 1990 and November 2014. We then supplemented this search by reviewing the reference lists of the retrieved articles and the latest reviews to identify additional studies. We focused on studies written in English or Spanish.

Eligibility criteria

We included studies that met all of the following criteria: (i) the study involved patients with CSU or chronic idiopathic urticaria, (ii) the patients received antihistamine treatment at different dosages and (iii) the study was written in English or Spanish. We provide as an example the full search term for two databases in the supplementary online information Data S1 (see Supporting Information).

We excluded studies if they met any of the following criteria: (i) the publications were reviews, commentaries or studies involving participant groups with a variety of conditions (such as CSU and other subtypes of urticaria), (ii) the study analysed the effect of only one antihistamine dosage, (iii) the study analysed a combination of drugs, (iv) the study had a follow-up period shorter than 2 weeks or (v) the study did not provide adequate epidemiological data regarding the effect of updosing in CSU.

Study selection

Two independent reviewers (S.G.-A. and I.J.P.) evaluated the studies, and discrepancies were resolved by discussion with a third researcher (M.F.) (Fig. S1; see Supporting Information).

Exclusion criteria owing to missing data

The criteria for exclusion owing to missing data were (i) failure to report the proportion of response to standard dosages, (ii) failure to differentiate between responses with standard dosages and high dosages, (iii) failure to differentiate between chronic urticaria and acquired urticaria and (iv) failure to provide data for nonrespondent patients.
Data extraction

One of the investigators conducted the data extraction. The following characteristics were recorded from each study: (i) the year of publication and the first author’s name, (ii) patient information, namely age range, the proportion of female patients and sample size, (iii) the scale used for the evaluation of efficacy, (iv) intervention information, including the type of antihistamine, dosages and follow-up period and (v) data regarding outcomes following updosing in patients with CSU.

Risk of bias in individual studies

A quality score based on Jadad et al.8 was determined using the Oxford calculator (http://www.pmidcalc.org/?sid=8721797&newtest=Y). This score evaluates the quality of randomization, double-blinding and losses to follow-up, and establishes a score of ≥3 points as high quality and <3 points as low quality. Quality scores were not used in the analysis; they were provided for informative purposes only.

Quantitative analysis (meta-analysis)

When selecting studies, we identified two different types of approaches. Our primary research aim was to investigate whether updosing was superior to regular dosages of antihistamines in controlling urticaria. The secondary analysis investigated whether those patients whose urticaria was not controlled using regular dosages achieved control of their symptoms as a result of the updosing of antihistamines. One group of publications generally corresponded to phase II studies comparing different populations that received different antihistamine dosages. The second group of studies evaluated the responses to increasing antihistamine dosages within the same population. Therefore, we performed separate meta-analyses for each of the two categories.

We presented the dichotomous outcomes data as risk ratios (RRs) and numbers needed to treat (NNTs) along with their associated 95% confidence intervals (CIs). We analysed these in Synergy (GlaxoSmithKline, Madrid, Spain) using the DerSimonian–Laird test (fixed-effects model), unless otherwise stated. Those articles that provided continuous data were analysed in a subgroup for which we reported standardized mean differences (SMDs). If similar outcomes were reported using different scales, we standardized these to the Urticaria Activity Score (UAS) for pruritus (0–3) or weals (0–3). We provide symptom equivalence information in Table S1 (see Supporting Information).

The existence of heterogeneity was assessed using a Q-test. When there was no heterogeneity, we used the fixed-effects model. If the heterogeneity was significant (P < 0·1), analyses were calculated using a random-effects model. In these cases, we also performed a sensitivity analysis.

To estimate the proportion of patients with CSU who responded to an updosing of the antihistamine, we performed a proportion meta-analysis using the confidence profile method with Fast*Pro software (Boston, MA, U.S.A.), as this Bayesian method deals more adequately with heterogeneity.9–13 To estimate the statistical heterogeneity, we used χ²-test values, P-values and the I² proportion of the total variability explained by the heterogeneity. To determine the source of the heterogeneity, we performed a sensitivity analysis by removing one study at a time and performing the same calculations on the remaining studies.

Results

Study selection

Initially, we identified 1042 articles. Of these, 1038 were from international databases. Using the additional strategies of reviewing bibliographies and reviewing the lists of cited works, we identified five additional studies. We identified the following numbers of articles from the databases: Scopus (n = 346), Google Scholar (n = 334), Embase (n = 148), Medline (n = 142) and Web of Knowledge (n = 68). Of these articles, 428 were removed owing to duplication. Of the remaining articles 615 were screened, 584 of which were excluded. From the 31 studies retrieved for detailed evaluation, 16 were excluded after full-text examination because of missing data (n = 9), other interventions (n = 1) or because they included an analysis of other types of urticaria (n = 6). A total of 15 articles were included in the final evaluation. The PRISMA template for the study selection is displayed in Figure S1 (see Supporting Information).14 Characteristics of the included studies are displayed in Tables 1 and 2. The number of participants in these studies ranged from 20 to 418, with an average of 190 and 107 participants in each meta-analysis study, respectively.

Quality assessment

A relative risk of bias was identified in the Category 1 studies using the Jadad score, which specializes in detecting risk of bias (Table 1). Only one of the six included studies scored 5 and one scored 0 according to the Jadad score.8

The studies included in the Category 2 group (Table 2) appeared to have an overall high risk of bias as those studies were neither randomized nor double-blinded. The Staevska et al.15 study was a randomized, double-blind crossover study that compared the efficacy of levocetirizine and desloratadine in 80 patients with CSU receiving increasing dosages of 5, 10, 15 and 20 mg of both antihistamines. Despite its quality, this study conducted a randomized and double-blind clinical trial aimed at comparing both antihistamines and not the efficacy of different dosages. For this reason, there is a lack of randomization and double-blindness for different dosages in this study. We considered each drug individually, thereby increasing the risk of bias in our analysis.

Meta-analysis of the studies

As stated above, we performed a different meta-analysis for each category. The first category included those studies that

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<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Scale</th>
<th>No. of patients</th>
<th>Duration</th>
<th>Antihistamine Dosages, mg</th>
<th>Definition of lack of response</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nelson et al.</td>
<td>Phase II, dose-response, randomized, double-blind, placebo-controlled, parallel</td>
<td>MPS, MNW</td>
<td>418</td>
<td>4 weeks</td>
<td>Fexofenadine 120 and 480</td>
<td>Discontinuation owing to treatment failure</td>
<td>CSU 70, 12–65, High 3</td>
</tr>
<tr>
<td>Tanizaki et al.</td>
<td>Uncontrolled clinical trial VAS pruritus No. of weals</td>
<td>VAS pruritus, No. of weals</td>
<td>20</td>
<td>8 weeks</td>
<td>Fexofenadine 120 and 240</td>
<td>–</td>
<td>NR-CSU 40, Mean 36, Low 0</td>
</tr>
<tr>
<td>Weller et al.</td>
<td>Phase II, dose-response, randomized, double-blind, placebo-controlled, parallel</td>
<td>MPS, MNW</td>
<td>277</td>
<td>4 weeks</td>
<td>Desloratadine 5 and 20</td>
<td>Discontinuation owing to treatment failure</td>
<td>CSU 73, 12–65, High 3</td>
</tr>
<tr>
<td>Dubertret et al.</td>
<td>Phase II, dose-response, randomized, double-blind, placebo-controlled, parallel</td>
<td>MPS, MNW</td>
<td>178</td>
<td>4 weeks</td>
<td>Rupatadine 10 and 20</td>
<td>Discontinuation owing to treatment failure</td>
<td>CSU 74, 12–65, High 3</td>
</tr>
<tr>
<td>Finn et al.</td>
<td>Placebo-controlled, randomized, double-blind</td>
<td>MPS, MNW</td>
<td>221</td>
<td>4 weeks</td>
<td>Rupatadine 10 and 20</td>
<td>Discontinuation owing to treatment failure</td>
<td>CSU 77, 12–65, High 4</td>
</tr>
</tbody>
</table>

CSU, chronic spontaneous urticaria; MNW, mean number of weals; MPS, mean pruritus score; VAS, visual analogue scale. *Jadad score: ≥ 3 high quality; < 3 low quality. aWe did not include the study by Tanizaki et al. in comparisons 1–3 because all patients were nonresponsive to standard dosages (NR-CSU).
Table 2: Category 2: studies analysing antihistamine updosing responses in patients who did not respond to standard dosages

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>No. of patients</th>
<th>Duration</th>
<th>Antihistamine</th>
<th>Dosages, mg</th>
<th>Definition of lack of response</th>
<th>Type of patients</th>
<th>Sex, % female patients</th>
<th>Age, years</th>
<th>Quality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asero et al.</td>
<td>Uncontrolled, nonrandomized open-label clinical trial</td>
<td>22</td>
<td>4 weeks</td>
<td>Cetirizine</td>
<td>10 and 30</td>
<td>Not reported</td>
<td>NR-CSU</td>
<td>86</td>
<td>28–67</td>
<td>Low 0</td>
</tr>
<tr>
<td>Asero et al.</td>
<td>Uncontrolled, nonrandomized open-label clinical trial</td>
<td>68</td>
<td>3 weeks</td>
<td>Cetirizine</td>
<td>10 and 30</td>
<td>Nonresponse or partial response</td>
<td>CSU and NR-CSU</td>
<td>77</td>
<td>14–68</td>
<td>Low 0</td>
</tr>
<tr>
<td>Godse et al.</td>
<td>Uncontrolled, nonrandomized open-label clinical trial</td>
<td>37</td>
<td>3 weeks</td>
<td>Fexofenadine</td>
<td>180 and 360–540</td>
<td>Remaining symptomatic</td>
<td>CSU and NR-CSU</td>
<td>46</td>
<td>16–60</td>
<td>Low 0</td>
</tr>
<tr>
<td>Godse et al.</td>
<td>Uncontrolled, nonrandomized open-label clinical trial</td>
<td>20</td>
<td>3 weeks</td>
<td>Levocetirizine</td>
<td>5 and 10–20</td>
<td>Remaining symptomatic</td>
<td>CSU and NR-CSU</td>
<td>60</td>
<td>20–60</td>
<td>Low 0</td>
</tr>
<tr>
<td>Godse et al.</td>
<td>Uncontrolled, nonrandomized open-label clinical trial</td>
<td>30</td>
<td>3 weeks</td>
<td>Ebastine</td>
<td>10 and 20–40</td>
<td>Remaining symptomatic</td>
<td>CSU and NR-CSU</td>
<td>53</td>
<td>20–60</td>
<td>Low 1</td>
</tr>
<tr>
<td>Magen et al.</td>
<td>Uncontrolled, nonrandomized open-label clinical trial</td>
<td>276</td>
<td>16 weeks</td>
<td>Fexofenadine</td>
<td>180 and 360, 540–720</td>
<td>Improvement &lt; 50% of UAS baseline</td>
<td>CSU and NR-CSU</td>
<td>73</td>
<td>&gt; 18</td>
<td>Low 0</td>
</tr>
<tr>
<td>Staevska et al.</td>
<td>Uncontrolled clinical trial nested in double-blind clinical trial</td>
<td>40</td>
<td>3 weeks</td>
<td>Desloratadine</td>
<td>5 and 10–20</td>
<td>Remaining symptomatic</td>
<td>CSU and NR-CSU</td>
<td>72</td>
<td>19–67</td>
<td>High 3</td>
</tr>
<tr>
<td>Staevska et al.</td>
<td>Uncontrolled clinical trial nested in double-blind clinical trial</td>
<td>40</td>
<td>3 weeks</td>
<td>Levocetirizine</td>
<td>5 and 10–20</td>
<td>Remaining symptomatic</td>
<td>CSU and NR-CSU</td>
<td>60</td>
<td>19–67</td>
<td>High 3</td>
</tr>
<tr>
<td>Tharp et al.</td>
<td>Uncontrolled, nonrandomized open-label clinical trial</td>
<td>217</td>
<td>6 weeks</td>
<td>Cetirizine</td>
<td>5 and 10</td>
<td>Patient decision</td>
<td>CSU and NR-CSU</td>
<td>67%</td>
<td>&gt; 12</td>
<td>Low 1</td>
</tr>
<tr>
<td>Weller et al.</td>
<td>Patient survey, retrospective cohort study</td>
<td>319</td>
<td>Not reported</td>
<td>Any antihistamine</td>
<td>Standard vs updosing</td>
<td>Slightly better, equal or worse</td>
<td>CSU and NR-CSU</td>
<td>77%</td>
<td>18–76</td>
<td>Low 1</td>
</tr>
</tbody>
</table>

CSU, chronic spontaneous urticaria; NR-CSU, nonresponder to standard dosage of antihistamine for treatment of CSU; UAS, Urticaria Activity Score. Jadad score: ≥ 3 high quality; < 3 low quality.
analysed responses to treatment among groups who received various dosages vs. placebo (Table 1). The second category corresponded to studies of antihistamine updosing in patients who did not respond to standard dosages (Table 2).

Comparison 1: Response rate to antihistamines at the standard dosage vs. a high dosage

When analysing the response rate, three of the six studies included in Table 1 compared global responses with treatment across groups receiving different dosages of the same drug vs. placebo. Nonrespondent patients were defined as those who had <50% improvement or those who left the clinical trial because of treatment failure. A pooled analysis of the three articles\textsuperscript{16–18} estimated no significant improvement, with an RR of 1.004 (95% CI 0.96–1.05) in patients undergoing treatment with high dosages of antihistamines. Heterogeneity was not significant (Q = 1.67, P = 0.43) (Fig. 1). We performed a subgroup analysis for rupatadine, but it was not statistically significant (Table S2; see Supporting Information).

Comparison 2: Change in pruritus at the standard dosage vs. a high dosage of antihistamines

Four trials compared the changes in the degree of pruritus with baseline at different dosages.\textsuperscript{16–19} The estimated SMD was 0.13 (95% CI 0.04–0.23), with a significant improvement of 0.13 points in the UAS for pruritus (0–3), which favours treatment with higher dosages. Heterogeneity was not significant (Q = 2.37, P = 0.49) (Fig. 2). Comparison symptom scores are provided in Table S1 (see Supporting Information). Analysis of the subgroup treated with rupatadine detected an improvement, with an SMD in pruritus of 0.187 (95% CI 0.05–0.32) (Table S2; see Supporting Information).

Comparison 3: Change in weals at the standard dosage vs. a high dosage of antihistamines

Some of the studies analysed improvement in the number of weals using an estimation of the change from the baseline score.\textsuperscript{16,17,20} A pooled analysis of three studies using the SMD

<table>
<thead>
<tr>
<th>No.</th>
<th>Year</th>
<th>Author</th>
<th>No. of patients</th>
<th>CI lower limit</th>
<th>CI upper limit</th>
<th>Relative risk</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1999</td>
<td>Finn\textsuperscript{17}</td>
<td>165</td>
<td>0.921</td>
<td>1.055</td>
<td>0.986</td>
<td>0.034</td>
</tr>
<tr>
<td>2</td>
<td>2007</td>
<td>Giménez-Arnau\textsuperscript{18}</td>
<td>218</td>
<td>0.935</td>
<td>1.334</td>
<td>1.117</td>
<td>0.091</td>
</tr>
<tr>
<td>3</td>
<td>2007</td>
<td>Dubertret\textsuperscript{16}</td>
<td>162</td>
<td>0.939</td>
<td>1.081</td>
<td>1.008</td>
<td>0.035</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Summary measure</td>
<td>0.958</td>
<td>1.053</td>
<td>1.004</td>
<td>0.024</td>
<td></td>
</tr>
</tbody>
</table>

Test for heterogeneity: $Q_h = 1.6777, P = 0.432$
Test for overall effect: $Q_A = 0.0419, P = 0.838$

Fig 1. Forest plot showing rate of response to antihistamines at standard vs. high dosages. Analyses were carried out using DerSimonian–Laird test (fixed-effects model). CI, 95% confidence interval.
found a nonsignificant improvement in the UAS for weals (SMD = 0.053, 95% CI −0.109 to 0.216) when antihistamines were used at high dosages. Heterogeneity was not significant (Q = 0.33, P = 0.98) (Fig. 3). Comparison symptom scores are provided in Table S1 (see Supporting Information).

Comparison 4: Rate of response at the standard dosage vs. the standard dosage plus updosing

When comparing antihistamine updosing in patients who did not respond to standard dosages, the estimated RR was 2.27 (95% CI 1.68–2.69), favouring the second-line treatment (high dosage) recommended for those patients who did not respond to a standard dosage.21–27 The NNT was 2.27 (95% CI 2.1−2.47). The heterogeneity between these studies was significant. We conducted a sensitivity analysis but did not identify a clear source for the heterogeneity. The range of the RRs was 2.01–2.42. The funnel plot graph showed that studies with both positive and negative findings were published, and thus there does not seem to be a publication bias (Fig. 4a,b). Analysis of studies with cetirizine presented an NNT of 2.54 (95% CI 2.14–3.14), while the NNT of those with fexofenadine was 2.81 (95% CI 2.4–3.34) (Table S2; see Supporting Information).

Proportion of patients with chronic spontaneous urticaria who responded to standard dosages of antihistamine

The rate of response to standard dosages of antihistamine in patients with CSU was 38.6% (95% CI 34.7–42.7), using the Bayesian model. We also estimated the rate with a frequentist model (32.5%, 95% CI 20.7–44.4). As stated above, given

<table>
<thead>
<tr>
<th>No.</th>
<th>Year</th>
<th>Study</th>
<th>High dosage, n</th>
<th>Standard dosage, n</th>
<th>Lower CI</th>
<th>Upper CI</th>
<th>SMD</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1999</td>
<td>Finn</td>
<td>83</td>
<td>86</td>
<td>−0.066</td>
<td>0.286</td>
<td>0.11</td>
<td>0.09</td>
</tr>
<tr>
<td>2</td>
<td>2000</td>
<td>Nelson</td>
<td>82</td>
<td>90</td>
<td>−0.189</td>
<td>0.229</td>
<td>0.02</td>
<td>0.106</td>
</tr>
<tr>
<td>3</td>
<td>2007</td>
<td>Giménez-Arnau</td>
<td>108</td>
<td>110</td>
<td>−0.071</td>
<td>0.331</td>
<td>0.13</td>
<td>0.103</td>
</tr>
<tr>
<td>4</td>
<td>2007</td>
<td>Dubertret</td>
<td>67</td>
<td>73</td>
<td>0.056</td>
<td>0.404</td>
<td>0.23</td>
<td>0.088</td>
</tr>
</tbody>
</table>

Test for heterogeneity: $Q_h = 2.378, P = 0.497$
the heterogeneity of this group of studies, the Bayesian model was considered to be the most appropriate (Fig. 5a). Fexofenadine was the drug that showed the highest proportion of patients with CSU who responded to standard dosages, at 58.47% (95% CI 50.3–67.23); cetirizine had a lower proportion of responders, at 41.98% (95% CI 34.51–50.18) (Table S2; see Supporting Information).

**Proportion of patients with nonrespondent chronic spontaneous urticaria who responded to antihistamine updosing**

The rate of response to updosing in patients with CSU who were nonresponsive to standard dosages was 63.2% (95% CI 57.69–69.6) according to the Bayesian model. We also estimated the rate with a frequentist model (59.7%, 95% CI 36.8–82.6). Again, the Bayesian model was the most appropriate because of the heterogeneity of this group of studies (Fig. 5b, Table 2). Fexofenadine was the drug that showed the highest proportion of patients who had not responded to a standard dosage but did respond to antihistamine updosing, at 83.07% (95% CI 68.14–99.45). Levocetirizine and cetirizine had lower proportions of responders, at 55.26% (95% CI 39.82–73.19) and 53.8% (95% CI 33.3–79.2), respectively (Table S2; see Supporting Information). However, it should be noted that available data does not allow us to perform statistical comparisons among different antihistamines and consequently significant data is not provided.

**Discussion**

There is general agreement regarding the use of higher dosages of second-generation antihistamines as a second-line...
Comparison 4: Rate response at standard dosage vs. standard dosage plus updosing

<table>
<thead>
<tr>
<th>Year</th>
<th>Study</th>
<th>No. of patients</th>
<th>Drug</th>
<th>Lower CI</th>
<th>Upper CI</th>
<th>Relative risk</th>
<th>SE (LnRR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>Magen</td>
<td>276 Fexofenadine</td>
<td>0.731</td>
<td>3.005</td>
<td>1.482</td>
<td>0.361</td>
<td></td>
</tr>
<tr>
<td>1996</td>
<td>Tharp</td>
<td>194 Cetirizine</td>
<td>1.170</td>
<td>5.450</td>
<td>2.526</td>
<td>0.392</td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td>Asero</td>
<td>68 Cetirizine</td>
<td>1.680</td>
<td>9.184</td>
<td>3.928</td>
<td>0.433</td>
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</tr>
<tr>
<td>2010</td>
<td>Godse</td>
<td>20 Levocetirizine</td>
<td>0.746</td>
<td>3.601</td>
<td>1.640</td>
<td>0.401</td>
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</tr>
<tr>
<td>2010</td>
<td>Godse</td>
<td>37 Fexofenadine</td>
<td>1.386</td>
<td>7.727</td>
<td>3.272</td>
<td>0.438</td>
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<tr>
<td>2011</td>
<td>Godse</td>
<td>30 Ebastine</td>
<td>0.809</td>
<td>3.751</td>
<td>1.742</td>
<td>0.391</td>
<td></td>
</tr>
<tr>
<td>2011</td>
<td>Weller</td>
<td>319 Antihistamines</td>
<td>1.343</td>
<td>5.657</td>
<td>2.757</td>
<td>0.366</td>
<td></td>
</tr>
</tbody>
</table>

Relative risk: 1.684 3.059 2.269 0.152

NNT: 2.1 2.47 2.27

Test for heterogeneity: $Q = 62.831, P < 0.001$

Fig 4. Funnel and forest plot showing rate of response to antihistamines at standard dosage vs. standard dosage plus updosing. Analyses were carried out using DerSimonian–Laird test (random-effects model). CI, 95% confidence interval; NNT, number needed to treat; SE (LnRR) standard error of the log risk ratio.
### Sensitivity analysis

<table>
<thead>
<tr>
<th>Discounted study</th>
<th>No. of patients</th>
<th>Relative risk</th>
<th>NNT</th>
<th>Q heterogeneity</th>
<th>Q%</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magen\textsuperscript{25}</td>
<td>668</td>
<td>2·452</td>
<td>1·994</td>
<td>16·317</td>
<td>74·029</td>
<td>( P = 0·021 )</td>
</tr>
<tr>
<td>Tharp\textsuperscript{26}</td>
<td>750</td>
<td>2·233</td>
<td>2·141</td>
<td>57·197</td>
<td>8·967</td>
<td>( P &lt; 0·001 )</td>
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<tr>
<td>Asero\textsuperscript{21}</td>
<td>876</td>
<td>2·103</td>
<td>2·340</td>
<td>51·427</td>
<td>18·150</td>
<td>( P &lt; 0·001 )</td>
</tr>
<tr>
<td>Godse\textsuperscript{23}</td>
<td>924</td>
<td>2·398</td>
<td>2·264</td>
<td>60·844</td>
<td>3·162</td>
<td>( P &lt; 0·001 )</td>
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<td>Godse\textsuperscript{22}</td>
<td>907</td>
<td>2·161</td>
<td>2·343</td>
<td>55·981</td>
<td>10·903</td>
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<td>Godse\textsuperscript{24}</td>
<td>914</td>
<td>2·383</td>
<td>2·268</td>
<td>61·131</td>
<td>2·705</td>
<td>( P &lt; 0·001 )</td>
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<tr>
<td>Weller\textsuperscript{27}</td>
<td>625</td>
<td>2·171</td>
<td>2·673</td>
<td>31·344</td>
<td>50·113</td>
<td>( P &lt; 0·001 )</td>
</tr>
</tbody>
</table>

**Fig 5.** Forest plot showing the proportion of patients with chronic spontaneous urticaria who improved with (a) standard dosages and (b) updosing of antihistamines. The heterogeneity analysis shown in (b) meant that a sensitivity analysis was not required; therefore, no accompanying data is provided for this plot. Further information regarding these studies is provided in Table 2. NNT, number needed to treat.
therapy in patients with severe, recalcitrant CSU for whom the standard dosage was not effective. However, this agreement is mainly supported by isolated clinical studies. Well-designed, randomized, double-blind clinical trials comparing the efficacy of therapeutic and upgraded dosages are sparse, and well-conducted meta-analyses on this subject are lacking. To our surprise, when we performed a meta-analysis, we found no differences in weal number or response rates. We found significant differences between the standard and higher antihistamine dosages with respect to the control of pruritus, with a low improvement magnitude (0.13 on a scale of 0–3). We consider these data to be robust, as the three high-evidence studies were included in this group and there was no heterogeneity among them.

When dealing with patients who do not respond to standard antihistamine dosages, updosing second-generation antihistamines according to the recommended guidelines multiplies the response rate by 2–3. Nevertheless, this result should be evaluated with caution because of the observed heterogeneity and the low quality of the studies. Moreover, these studies were performed using different time frames for patients who responded to a standard dosage and those who received higher dosages. This factor is important when taking into account the fact that CSU is a self-limited disease and that some patients could have experienced spontaneous symptom remission while taking part in the study. Furthermore, these studies lacked randomization, blinding and control groups.

Interestingly, antihistamine dosage increases were as high as four times the licensed dosage. As Kaplan notes, this increase is extrapolated from results obtained with first-generation antihistamines for controlling physical urticarias. This might be the reason for the discrepancy between expert perceptions and our data. Physical urticarias are mainly mediated by histamine and demonstrate clear dose responses in the majority of cases. However, CSU is an inflammatory disease in which histamine plays a key role in a much more complex disease. It is not unusual to find trials on the efficacy of antihistamines that combine different physical urticaria subtypes with CSU. In this report, we had to withdraw six of 21 studies from the analysis for this reason.

When analysing the CSU guidelines, we observed that many recommendations are not supported by a high level of evidence in studies such as meta-analyses or systematic reviews. For example, the European guidelines for using high dosages of antihistamines for chronic urticaria are based on 10 studies; among these, four dealt with cold-induced urticaria that is one subtype of chronic urticaria, but not CSU. Three of the other six CSU studies are presented as high-evidence studies and the remaining three are low-evidence studies. However, one study was nonsignificant for updosing, the second study consisted of a pool of two analyses and the third found significant differences but lacked randomization and double-blinding for different dosages. British guidelines give a grade B for the recommendation to use higher dosages of antihistamines, and this is also supported by the Staevska et al. study. Similarly, Japanese guidelines give a recommendation level B–C1 and an evidence level II, V for increasing the dosage of antihistamines up to twice the recommended amount when no response is achieved at standard dosages. This evidence level is based on a structured abstract of a 2011 review published in Japanese, which we were unable to translate.

In contrast, American guidelines agree that the data are limited and conflicting regarding the recommendation of updosing antihistamines for patients who are not responsive to standard dosages. Similarly, the World Allergy Organization (WAO) position paper states that limited data are available on antihistamine dosing and reviews several studies that were analysed in our meta-analysis. The recommendation of the WAO is based on the safety profile of antihistamines as a corticosteroid-sparing agent.

Notably, all of the guidelines have concluded that there is a need for double-blinded controlled trials to compare different second-generation antihistamines at higher dosages.

Another conclusion that emerged from our results is that it would have been extremely useful to have also performed quality-of-life assessments in the included studies because minimal changes to scores on an itching scale might have a large impact on quality of life. Furthermore, we should take into account that when treating CSU the aim is to achieve complete control of the disease and although reducing itching severity is very important, it may not be sufficient for the patient. Also, 40% of patients with CSU also have angio-oedema, which has a considerable impact on quality of life.

One very interesting finding of our study is the 38.6% rate of response to standard dosages of antihistamines for patients with CSU and the 60% likelihood of responding, to some extent, to an increased dosage of antihistamines. Given the striking efficacy of omalizumab, this treatment should be reconsidered for shortening and simplifying the stepwise treatment approach for CSU. Despite their high cost, supplementary stepladders that are typically added to antihistamine treatments but have only weak evidence for their efficacy should probably be avoided, even when the high safety profile of certain add-on therapies, such as anti-IgE antibodies or anti-H2 histamines, might justify their tentative inclusion in the treatment of patients with refractory CSU. However, omalizumab should be tried only when antihistamines have shown no efficacy. As the European guidelines note, the response to antihistamines should be assessed within 2–4 weeks so as not to delay symptom control if the treatments are ineffective.

Our meta-analysis did not find that updosing antihistamines significantly improves response control or weal number. Updosing appears to have a significant (but weak) improvement in itch control only, which is the most important symptom that affects patient well-being. We suggest that the evaluation of whether a product or dosage works should primarily be based on validated CSU assessment tools, paying special attention to itch control. It should also include angio-oedema, and the Chronic Urticaria Quality of Life Questionnaire. Moreover, including a specific quality-of-life scoring as an outcome could have had an impact on the results. There
might have been a more positive result for the updosing of antihistamines if this measure had been included, as itching rather than the appearance of weals is the primary debilitating symptom for most patients with CSU.

Studies that analysed the improvements in patients who were not responsive to standard dosages have shown a 2:3 odds ratio for controlling urticaria at higher doses. The low quality of these studies, as estimated by their Jadad scores, limits the consistency of their findings. However, in spite of the low quality of these studies, updosing has a tendency to result in a beneficial effect for some patients. For this reason, further high-quality studies on updosing are required.

References


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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher’s website:

- Figure S1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2009 flowchart.
- Data S1. Example of full search term for two databases.
- Data S2. Articles selected.
- Table S1. Score equivalence table.
- Table S2. Subanalysis of the data for individual antihistamines.
- Video S1. Author video.