

Efficacy and Safety of Intensive Nonsedating Antihistamines for Chronic Spontaneous Urticaria: A Meta-Analysis of Randomized Controlled Trials

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Keywords

Intensive nonsedating antihistamines · Chronic spontaneous urticaria · Meta-analysis

Abstract

Introduction: The aim of this study was to determine the efficacy and safety of intensive versus standard nonsedating antihistamines (NSAs) for chronic spontaneous urticaria (CSU) patients. **Methods:** An electronic search was performed on the PubMed, Embase, and the Cochrane Library databases to identify eligible randomized controlled trials (RCTs) throughout January 2021. The weighted mean difference (WMD) and relative risk (RR) with 95% confidence interval (CI) were applied to calculate the pooled outcomes for the continuous and categorical data using the random-effects model. **Results:** Nine RCTs involving 1,996 CSU patients were selected. We found that intensive NSA was associated with greater reduction in the mean pruritus score than the standard dose of NSA (WMD: -0.13 ; $p = 0.005$). However, there was no significant difference between the intensive and standard dose of NSA in terms of the rate of response to antihistamines (RR: 1.00; $p = 0.865$). Finally, the use of intensive NSA was associated with a higher risk of somnolence

than the use of standard NSA (RR: 3.28; 95% CI: 1.55–6.95; $p = 0.002$). **Conclusion:** We found that the use of intensive NSA could achieve greater reduction in the mean pruritus score, without increasing the risk of adverse events.

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Introduction

Chronic spontaneous urticaria (CSU) is a common dermatological allergy characterized by wheals, angioedema, and pruritus for >6 week [1]. CSU could last for a long time; the average disease duration ranges from 1 to 5 yr, and the prevalence rate is 0.5%–1% in the population [2]. CSU not only affects adults but also pediatric subjects [3]. Studies have shown that women are nearly twice as likely as men are to experience the progression of CSU [4, 5]. CSU plays a critical role in terms of impaired quality of life owing to swelling, itching, pain, and fatigue [6].

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Moreover, the patient's mental health could be affected, owing to unpredictable nature of CSU outbreaks [7].

Today, antihistamines are the standard treatment strategy for CSU, considering that they are inexpensive, effective, and available in various suitable doses. The Cochrane review identified 34 randomized controlled trials (RCTs) for 23 pairs; cetirizine used at a dose of 10 mg/day could effectively suppress urticaria, irrespective of whether it was used for the short term or intermediate term. Moreover, the treatment effect of desloratadine was limited when it was used for an intermediate duration at a dose of 5 mg/day or for a short duration a dose of 20 mg/day. Furthermore, the intermediate-duration use of levocetirizine at 5 mg/day and short-duration use at 20 mg/day were associated with an improved incidence of complete suppression [8]. However, all CSU patients do not respond to antihistamine at a standard dose, and whether an intensive dose of nonsedating antihistamines (NSAs) can provide superior effects in CSU patients remains controversial. Therefore, we conducted a systematic review and meta-analysis based on RCTs to compare the efficacy and safety of an intensive dose of NSA with those of a standard dose of NSA for CSU patients.

Materials and Methods

Literature Search and Selection Criteria

This systematic review and meta-analysis was performed as per the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines [9]. RCTs that investigated the treatment effects of intensive NSA versus standard NSA for CSU patients were eligible for inclusion in our meta-analysis, and the publication language and status were not restricted. We systematically searched the PubMed, Embase, and Cochrane Library databases for eligible studies published throughout January 2021, and used the following search terms: "(chronic spontaneous urticaria or chronic idiopathic urticaria [MeSH]); (bilastine or ebastine or azelastine or meclozine or olopatadine or rupatadine or astemizole or cinnarizine or cyclizine or flunarizine or meclizine or cetirizine or ketotifen or methapyrilene or mianserin or carbinoxamine or pheniramine or loratadine or desloratadine or fexofenadine or levocetirizine; and randomized controlled trial). Moreover, the website clinicaltrials.gov was reviewed to identify completed trials where the data were already upload but not published. Finally, the reference lists of relevant reviews and original articles were manually reviewed to identify any new eligible study that met the inclusion criteria.

Two authors independently conducted the literature search and study selection processes as per the standardized approach; conflicts between the authors were resolved via mutual discussion. The details of the inclusion criteria are listed here: (1) patients diagnosis: CSU, irrespective disease status; (2) intervention: any type of NSA at an intensive dose; (3) control: NSA at a standard dose; (4) outcome: mean pruritus score, response to antihistamines, and any potential adverse events; and (5) study design: RCTs.

Data Extraction and Quality Assessment

The following information from individual trials were independently abstracted by 2 authors: first author's name, publication year, country, sample size, age, proportion of male subjects, status of disease, definition of lack of response, intervention, control, treatment duration, and reported outcomes. Thereafter, these 2 authors assessed the quality of the individual trial using the Jadad scale that is based on randomization, blinding, allocation concealment, withdrawals and dropouts, and use of intention-to-treat analysis [10]. Inconsistencies regarding the abstracted data and quality assessment between the authors were settled by the corresponding author via referring to the full-text of the original article.

Statistical Analyses

The treatment effects of intensive NSA versus standard NSA for CSU patients were assigned as continuous and categorical data; then, weighted mean difference (WMD) and relative risk (RR) with 95% confidence interval (CI) were calculated for each trial before data pooling. All the pooled analyses used the random-effects model, considering the underlying heterogeneity of the included trials [11, 12]. The heterogeneity among the included trials was assessed using I^2 and Cochran Q test, and significant heterogeneity was defined as $I^2 > 50.0\%$ or $p < 0.10$ [13, 14]. Sensitivity analyses were performed to assess the stability of the pooled conclusion through sequential removal of one trial at a time [15]. Subgroup analyses for the mean pruritus score and response to antihistamines were conducted based on the intervention. Publication bias for the mean pruritus score and response to antihistamines were evaluated using the funnel plot as well as the Egger and Begg tests [16, 17]. All the reported p values are 2-sided, and $p < 0.05$ was considered as statistically significant. Statistical analyses in this study were performed using the software STATA (Version 10.0; StataCorp, College Station, TX, USA).

Results

Literature Search

The electronic searches yielded 472 articles; 257 studies were retained after removing the duplicate articles. A total of 129 studies were excluded because the study content did not match the inclusion criteria. The remaining 128 studies were retrieved for further full-text evaluations; of these, 119 studies were excluded because they were not RCTs ($n = 51$), did not have an appropriate control ($n = 43$), and did not report desirable outcomes ($n = 25$). A review of the reference lists did not yield new eligible RCTs, and 9 RCTs were selected for the final meta-analysis [18–26]. The details of the literature search and study selection process are shown in Figure 1.

Characteristics of the Included Studies

Table 1 summarizes the baseline characteristics of the included trials and involved patients. A total of 1,996 CSU patients from 9 RCTs were identified, and the sample size

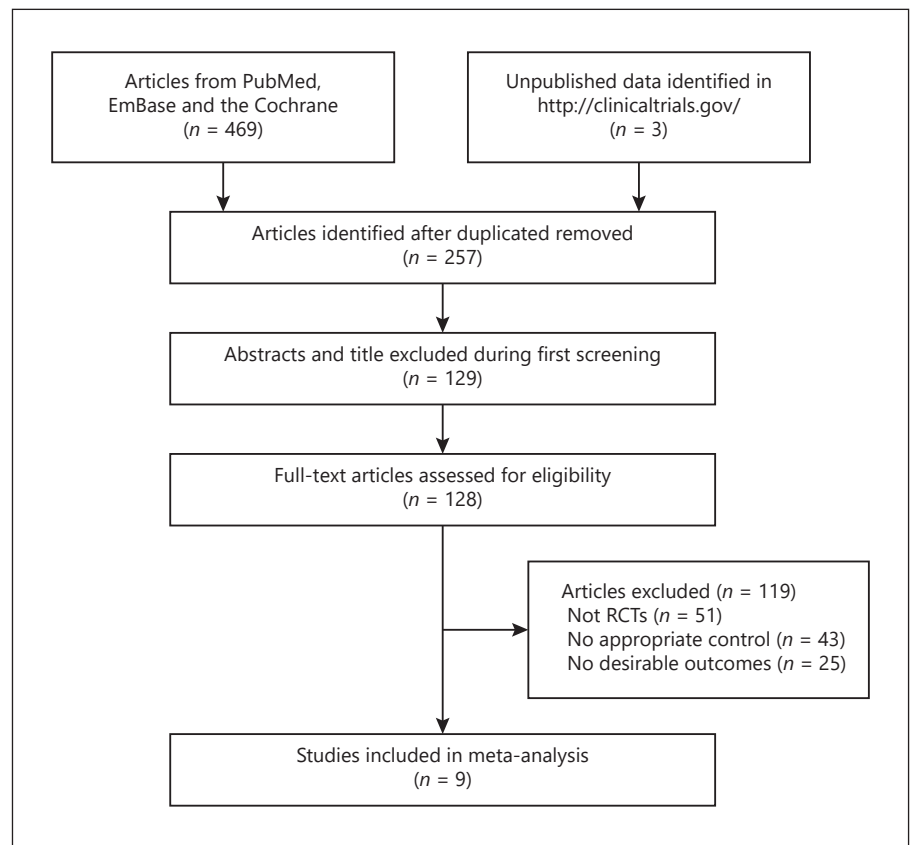


Fig. 1. Flowchart for literature search and study selection processes.

Table 1. The characteristics of identified studies and involved patients

Study	Country	Sample size	Age, years	Male, %	Disease status	Definition of lack of response	Intervention, mg	Control, mg	Treatment duration, weeks	Study quality
Finn et al. [18]	USA	381	>12.0	26.0	CSU	Discontinuation due to treatment failure	Fexofenadine 240 or 480	Fexofenadine 40 or 120	4	3
Nelson et al. [19]	USA	339	>12.0	30.0	CSU	Discontinuation due to treatment failure	Fexofenadine 240 or 480	Fexofenadine 40 or 120	4	3
Gimenez-Arnau et al. [21]	Argentina, Germany, Italy, Poland, Romania, and Spain	221	>12.0	23.0	CSU	Discontinuation due to treatment failure	Rupatadine 20	Rupatadine 10	4	4
Dubertret et al. [20]	France	277	>12.0	27.0	CSU	Discontinuation due to treatment failure	Rupatadine 20	Rupatadine 10	4	3
Wu et al. [22]	China	103	>16.0	52.0	CSU	NA	Azelastine 4	Azelastine 2	4	1
Weller et al. [23]	Germany	319	>18.0	23.0	CSU and non-responder CSU	Slightly better, equal, or worse	Antihistamine (up-dosing)	Antihistamine (standard-dosing)	NA	1
NCT00536380 2013 [26]	Germany	208	>18.0	NA	CSU	NA	Desloratadine 20	Desloratadine 5	4	4
Abajian et al. [24]	Germany and Spain	45	>19.0	25.0	CSU	NA	Rupatadine 40	Rupatadine 20	1	3
Sarkar et al. [25]	India	103	> 18.0	38.0	CSU and non-responder CSU	Discontinuation due to treatment failure	Levocetirizine 10	Levocetirizine 5	4	4

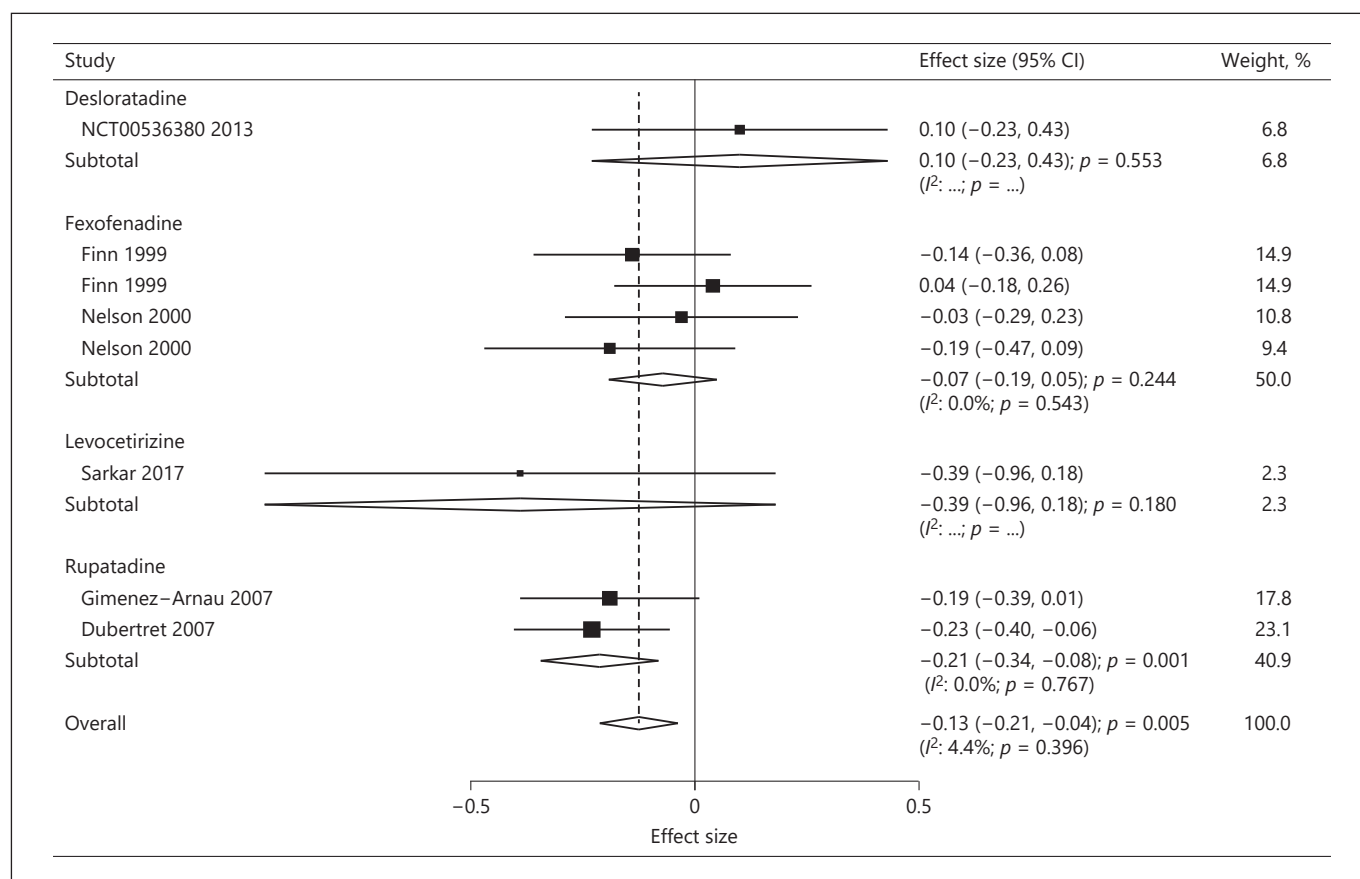


Fig. 2. Effect of intensive NSAs versus standard NSA on the change in the mean pruritus score.

in each trial ranged from 45 to 381. Seven trials included patients with simple CSU, and the remaining 2 trials included patients with both CSU and nonresponder CSU. The age of the included patients in all the trials was >12 yr. Seven trials were performed in Europe and America, and the remaining 2 were performed in Asia. The study quality was assessed using the Jadad scale; 3 trials had a score of 4, 4 had a score of 3, and the remaining 2 had a score of 1.

Mean Pruritus Score

Six trials containing 8 cohorts reported the effect of intensive NSA on the reduction in the mean pruritus score. We noted that intensive NSA was associated with a greater reduction in the mean pruritus score than standard NAS (WMD: -0.13; 95% CI: -0.21 to -0.04; $p = 0.005$; Fig. 2), and nonsignificant heterogeneity was observed across the included trials ($I^2 = 4.4\%$; $p = 0.396$). Sensitivity analysis found that the pooled conclusion was changed after removing the trial by Dubertret et al. [20]

(Fig. 3a). Subgroup analysis showed the beneficial effect of intensive NSA, mainly with the use of 20 mg rupatadine than with 10 mg rupatadine (Fig. 2).

Response to Antihistamines

Seven trials have reported the effect of intensive NSA on the rate of response to antihistamines. There was no significant difference between intensive NSA and standard NSA in terms of the response to antihistamines (RR: 1.00; 95% CI: 0.96–1.05; $p = 0.865$; Fig. 4), and no evidence of heterogeneity was observed ($I^2 = 0.0\%$; $p = 0.503$). The pooled conclusion was robust and not altered by sequential exclusion of individual trials (Fig. 3b). Subgroup analyses did not show any significant difference between intensive NSA and standard NSA in terms of the response to antihistamines (Fig. 4).

Adverse Events

The pooled risk of adverse events between intensive NSA and standard NSA is shown in Table 2. The use of

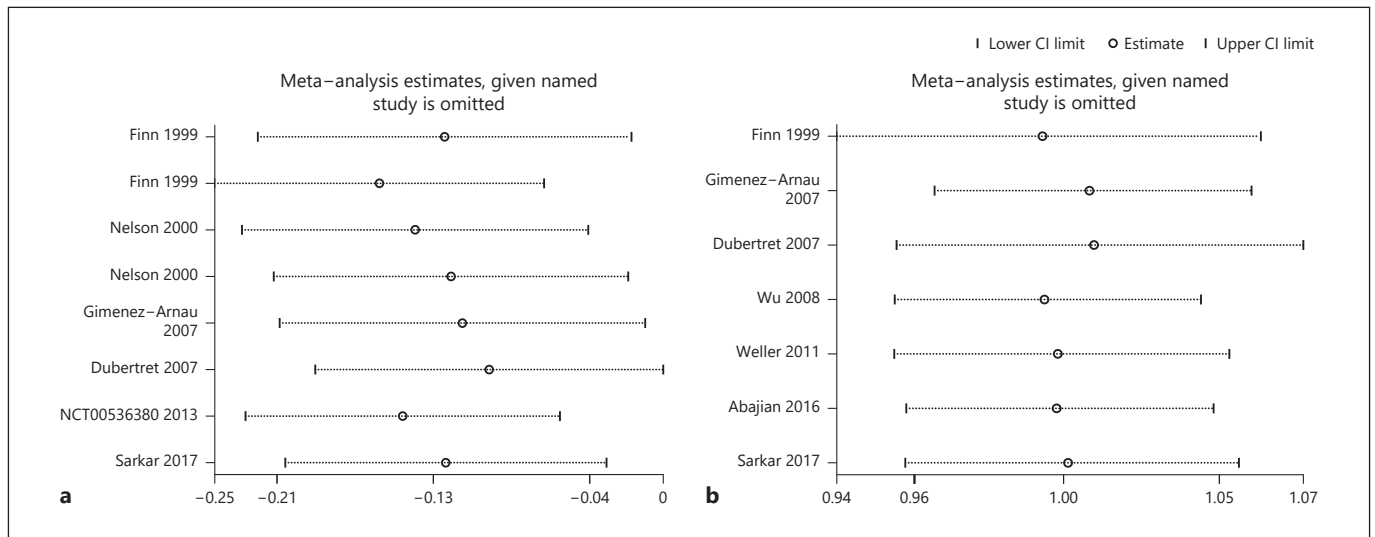


Fig. 3. Sensitivity analyses for the mean pruritus score and response to the antihistamine rate. **a** Mean pruritus score. **b** Response to antihistamines.

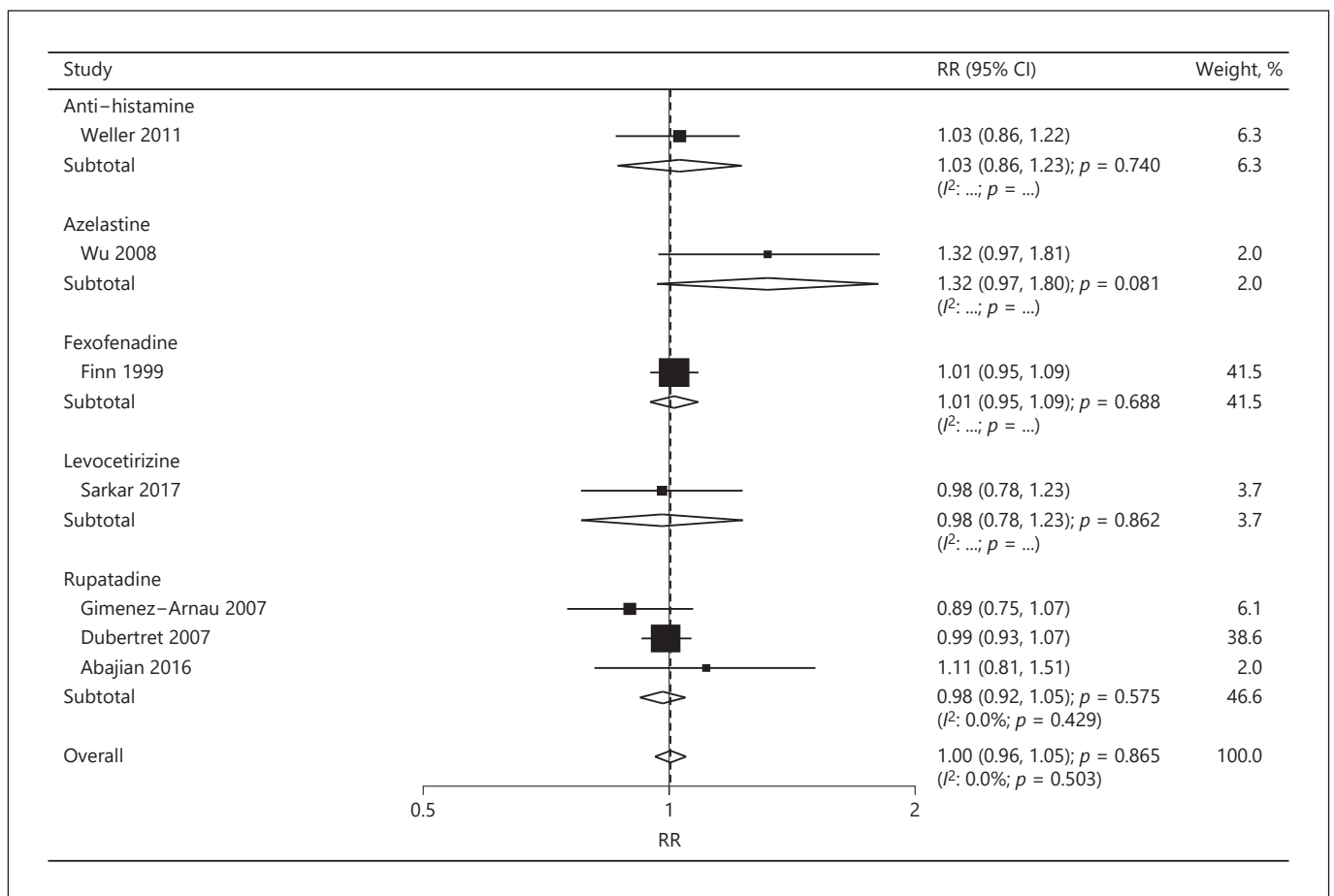


Fig. 4. Effect of intensive NSAs versus standard NSA on the rate of response to antihistamines.

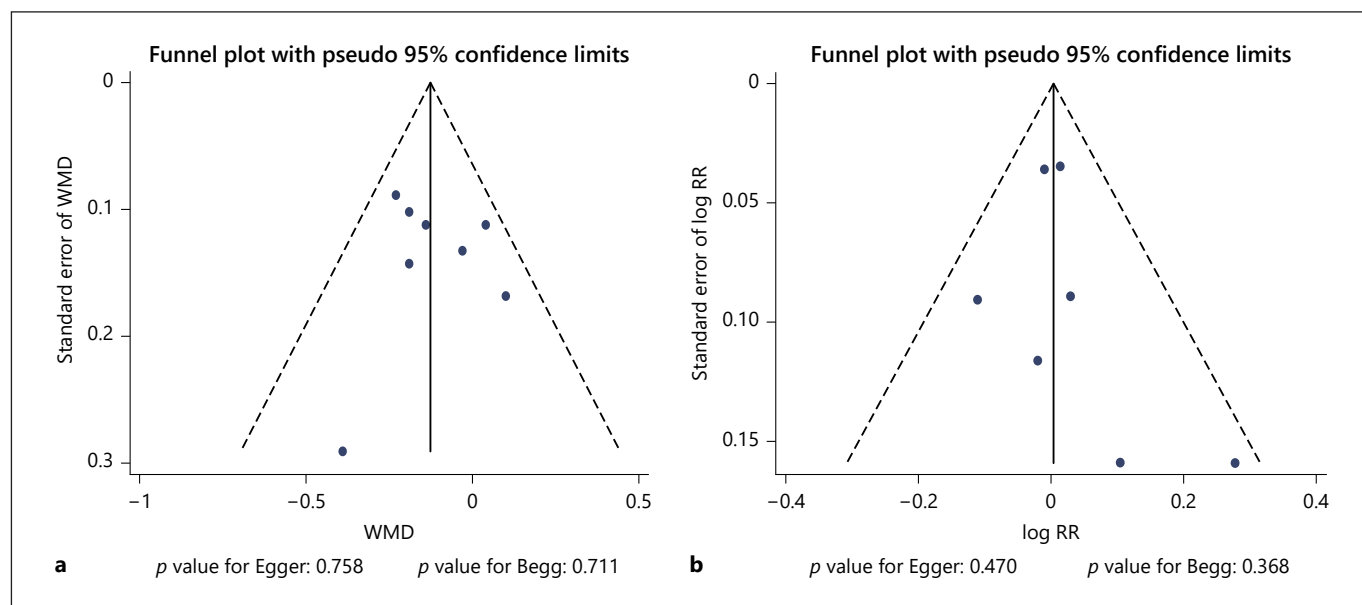


Fig. 5. Funnel plots for the mean pruritus score and the rate of response to antihistamines. **a** Mean pruritus score. **b** Response to antihistamines.

Table 2. The summary results for adverse events

Outcomes	Studies, <i>n</i>	RR and 95% CI	<i>p</i> value	<i>I</i> ² , %	<i>p</i> value for <i>Q</i>
Headache	6	0.99 (0.77–1.28)	0.957	0.0	0.892
Dizziness	2	0.98 (0.26–3.72)	0.980	20.1	0.286
Upper respiratory infection	2	1.56 (0.91–2.66)	0.106	11.6	0.335
Pharyngitis	2	0.97 (0.44–2.17)	0.947	25.3	0.260
Rhinitis	2	0.76 (0.26–2.22)	0.621	26.9	0.250
Nausea	2	1.20 (0.57–2.54)	0.636	13.5	0.325
Dyspepsia	2	0.80 (0.36–1.77)	0.580	11.4	0.336
Diarrhea	2	0.74 (0.28–1.96)	0.541	0.0	0.595
Pain	2	0.70 (0.32–1.56)	0.388	0.0	0.782
Somnolence	4	3.28 (1.55–6.95)	0.002	0.0	0.971
Tiredness	2	2.03 (0.39–10.66)	0.405	0.0	0.970

intensive NSA was associated with an increased risk of somnolence as compared to that with standard NSA (RR: 3.28; 95% CI: 1.55–6.95; $p = 0.002$). However, there were no significant differences in the risks of headache, dizziness, upper respiratory infection, pharyngitis, rhinitis, nausea, dyspepsia, diarrhea, pain, and tiredness between intensive NSA versus standard NSA therapy.

Publication Bias

Review the funnel plots could not rule out the publication bias for mean pruritus score and response to antihistamines (Fig. 5). There was no significant publication bias

for the mean pruritus score (p value for Egger: 0.758; p value for Begg: 0.711) and response to antihistamines (p value for Egger: 0.470; p value for Begg: 0.368) using the Egger and Begg tests.

Discussion

The current systematic review and meta-analysis included RCTs that compared the treatment effects of intensive NSA and standard NSA on the following outcomes: mean pruritus score, response to antihistamines, and any

potential adverse events in CSU patients. A total of 1,996 CSU patients from 9 RCTs were included, and there was considerable variation in the patient characteristics. We found that intensive NSA was associated with a greater reduction in the mean pruritus score, while it exerted no significant effect on the response to antihistamines. Moreover, the use of intensive NSA could induce excess risk of somnolence. Finally, the beneficial effect of intensive NSA on the mean pruritus score was mainly owing to the use of 20 mg rupatadine than to the use of 10 mg rupatadine.

A previous systematic review and meta-analysis identified 15 articles and found no significant differences in the response to antihistamines and the number of wheals between patients who were given high-dose and those who were administered standard-dose NSA therapy. Moreover, intensive NSA was significantly associated with an improved control of pruritus [27]. However, this study contained both RCTs and observational studies, and the pooled conclusions had a low level of evidence. Moreover, subgroup analyses were not performed, and the risk of potential adverse events was not calculated. Therefore, the current systematic review and meta-analysis was conducted based on RCTs to systematically assess the efficacy and safety of intensive NSA versus those of standard NSA for CSU patients.

In the present study, we found that the use of intensive NSA was associated with greater reduction in the mean pruritus score than standard NSA. Moreover, the beneficial effect of intensive NSA on the mean pruritus score was mainly observed with the use of 20 mg rupatadine than that with 10 mg rupatadine. Although the use of mostly intensive NSA provides a similar trend effect on the mean pruritus score, the use of desloratadine at 20 mg did not provide a better effect on control of pruritus than desloratadine at 5 mg. This result could explain by the disease characteristics, and only 1 RCT reported this result. Desloratadine was able to diminish the histamine-induced activation of endothelial cells and inhibits the secretion of endothelial cytokines. The dose-dependent administration could inhibit both IgE- and non-IgE-induced leukocyte histamine release from basophils [28]. Moreover, we noted that in comparison to 10 mg rupatadine, 20 mg rupatadine was associated with greater improvement in the mean pruritus score. The potential reason for this could be that rupatadine shows both antihistamine- and antiplatelet-activating factor effects, owing to the interaction of rupatadine with specific receptors [29].

There were no significant differences between intensive NSA and standard NSA therapy in terms of the response to antihistamines. Moreover, subgroup analysis showed no

significant differences between the groups in terms of the rate of response to antihistamines with any specific drug. However, an interesting result was that the use of 4 mg azelastine might be associated with an increased response to antihistamines than the use of 2 mg azelastine. This result was not robust, and the 95% CI was broad because only 1 trial was included in this subgroup. Finally, we noted that the use of intensive NSA significantly increased the risk of somnolence as compared to the use of standard NSA. This result could be explained by the significant efficacy of rupatadine, represented by a greater reduction in general discomfort and improvement in the quality of life.

There are certain limitations of this study. First, the details regarding the disease status were not addressed; this might affect the prognosis of CSU. Second, the background therapies for CSU were not reported, and these could have influenced the treatment effects of intensive NSA. Third, there were smaller number of trials reported specific drug on the prognosis of CSU, and the pooled conclusion might variable. Finally, the inherent limitations for meta-analysis based on pooled data, including varied study quality, inevitable publication bias, and the detailed analyses, were restricted.

The present study showed that intensive NSA is associated with a greater reduction in the mean pruritus score than standard NSA in CSU patients, especially for 20 mg rupatadine than with 10 mg rupatadine. However, as compared to standard NSA, intensive NSA had no significant effect on the rate of response to antihistamines. Moreover, the risk of somnolence was significantly increased with the use of intensive NSA. Further large-scale RCTs are needed to assess the treatment effects of NSA in patients with specific characteristics.

Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on published literature.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

P.M.Z. and L.X.F. designed the study; S.H.Z., L.L., and H.C. collected the data; H.C. and S.H.Z. analyzed the data; L.X.F. and L.L. contributed to literature search; and P.M.Z. prepared the manuscript. All the authors read and approved the final manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this published article.

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