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Systematic reviews of pharmacological and nonpharmacological treatments for patients with chronic urticaria

An umbrella systematic review

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Abstract

A wide range of pharmacological and nonpharmacological interventions for chronic urticaria (CU) have been evaluated in systematic reviews (SRs). We conducted an umbrella review of SRs of the effectiveness and safety of pharmacological and nonpharmacological interventions for CU, which allow the findings of separate reviews to be compared and contrasted and thereby provide decision makers in healthcare with the evidence they need.

We included SRs evaluating pharmacological and nonpharmacological interventions for CU. Comprehensive searches were conducted in 7 bibliographic databases, relevant journals up to July 2018. Two reviewers independently assessed the studies' relevance and quality. The assessment of multiple systematic reviews tool and grading of recommendations assessment, development and evaluation method was used to assess the methodological quality of the SRs and classify the quality of the outcomes.

In total, 41 SRs were included. Thirty-seven reviews performed quantitative research syntheses, and 4 reviews performed qualitative research syntheses. The majority of SRs evaluated interventions based on combination therapies, antihistamines, traditional Chinese medicines, autohemotherapy, omalizumab, acupuncture, cyclosporine, and leukotriene receptor antagonist. Positive intervention outcomes were reported in the majority (75.32%) of the reviews. However, the methodological quality and evidence quality of the reviews were generally poor.

There is some evidence to support a variety of interventions for CU. However, there was much heterogeneity in evidence quality among SRs. Many of the SRs had methodological weaknesses that make them vulnerable to bias. Moreover, there remained little information on the relative effectiveness of one intervention compared with another. Therefore, further SRs that adherence to strict scientific methods are necessary, and primary studies make comparisons between the different treatment options directly.

Abbreviations: AEs = adverse events, AMSTAR = the assessment of multiple systematic reviews tool, CIU = chronic inducible urticaria, CsA = cyclosporine A, CSU = chronic spontaneous urticaria, CU = chronic urticaria, EAACI/GA2LEN/EDF/WAO = European Academy of Allergology and Clinical Immunology, the Global Allergy and Asthma European Network, World Allergy Organization, GRADE = the grading of recommendations assessment, development, and evaluation, LTRA = leukotriene receptor antagonist, RCTs = randomized controlled trials, SRs = systematic reviews.

Keywords: chronic urticaria, pharmacological and nonpharmacological treatments, systematic reviews, umbrella

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1. Introduction

Urticaria is a condition characterized by the development of wheals (hives), angioedema, or both.[1] It is a mast-cell-driven disease. Histamine and other mediators, such as platelet-activating factor and cytokines released from activated mast cells, result in sensory nerve activation, vasodilatation, and plasma extravasation as well as cell recruitment to urticarial lesions.[1] Chronic urticaria (CU) is defined when an individual presents with transient wheals lasting more than 6 weeks in duration almost daily.[2,3] CU is divided into 2 types: chronic spontaneous urticaria (CSU) and chronic inducible urticaria (CIU).[1] CSU refers to the spontaneous appearance of wheals, angioedema or both for >6 weeks due to known or unknown causes. The guidelines recommend for only limited extended diagnostic measures in CSU based on patient history. The signs and symptoms of CIU are triggered by external specific factors, such as a mechanical stimulus (friction, pressure, and vibration), thermal stimulus (cold, heat), aquagenic stimulus (water), and electromagnetic stimulus (solar radiation).[4] Therefore, the most important diagnostic step of CU includes a thorough history, physical examination, and a ruling out of the severe systemic disease. CSU can occur at any age. Recent studies have shown that the proportion of women in men is 2:1, and the prevalence rate is between 0.5% and 1%.[5] Of the inducible urticaria, data showed that the proportion of physical urticaria among patients with any CU range from 7% to 44%,[6] yet up to 36.3% of CSU patients have been reported to concomitantly react to physical trigger tests.[7] CU can induce misery, embarrassment, and lead to severe quality of life impairments,[8–11] and its destructiveness may be comparable to severe coronary artery disease.[12] There are high direct and indirect health care costs for treating CU due to the large socioeconomic implications of a 20% to 30% reduction in performance.[13] Evidence suggested that patients with CSU can suffer from a considerable loss of productivity at work, school, or daily activities.[14–16]

The European Academy of Allergology and Clinical Immunology, the Global Allergy and Asthma European Network, World Allergy Organization (EAACI/GA2LEN/EDF/WAO) guidelines recommend to use the Average Urticaria Activity Score for 7 days to assess severity and the validated Chronic Urticaria Quality of Life Questionnaire and the Angioedema Quality of Life Questionnaire instruments to assess quality of life impairment and monitor disease activity.[1] Besides, the current treatment guidelines[1,17] and consensus statement[3,18] recommend a stepwise approach for the complete control of CU symptoms. The EAACI/GA2LEN/EDF/WAO guidelines recommend the use of second-generation H1-antihistamines as the first line of treatment. If there is no response at a regular dose, the dose will be increased up to a 4-fold standard or licensed dose. If the response is still no improvement, the guidelines recommend the use of omalizumab and cyclosporine A (CsA) as the third-line treatment. However, a narrative medicine project in Italy showed that the medicine therapeutic pathways were described as unsatisfactory in 83% of included cases.[19] All H1-antihistamine treatment options containing the use of higher-than-standard doses, do not have an approved label for the treatment of CU, and many patients do not respond adequately to most of these drugs.[20] Furthermore, the guidelines do not provide guidance on the choice, dose, and duration of alternative treatment options in patients who still remain symptomatic despite the use of H1-antihistamines. In addition, although the omalizumab and CsA proved to be effective,[21–23] the prices are expensive and can impose a serious economic burden on patients. Widespread use will depend on legal and economic factors.[24] Therefore, an increasing number of patients have sought nonpharmacological treatments. Recently, nonpharmacological treatments for CU, such as acupuncture and autohemotherapy, have been promisingly developed. Several randomized controlled trials (RCTs) and systematic reviews (SRs) have confirmed the effectiveness of certain nonpharmacological treatments.[25,26]

In the past decade, many SRs had been published on a variety of CU interventions and with varying recommendations of treatment effectiveness. However, according to a structured methodological approach, there is still a need to evaluate whether the SRs of pharmacological and nonpharmacological interventions for CU had been conducted. It ensures the control of systematic errors in the review process, allowing greater confidence in the results and conclusions. The objective of the present study is to present an umbrella review of the clinical findings of these SRs about pharmacological and nonpharmacological interventions for CU and to identify some potential predictive factors that are associated with the quality of SRs in this area of inquiry.

2. Materials and methods

2.1. Search strategy

We searched the electronic databases PubMed, Ovid Medline, Web of Science, Chinese Biological Medicine Database, Chinese National Knowledge Infrastructure, China Science Journals Full Text Database, and Wang Fang Data Database from inception to July 2018. The search strategy consisted of keywords and medical subject headings for "urticaria," "systematic review," and synonymous words. In addition, manual searches of the reference lists and searches of personal collections were conducted to identify additional citations. A detailed search strategy for PubMed, which was adapted for all other electronic database searches, is provided in Appendix 1, http://links.lww.com/MD/C992.

2.2. Study selection

All interventional SRs that identified the effectiveness and safety of any treatments for CU were eligible for inclusion. Patients had no age, gender, nationality, or regional restrictions. Diagnostic SRs, comments, incomplete articles, proceedings, and replies were excluded. Titles and abstracts of the remaining articles were screened by 2 independent reviewers (MX and LZ) for their eligibility on the basis of inclusion criteria. Full texts were then obtained and reviewed for eligibility by the 2 reviewers (MX and LZ). Disagreements were resolved by discussion and consensus.

2.3. Data abstraction

Descriptive data were extracted by 1 reviewer (YS) using a standard form and verified by a second reviewer (XX). Data collection included published country, age, study type, number of trials included, patient demographics and clinical data, methods for quality assessment of primary studies, outcomes, and main conclusions. Data from reviews were quoted in the form of the standardized mean difference, weighted mean difference, odds ratio or relative risk, depending on what the review authors

reported. Whenever possible, meta-analysis results were also reported with 95% confidence intervals.

2.4. Quality assessment

The methodological quality of the SRs was assessed independently by 2 reviewers (SZ and QZ) according to the Assessment of Multiple Systematic Reviews (AMSTAR) tool. As a methodological quality assessment tool for SRs, AMSTAR has a good face and content validity for measuring the methodological quality of SRs.[27,28] The tool consists of 11 items. If the item explanation was basically satisfied, it was evaluated as "Y" and received a score of 1. If the item explanation was not satisfied, it was evaluated as "N;" if the item explanation could not be answered, it was evaluated as "C;" and if the item explanation could not be applied to an SR, it was evaluated as "NA;" all 3 of these situations received a score of 0. The AMSTAR scale ranged from 0 to 11, where a score of 0 to 4 indicated extensive flaws, a score of 5 to 8 indicated moderate quality, and a score of 9 to 11 indicated high quality.

The quality of SRs was assessed by using the grading of recommendations assessment, development, and evaluation (GRADE).[29–31] The GRADE pro 3.2 software contained 5 downgrading factors (risk of bias, inconsistency, indirectness, imprecision, and publication bias) and 3 upgrading factors (a large magnitude of the effect, the influence of all plausible residual confounding, and the dose-response gradient). Two reviewers evaluated each outcome of the included study. Disagreements were resolved by consensus or by consultation with a third investigator (HZ).

3. Results

A total of 25,232 articles were detected in the initial search. Upon further examination of titles and abstracts, 181 articles were retrieved; 102 duplicate documents were excluded by using NoteExpress software Version 2.6.1(Aegean Sea software company Beijing, China) and manual searches (YS). Then, full texts were screened according to inclusion and exclusion criteria, and 38 documents were excluded. Ultimately, 41 SRs were included in the present study. Figure 1 presents the flow of studies through the selection process.

3.1. Descriptive characteristics of SRs

Forty-one SRs were published between 2009 and 2018 and involved a total of 8 countries. A total of 23 outcome indicators were reported in the 41 SRs, of which 37 (90.24%) reviews

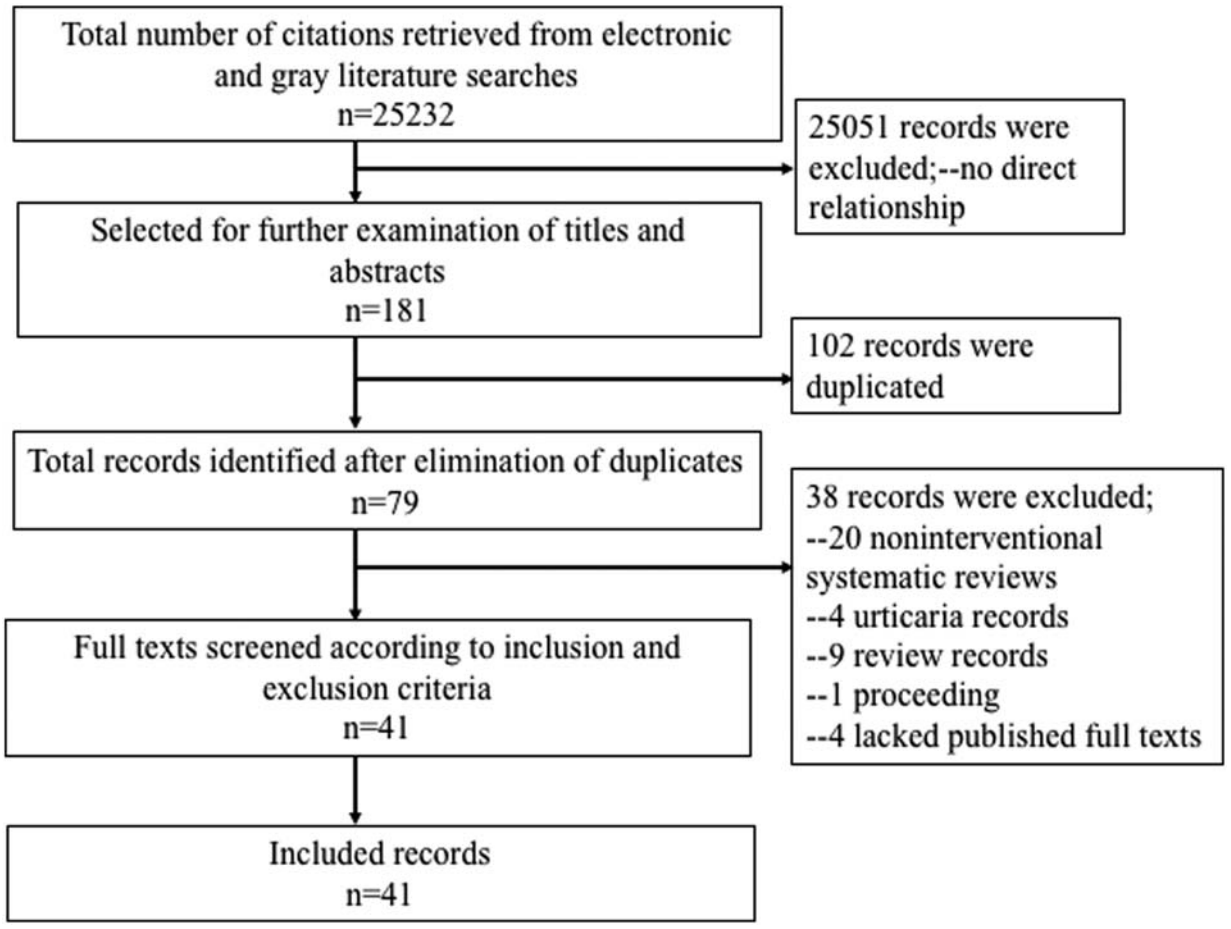

Figure 1. Quorum flow diagram.

conducted meta-analyses for 14 outcome indicators. Among the 41 SRs, 33 (80.49%) reviews were pharmacological interventions, and 8 (19.51%) reviews were nonpharmacological interventions that contained 5 autohemotherapy and 3 acupuncture treatments. Of the 33 pharmacological SRs, 13 reviews reported the effectiveness and safety of traditional Chinese medicine and traditional Chinese medicine extracts alone or in combination with western medicine in the treatment of CU. Ten reviews reported the effectiveness and safety of antihistamines for CU. Five reviews reported the effectiveness and safety of omalizumab for CU. The remaining 5 reviews reported the effectiveness and safety of BCG polysaccharide and nucleic acid injection, leukotriene receptor antagonist (LTRA), Allergen-specific immunotherapy, CsA, and Narrow Bound Ultra Violet B Light for CU. The general characteristics of these SRs are summarized in Table 1 and Appendix 2, http://links.lww.com/MD/C992.

3.2. Methodological quality

The AMSTAR scale was used to assess the methodological quality of the included SRs. Overall, the methodological quality of these reviews was moderate. Appendix 3, http://links.lww.com/MD/C992 shows the review ratings of the individual quality components. The median AMSTAR score was 6.20 on a scale of 0 to 11. Five reviews were of low quality, and 35 reviews were of moderate quality. One review was of high quality.

Table 1

Descriptive characteristics of SRs of interventions for CU included in the present overview (n = 41).

Item	Amount
Publication type	
Journal article	37
Dissertation	4
Country of corresponding author	
China	32
Germany	2
United Kingdom	2
Netherlands	1
United States	1
Sri Lanka	1
Thailand	1
Spain	1
Funding reported	14
Type of populations studied	
Any age	27
Age ≧8 yr old	3
Age ≧12 yr old	9
Age ≧18 yr old	2
Type of diagnosis studied	
CSU	8
CIU	5
Included 2 diagnoses	28
Type of primary study designs included in the reviews	
RCT/quasi-RCT/CCT	32
Observational study	1
Included 2 types	8

CIU = chronic inducible urticaria, CSU = chronic spontaneous urticaria, CCT = controlled clinical trial, RCT = randomized controlled trial.

3.3. Quality of the review evidence

Among the 41 reviews, 37 reviews with quantitative analyses were subjected to GRADE analysis. Seventeen reviews were rated as low quality, 14 reviews were rated as very low quality, 5 reviews were rated as moderate quality, and 1 review was rated as high quality. Overall, the quality of these reviews evidence was poor. Appendix 4, http://links.lww.com/MD/C992 shows the review ratings for individual quality components.

3.4. Evidence from quantitative research syntheses

Thirty-seven of the 41 reviews performed quantitative research syntheses. In the 37 reviews, the most studied outcomes were total efficiency, clinical efficacy rate, urticaria activity score, weekly itch score, weekly wheal score, response rate, curing rate, adverse events (AEs) and recurrence rate. For these 9 outcome indicators, the 77 meta-analyses and subgroup analyses synthesized data from 749 primary RCTs, quasi-RCTs, and controlled clinical trials. The main types of intervention included combination intervention, antihistamines, traditional Chinese medicines, autohemotherapy, omalizumab, acupuncture, and other interventions. The comparator was an active control (eg, different variant of the same intervention, a different drug or a different type of therapy) in 34 meta-analyses, an inactive control (eg, placebo, no treatment, standard care or a waiting list control) in 26 meta-analyses and both active and inactive controls in 17 meta-analyses. The detailed information of quantitative research syntheses is summarized in Table 2, which shows combined data from meta-analyses according to 9 different outcome indicators of interest.

3.5. Between-study heterogeneity

Of the 77 meta-analyses, statistically significant heterogeneity ($P \leq .10$, $I^2 > 50\%$) was observed in 14 (18.18%) meta-analyses (Table 2). Ten meta-analyses (12.99%) had large heterogeneity ($I^2 > 50\%$), and 4 (5.19%) had very large heterogeneity ($I^2 > 75\%$). Additionally, moderate heterogeneity was found in 10 (12.99%) meta-analyses, whereas 53 (68.83%) meta-analyses had low heterogeneity.

3.6. Treatment with moderate- and high-quality evidence of effectiveness and safety

Among 749 primary studies included in 77 meta-analyses, 58 (75.32%) had nominally significantly positive results. According to the GRADE analysis, of the 77 meta-analyses, moderate-quality evidence was observed in 11 (14.29%) meta-analyses, and high-quality evidence was observed in 5 (6.49%) meta-analyses. The detailed information of moderate- and high-quality evidence is summarized in Table 3.

3.7. Evidence from qualitative research syntheses

Four of the 41 reviews performed qualitative research syntheses. In these 4 reviews, the types of intervention were mainly omalizumab, LTRAs and cyclosporine, desloratadine plus dapsone or dipyridamole, and montelukast. Maurer et al[32] showed that the vast majority of results indicated a beneficial role for omalizumab in each case of CIU, and instances of AEs were low. Carrillo et al[33] compared omalizumab at different doses with placebo. The results showed that 300 mg of omalizumab

Table 2

Summary of evidence from quantitative research syntheses.

Item	Outcomes									
	Total efficiency n (%)	Clinical efficacy rate n (%)	Urticaria activity score n (%)	Weekly itch score n (%)	Weekly wheal score n (%)	Rate of response n (%)	Curing rate outcomes n (%)	AEs n (%)	Recurrence rate n (%)	All outcomes n (%)
Number of primary RCTs/CCTs	252 (33.64)	67 (8.95)	11 (1.47)	11 (1.47)	11 (1.47)	36 (4.81)	81 (10.81)	204 (27.24)	76 (10.15)	749 (100)
Number of meta-analyses and subgroup analyses	19 (24.68)	8 (10.39)	3 (3.90)	2 (2.60)	2 (2.60)	5 (6.49)	6 (7.79)	20 (25.97)	12 (15.58)	77 (100)
Interventional types										
Antihistamines	4 (21.05)	1 (12.5)	0 (0)	0 (0)	0 (0)	2 (40)	2 (33.33)	7 (35)	0 (0)	16 (20.78)
Omalizumab	0 (0)	0 (0)	2 (66.67)	2 (100)	2 (100)	2 (40)	0 (0)	3 (15)	0 (0)	11 (14.29)
Traditional Chinese medicines	3 (15.79)	4 (50)	0 (0)	0 (0)	0 (0)	0 (0)	2 (33.33)	1 (5)	2 (16.67)	12 (15.58)
Autohemotherapy	2 (10.52)	3 (3.75)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (10)	4 (33.33)	11 (14.29)
Acupuncture	2 (10.52)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (16.67)	0 (0)	1 (8.33)	4 (5.19)
Mixed intervention	7 (36.84)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (16.67)	6 (30)	4 (33.33)	18 (23.38)
Other	1 (5.26)	0 (0)	1 (33.33)	0 (0)	0 (0)	1 (20)	0 (0)	1 (5)	1 (8.33)	5 (6.49)
Comparator										
Active	8 (42.11)	7 (87.5)	0 (0)	0 (0)	0 (0)	1 (20)	4 (66.67)	9 (45)	5 (41.67)	34 (44.16)
Active and inactive	3 (15.79)	1 (12.5)	1 (33.33)	2 (100)	2 (100)	2 (40)	1 (16.67)	2 (10)	3 (25)	17 (22.08)
Inactive	8 (42.11)	0 (0)	2 (66.67)	0 (0)	0 (0)	2 (40)	1 (16.67)	9 (45)	4 (33.33)	26 (33.76)
Heterogeneity										
<25% (low)	12 (63.16)	4 (50)	3 (100)	1 (50)	1 (50)	3 (60)	4 (60)	17 (85)	8 (66.67)	53 (68.83)
25%–49% (moderate)	1 (5.26)	2 (25)	0 (0)	0 (0)	1 (50)	1 (20)	2 (40)	1 (5)	2 (16.67)	10 (12.99)
50%–74% (large)	4 (21.05)	2 (25)	0 (0)	1 (50)	0 (0)	0 (0)	0 (0)	1 (5)	2 (16.67)	10 (12.99)
>75% (very large)	2 (10.53)	0 (0)	0 (0)	0 (0)	0 (0)	1 (20)	0 (0)	1 (5)	0 (0)	4 (5.19)
Result										
Beneficial (effective)	19 (100)	8 (100)	3 (100)	2 (100)	2 (100)	3 (60)	6 (100)	3 (15)	12 (100)	58 (75.32)
No difference	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (40)	0 (0)	15 (75)	0 (0)	17 (22.08)
Detrimental or less effective	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (10)	0 (0)	2 (2.60)
Quality of the review evidence										
Very low	4 (21.05)	6 (75)	0 (0)	0 (0)	0 (0)	1 (20)	3 (50)	4 (20)	5 (41.67)	23 (29.87)
Low	12 (63.16)	2 (25)	2 (60)	1 (50)	1 (50)	1 (20)	3 (50)	10 (50)	6 (50)	38 (49.35)
Moderate	3 (15.79)	0 (0)	0 (0)	1 (50)	1 (50)	1 (20)	0 (0)	4 (20)	1 (8.33)	11 (14.29)
High	0 (0)	0 (0)	1 (40)	0 (0)	0 (0)	2 (40)	0 (0)	2 (10)	0 (0)	5 (6.49)

AEs = adverse events, CCTs = controlled clinical trials, RCTs = randomized controlled trials.

was effective in treating CIU refractory to H1 antihistamines. However, it was associated with a higher frequency of AEs, such as headache and upper respiratory infection. Silva et al[34] indicated that the use of LTRAs as monotherapy cannot be recommended. LTRAs were an effective add-on therapy to antihistamines, and their use in patients responding poorly to antihistamines is justifiable. Mitchell et al[35] showed that compared with placebo, cyclosporine, desloratadine plus dapsone or dipyridamole, montelukast reduced urticaria activity scores, wheals, and pruritus. The detailed information from qualitative research syntheses is summarized in Table 4.

4. Discussion

Umbrella reviews can supply a ready means for decision makers in healthcare to gain a clear understanding of a broad topic area, requiring the investigation of a range of interventions for a particular problem,[36] and when evidence is needed rapidly to notify a new policy or procedure.[37–39] It is obvious that existing research syntheses are available. In this umbrella review, we analyzed the evidence provided at the SR level regarding the effectiveness of pharmacological and nonpharmacological treatments for patients with CU. Currently, many SRs have been published on a variety of CU interventions and with varying recommendations of treatment effectiveness. This trend may reflect the need to summarize and critically appraise the evidence from this body of evidence to inform clinical practice and healthcare policy decisions regarding treatment for CU. The findings of the present study highlight the content and quality of SRs related to the pharmacological and nonpharmacological treatment of CU and identify important reporting and methodological issues that should be taken into consideration in CU reviews.

In the included 41 reviews, we found much heterogeneity in methodological quality among SRs of pharmacological and nonpharmacological interventions for CU that have been examined using the AMSTAR scale. Although a few reviews scored highly on the AMSTAR, the vast majority had substantial deficiencies. In particular, the reviews often lacked a previous research protocol, a comprehensive search strategy and an assessment of the quality of the primary studies characteristics that make these reviews especially prone to bias and limit the validity of their conclusions. In addition, a large proportion of the reviewers also did not assess publication bias or explain related conflicts of interest and sources of potential funding. These deficiencies may introduce the risk of biased results. Overall, the quality of reporting among these SRs was discouraging according to the Quality of Reporting of Meta-Analysis statement and Cochrane guidelines.[40,41] Future researchers will need to give careful attention to the design and quality of each primary

Table 3

Summary of treatment from moderate- and high-quality evidence of effectiveness and safety.

Outcomes	Included study	Total number of participants	Type of intervention	Control design	Estimate of heterogeneity	Summary effect size (95% CI)	*P*-value	AMSTAR score	Comments
High quality evidence of effectiveness									
Urticaria activity score	Urgert 2015	749	Omalizumab 300mg	Placebo	$I^2 = 0\%$	−11.58 [−13.39, −9.77]	$P < .00001$	7	Beneficial
Rate of response	Zhao 2016	1627	Omalizumab	Placebo	$I^2 = 26\%$	4.55 [3.33, 6.23]	$P < .00001$	8	Beneficial
	Urgert 2015	749	Omalizumab 300mg	Placebo	$I^2 = 0\%$	6.44 [3.93, 10.43]	$P < .00001$	7	Beneficial
AEs	Zhao 2016	1634	Omalizumab	Placebo	$I^2 = 0\%$	1.07 [1.00, 1.14]	$P = .05$	7	No difference
	Urgert 2015	749	Omalizumab 300mg	Placebo	$I^2 = 0\%$	1.05 [0.96, 1.16]	$P = .30$	7	No difference
Moderate quality evidence of effectiveness									
Total efficiency	Du 2016	1216	Traditional Chinese medicine + antihistamines	Antihistamines	$I^2 = 0\%$	1.21 [1.15, 1.28]	$P < .00001$	7	Beneficial
	You 2015	1188	Mizolastine + H2 recepter antagonists	Mizolastine	$I^2 = 0\%$	1.23 [1.16, 1.31]	$P < .001$	7	Beneficial
	Xu 2011	644	Ebastine + other medicine 28/30 day	Ebastine 28/30 day	$I^2 = 0\%$	0.28 [0.18, 0.43]	$P < .00001$	7	Beneficial
Weekly itch score	Zhao 2016	1629	Omalizumab	Placebo	$I^2 = 63\%$	−4.10 [−5.18, −3.03]	$P < .00001$	8	Beneficial
Weekly wheal score	Zhao 2016	1629	Omalizumab	Placebo	$I^2 = 42\%$	−4.59 [−5.29, −3.88]	$P < .00001$	8	Beneficial
Rate of response	Aguinaga 2016	944	Antihistamines at + up-dosing	Antihistamines at standard	$Q = 62.831$, $P < .001$	2.269 [1.684, 3.059]	Unclear	7	Beneficial
AEs	Sun 2015	701	Conventional treatment + Omalizumab 300 mg	Conventional treatment + placebo	$I^2 = 0\%$	1.07 [0.97, 1.18]	$P = .200$	7	No difference
	You 2015	1188	Mizolastine combined with H2 receptor antagonists	Mizolastine	$I^2 = 0\%$	1.01 [0.71, 1.44]	$P = .548$	7	No difference
	He 2015	975	Mizolastine	Loratadine	$I^2 = 0\%$	0.92 [0.65, 1.28]	$P = .61$	6	No difference
	Xu 2011	894	Ebastine + other medicine	Ebastine	$I^2 = 3\%$	1.03 [0.65, 1.63]	$P = .89$	7	No difference
Recurrence rate	Yang 2014	811	Chinese medicine prescription Dang gui Yin zi	Antihistamines	$I^2 = 0\%$	0.38 [0.26, 0.54]	$P < .00001$	7	Beneficial

AEs = adverse events, AMSTAR = assessment of multiple systematic reviews tool, CI = confidence intervals.

Table 4

Summary of evidence from qualitative research syntheses.

Phenomenon of interest	Author/yr	Interventions	Main outcomes	Synthesized finding
Clinical evidence of management strategies for patients with CSU who remain symptomatic despite approved use of nonsedating H1 antihistamines.	Mitchell 2015	Eyclosporine, desloratadine plus dapsone or dipyridamole, montelukast and omalizumab	1. Urticaria activity score 2. Change from baseline in the wheal scores 3. Change from baseline in the pruritus scores	1. Compared with placebo, cyclosporine, desloratadine plus dapsone or dipyridamole, montelukast and omalizumab reduced urticaria activity scores, wheals, and pruritus. 2. Optimal treatment doses and durations were unclear due to varying trial durations, outcome measurement scales, and assessment timings.
The role of LTRAs in the treatment of CU.	Silva 2014	LTRAs	1. Urticaria activity score 2. Total symptom score 3. Visual analog scale	1. The use of LTRAs as monotherapy cannot be recommended. 2. LTRAs were an effective add-on therapy to antihistamines, and their use in patients responding poorly to antihistamines was justifiable.
The efficacy and safety of omalizumab at different doses compared to those of placebo in controlling the symptoms of CIU/ CSU.	Carrillo 2014	Omalizumab at different doses	1. Urticaria activity score 2. Weekly itch score	1. Omalizumab 300 mg was effective in treating CIU refractory to H_1 antihistamines. 2. Omalizumab was associated with a higher frequency of AEs such as headache and upper respiratory infection.
From the current published literature, the strength of evidence for omalizumab efficacy and safety in the treatment of CIU.	Maurer 2017	Omalizumab	1. CU-Q2oL 2. DLQI 3. AEs	1. The vast majority of results indicated a beneficial role for omalizumab in each case of CIU. 2. Instances of AEs were low and rarely led to treatment discontinuation.

AEs = adverse events, CIU = chronic inducible urticaria, CSU = chronic spontaneous urticaria, CU = chronic urticaria, CU-Q2oL = chronic urticaria quality of life questionnaire, DLQI = dermatology life quality index, LTRAs = leukotriene receptor antagonists.

research study, which contributes to a larger body of evidence by meeting standards that allow inclusion in a SR approach.

We summarized the current evidence of pharmacological and nonpharmacological treatment effectiveness for a wide range of outcome indicators. Notably, all of the meta-analyses reported an effects summary estimate that favored the experimental group. However, many reviewers concluded that their findings have few significances for practice because of a lack of sufficient evidence. According to the GRADE analysis, there was much heterogeneity in evidence quality among SRs of pharmacological and non-pharmacological interventions for CU. Only 6 (16.22%) of the assessed quantitative studies were found to provide moderate- or

high-quality evidence, which included 2 omalizumab therapy reviews,[42,43] 2 antihistamine therapy reviews,[44,45] 1 combination therapy review[46] and 1 review of traditional Chinese medicine therapy.[47] The EAACI/GA2LEN/EDF/WAO guidelines recommended the use of second-generation H1-antihistamines and omalizumab as a first line and third line of treatment. In China, traditional Chinese medicine treatment for CU has been widely used in clinical practice,[48–50] but it has not been included in international guidelines. The extent to which a SR can guide health care decisions depends on the validity of the results obtained in the primary trials. From the result of this study, the quality of traditional Chinese medicine studies is poor and does not allow the conclusions for evidence-based decisions that are desired by clinicians and decision makers. Indeed, conducting clinical research is its high cost. Studies estimate that it now costs somewhere between US$161 million and US$2 billion to bring a new drug to market.[51–53] Seeing the primary studies of these included reviews, the high-quality evidence exists due to several primary studies with good study design and large sample size in the onset sponsored by pharmaceutical companies. However, the patent protection is short-lived and the clinical trial costs are substantial and rising.[54,55] Many cheaper drugs or other types of treatments for CU do not have enough funds to carry out high-level evidence of clinical trials without sponsors.

Looking at the comparator of these reviews, although some reviewers concluded that there was robust evidence to support an intervention, there remained little information on the relative effectiveness of one intervention compared with another. These reviews may provide evidence that the use of an intervention was better than no intervention, yet there was no adequate evidence to suggest that one intervention was superior to another among this diverse range of treatments. Currently, there is very limited evidence on the relative effectiveness of different interventions for CU. Therefore, future research should be focused on direct comparisons of various types of interventions, in addition to using a placebo or no treatment as comparators, to provide evidence that will assist patients and practitioners in choosing among many treatment options.

Our study had some limitations. First, while all attempts were made to search and access all relevant literature, it is possible that some publications may have been missed in the search process due to language restrictions. Furthermore, all efficacy evaluations of the included studies were positive, which may have led to publication bias. Second, as there was much heterogeneity in methodological quality and evidence quality among these SRs, the heterogeneity made it impossible to combine the findings across all included SRs and come to an absolute conclusion.

5. Conclusions

There is currently some evidence to support a variety of interventions for CU, such as reviews involving antihistamines, omalizumab, CsA, LTRAs combined with antihistamines, traditional Chinese medicines, acupuncture, autohemotherapy, and combination therapy. However, the quality of reporting among these SRs is low, and the authors concluded that the clinical results presented in the reviews are tentative and should be interpreted cautiously because of a lack of high-quality evidence. Therefore, this study suggests that primary studies make direct comparisons between different treatment options in the future and that the dissemination of evidence-based pharmacological and nonpharmacological treatments will comply through an array of efforts to minimize the potential effect of those biases when researchers conduct a meta-analysis and explain their results.

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Author contributions

Yunzhou Shi, Hui Zheng, and Ying Li contributed to the conception and design of the study. The search strategy was developed and run by Yunzhou Shi. Mingmin Xu and Leixiao Zhang screened the title and abstract of the studies after running the search strategy, and also screened full copies of the remaining studies after title and abstract selection, while Yunzhou Shi and Xianjun Xiao extracted information from the identified studies; Ying Huang and Pingsheng Hao checked the data entry for accuracy and completeness. Siyuan Zhou and Qianhua Zheng independently assessed the quality of the SRs. Hui Zheng and Ying Li provided advice for data analysis and presentation. All the authors drafted and revised this study and approved it for publication.

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