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Effect of a Psychological Stress-management Intervention on Quality of Life in Chronic Spontaneous Urticaria: A Randomized Clinical Trial

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ABSTRACT

Chronic spontaneous urticaria (CSU) is associated with anxiety, sleep disturbance, and impaired quality of life. Although psychological stress may exacerbate CSU, evidence from randomized structured stress-management interventions remains limited.

This two-arm randomized controlled trial evaluated whether adding a 12-week multicomponent stress-management program to guideline-based pharmacologic therapy improved patient-reported outcomes in adults with CSU. Participants were randomly assigned to receive the stress-management program plus guideline-based pharmacologic therapy or guideline-based pharmacologic therapy alone. The primary outcome was disease-specific quality of life at week 12, assessed using the Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL). Secondary outcomes were anxiety symptoms, assessed using the Beck Anxiety Inventory (BAI), and urticaria activity, assessed using the Urticaria Activity Score over 7 days (UAS7). Between-group comparisons were adjusted for baseline values using analysis of covariance (ANCOVA).

Of 122 patients screened, 113 were randomized, and 100 completed the 12-week follow-up and were included in the final analysis (50 per group). After adjustment for baseline values, the intervention group showed significantly greater improvement in disease-specific quality of life and anxiety symptoms than the control group. UAS7 scores improved substantially in both groups, without a significant between-group difference. Exploratory analyses suggested greater improvements in the itch, swelling, sleep disturbance, and life activities domains of the CU-Q2oL.

These findings support psychological stress management as an adjunct to CSU care, particularly for patient-reported outcomes.

Keywords: Anxiety; Chronic urticaria; Mind-body therapies; Psychological; Quality of life; Stress

INTRODUCTION

Chronic spontaneous urticaria (CSU) is a mast cell–mediated skin disease characterized by recurrent, transient wheals and/or angioedema that persist for more than 6 weeks without an identifiable trigger.[1,2] CSU affects approximately 1% of the population and often follows a prolonged, unpredictable course.[3] Near-daily itching and swelling disrupt sleep, impair daily functioning, and reduce productivity.[4] Psychologically, the uncertainty of symptom flares contributes to anxiety, distress, and social withdrawal. CSU is also associated

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with quality-of-life (QoL) impairments comparable to those observed in other chronic dermatologic conditions.[5] Many patients experience moderate to severe QoL reduction, which generates substantial healthcare costs and productivity loss.[1] Mental health comorbidities are common in CSU, with higher rates of anxiety and depression compared with the general population.[6,7] Recent studies indicate that nearly one-third of CSU patients have a psychiatric disorder, which is associated with more severe symptoms and poorer quality of life.[5]

Psychological stress appears to play a significant role in CSU, as stressful life events and high perceived stress have been linked to disease onset, more frequent relapses, greater wheal activity, and worse quality of life, likely via stress-related neuroendocrine pathways that promote mast cell activation. At the same time, CSU symptoms themselves exacerbate stress and anxiety, creating a self-perpetuating brain–skin cycle in which flares and distress reinforce one another.[8–10] The rationale for psychological stress management in CSU is supported by a biopsychosocial and psychoneuroimmunological framework. Psychological stress may influence CSU through activation of the hypothalamic–pituitary–adrenal axis, autonomic nervous system dysregulation, stress-related mast-cell activation, and release of inflammatory mediators. In addition, stress may amplify itch perception, increase emotional reactivity to symptoms, disrupt sleep, and weaken adaptive coping responses. Therefore, interventions targeting stress appraisal, physiological arousal, emotional regulation, sleep behavior, and coping may help reduce the patient-perceived burden of CSU, even when pharmacologic treatment remains the main strategy for controlling mast cell–driven disease activity.

Given the link between stress and CSU, interest in psychological interventions has increased. Standard treatments, including standard-dose or up-dosed second-generation H1-antihistamines and omalizumab in refractory cases, often provide only partial symptom control and do not directly address psychological well-being.[1,2,6] Although mind–body approaches are not part of routine CSU care, evidence from other chronic dermatologic conditions suggests that meditation, relaxation training, and stress-reduction techniques may help alleviate symptoms.[6,11] Early studies in CSU have shown similar trends, with small trials reporting improvements in symptom severity, urticaria control, and mood.[8,11,12] However, these findings are based mainly on small or uncontrolled studies, and rigorous randomized trials remain limited, leaving uncertainty about the added benefit of psychological stress management alongside guideline-based pharmacologic therapy.[8,11–14] To address these gaps, we conducted a randomized controlled trial in Iran to evaluate whether adding a structured psychological stress-management program to guideline-based pharmacologic therapy would improve outcomes in patients with CSU. Our multicomponent intervention, which included psychoeducation, relaxation and mind–body techniques, and lifestyle guidance, was hypothesized to improve quality of life, reduce anxiety symptoms, and reduce urticaria activity beyond guideline-based pharmacologic therapy alone.

PATIENTS AND METHODS

Participants

Participants were consecutively recruited from adults with chronic spontaneous urticaria (CSU) attending an outpatient allergy clinic in Tehran, Iran. Eligible participants were aged≥18 years, had a confirmed diagnosis of CSU for more than 6 weeks, and provided written informed consent.

Exclusion criteria included inducible urticarias, including cold-induced urticaria; known or clinically significant severe or unstable psychiatric disorders, such as active psychosis, bipolar disorder with recent manic or hypomanic episodes, or active suicidal ideation; severe medical conditions likely to interfere with study participation, such as uncontrolled endocrine disease, advanced cardiac or renal disease, or acute systemic infection; cognitive or functional impairments that would prevent participation in the intervention; and inability to attend study sessions or complete study assessments. Psychological eligibility was assessed during screening by the study psychologist using clinical history and a brief unstructured psychological screening interview. Psychiatric exclusion criteria were operationalized as conditions judged likely to interfere with safe participation, adherence to the intervention, attendance at study sessions, or completion of study questionnaires. No formal structured psychiatric diagnostic interview was administered.

Study Design, Setting, Randomization, and Blinding

This 2-arm randomized controlled trial was conducted

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in an outpatient allergy clinic in Tehran, Iran. Adult patients with a confirmed diagnosis of chronic spontaneous urticaria (CSU) for more than 6 weeks were screened consecutively during routine clinic visits. The study protocol was approved by the Ethics Committee of Islamic Azad University, Tehran North Branch (IR.IAU.TNB.REC.1404.113) on July 2, 2025, and the study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. Written informed consent was obtained from all participants before any study procedures were performed.

Participant screening and recruitment began in July 2025. Eligible participants underwent baseline clinical assessment and completed study questionnaires before randomization. They were then assigned in an approximately 1:1 ratio to either the intervention group, which received a structured psychological stress-management program in addition to standard pharmacologic treatment, or the control group, which received standard pharmacologic treatment alone. The random allocation sequence was generated by an independent researcher using a computer-generated random-number sequence. Allocation concealment was ensured using sequentially numbered, opaque, sealed envelopes opened only after participant enrollment. Randomization was not stratified or blocked; simple randomization resulted in 60 participants being allocated to the intervention group and 53 to the control group.

Because of the nature of the intervention, blinding of participants and intervention providers was not feasible. However, personnel responsible for data entry and statistical analysis remained blinded to treatment allocation throughout the study.

Medication selection and dose adjustment were determined solely by the treating allergist and were independent of study allocation. The psychological stress-management program was delivered individually in weekly 60–90-minute sessions over 12 weeks, either in person or by telephone according to participant preference and clinic logistics. Outcomes were assessed at baseline and after the 12-week intervention period.

The trial was retrospectively registered in the Iranian Registry of Clinical Trials (IRCT20250912067222N1), with final registration approval granted on December 7, 2025. The study protocol, including the intervention, prespecified outcomes, and statistical analysis plan, had been finalized before participant recruitment commenced and remained unchanged throughout the study.

Interventions

Participants in both study groups continued to receive
standard pharmacologic treatment for CSU throughout the study. The intervention group additionally received a structured psychological stress management program as an adjunct to pharmacologic therapy. The control group received standard pharmacologic treatment alone. Details of pharmacologic treatment and the psychological intervention are described below.

Pharmacologic Treatment

Pharmacologic treatment followed current international CSU guideline recommendations and was prescribed by the treating allergist independently of study group allocation. Treatment included standard-dose second-generation non-sedating H1-antihistamines, with dose escalation up to fourfold when clinically indicated. For inadequate disease control despite high-dose antihistamines, omalizumab was administered when clinically indicated, typically as 300 mg subcutaneously every 4 weeks. Cyclosporine was considered for refractory disease according to guidelines; however, no participant in either group received cyclosporine during the study period.

Psychological Stress-management Intervention

Participants assigned to the intervention group additionally received a structured psychological stress-management program consisting of 12 weekly individual sessions, each lasting approximately 60–90 minutes. Sessions were delivered either in person or by telephone according to participants' preferences and clinic logistics, with the same standardized content provided in both formats.

The intervention was delivered by a master's-level psychology student who had been trained in the study protocol and stress-management counseling before the start of the trial, under the supervision of a clinical psychologist. Intervention fidelity was supported through a predefined structured protocol and session checklist. After each session, the intervention provider completed the checklist to document delivery of the planned core components and to record any major deviations from the protocol. No audio or video recordings or independent fidelity ratings were used; therefore, fidelity monitoring relied on structured session documentation and supervision by the clinical psychologist. The program was designed as an adjunct

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to pharmacologic therapy and did not replace routine medical treatment.

The intervention was a structured, evidence-informed psychological stress-management program,[5,6,8,10,13] consisting of three integrated components: psychoeducation; relaxation and mind–body techniques; and lifestyle and behavioral modification guidance.

Psychoeducation

Participants received education about the relationship between psychological stress, neuroimmune activation, and fluctuations in chronic spontaneous urticaria symptoms. This component included identification of individual stressors, discussion of the itch–scratch cycle, and guidance on adaptive cognitive and behavioral coping strategies. The aim was to improve understanding of stress-related symptom variation, reduce catastrophic interpretations of symptom flares, and strengthen self-regulation and coping.

Relaxation and Mind–body Techniques

Participants were instructed in stress-reduction techniques for regular home practice, including guided or progressive muscle relaxation (approximately 15 minutes daily), mindfulness or meditation (15–30 minutes daily), and calming pre-sleep routines such as limiting screen exposure and engaging in quiet activities before bedtime. Optional physical calming strategies, such as a lukewarm or cool shower when tolerated, were discussed only as general self-regulation techniques and not as disease-specific treatment for CSU. Patients with inducible urticarias, including cold-induced urticaria, were excluded from the study. Brief written or audio instructions were provided to reinforce home practice.

Lifestyle and Behavioral Modification Guidance

Participants received individualized recommendations regarding sleep hygiene, physical activity, and healthy lifestyle behaviors. Advice included maintaining regular sleep–wake schedules, aiming for 7–8 hours of sleep per night, engaging in at least 15 minutes of light physical activity daily as tolerated, limiting caffeine, alcohol, and heavy evening meals, identifying daily stressors, reducing exposure to stressful media content, and applying adaptive behavioral coping strategies. Although the intervention was individualized according to participants' needs, its overall structure and sequence were standardized. Early sessions focused on psychoeducation and identification of stressors, middle sessions emphasized relaxation and mindfulness training, and later sessions reinforced lifestyle modification, coping strategies, and maintenance of home practice. Participants were encouraged to practice the techniques throughout the 12-week intervention period while continuing their prescribed pharmacologic treatment. No booster sessions beyond the scheduled weekly sessions were provided. No additional psychiatric treatment or psychotherapy outside the study protocol was initiated by the study team in either group during the trial.

Outcomes

The primary outcome was change from baseline to week 12 in disease-specific quality of life, assessed using the total raw score of the Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL; range, 0–92), with higher scores indicating greater quality-of-life impairment. Secondary outcomes were changes from baseline to week 12 in anxiety symptoms, assessed using the Beck Anxiety Inventory (BAI; range, 0–63), and urticaria activity, assessed using the Urticaria Activity Score over 7 days (UAS7; range, 0–42). Higher BAI and UAS7 scores indicate greater anxiety severity and greater urticaria activity, respectively. Exploratory outcomes included the six CU-Q2oL domain scores: itch, swelling, life activities, sleep disturbance, limitations, and appearance. Raw, non-transformed CU-Q2oL total and domain scores were analyzed. The BAI was used to quantify anxiety symptom severity and was not used as a diagnostic tool for psychiatric disorders. Participants completed the UAS7 diary for 7 consecutive days before both the baseline and week-12 assessments; therefore, UAS7 scores reflected urticaria activity during the preceding 7-day periods.

Sample Size Calculation

Because no previous randomized controlled trial had evaluated a comparable multicomponent stress-management intervention in patients with chronic spontaneous urticaria, the sample size was informed by the most comparable randomized clinical trial of a mindfulness-based psychological intervention in adults with chronic inflammatory skin disease.[15] The sample size estimation was informed by the between-group difference in disease-specific quality-of-life scores and the corresponding variability reported in that trial, assuming

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a two-sided α level of 0.05, 80% statistical power, and an anticipated attrition rate of approximately 10%. This approach indicated that approximately 110 participants should be randomized to provide adequate statistical power after anticipated attrition. Recruitment was stopped after the prespecified approximate target had been reached. No interim sample size re-estimation or post hoc modification of the planned sample size was performed.

Adherence Assessment

Adherence to the psychological stress management intervention was assessed by attendance at the 12 weekly sessions, which were delivered either face to face or by telephone. Session attendance was recorded by the study psychologist. In addition, participants in the intervention group were asked during intervention sessions or follow-up telephone contacts about their self-reported use of the recommended stress-management techniques at home. All participants were also asked about continuation of their prescribed pharmacologic treatment during follow-up.

Adherence to home practice and pharmacologic treatment was assessed by patient self-report. No objective adherence monitoring tools, such as electronic monitoring devices, structured home-practice logs, or formal adherence scales, were used.

Statistical Analysis

Statistical analyses were performed using SPSS version 27. Descriptive statistics were used to summarize baseline demographic and clinical characteristics. Continuous variables are presented as mean and standard deviation (SD), and categorical variables as frequency and percentage. The distribution of continuous variables was assessed using normality tests and visual inspection of histograms.

Baseline characteristics were compared between the intervention and control groups using independent-samples t-tests or Mann–Whitney U tests for continuous variables, as appropriate, and chi-square or Fisher's exact tests for categorical variables.

Within-group changes from baseline to week 12 were assessed using paired-samples t-tests or Wilcoxon signed-rank tests, depending on data distribution. Between-group comparisons of week-12 outcomes were performed using analysis of covariance (ANCOVA). For each outcome, the week-12 score was entered as the dependent variable, treatment group as the fixed factor, and the corresponding baseline value of that outcome as the covariate. Separate ANCOVA models were fitted for BAI, CU-Q2oL, and UAS7.

This baseline-adjusted approach was used to account for baseline differences and improve the precision of between-group treatment effect estimates. Baseline adjustment was particularly relevant because the intervention group had significantly higher baseline total CU-Q2oL scores than the control group. Before applying ANCOVA, model assumptions were assessed, including linearity between baseline and week-12 values, homogeneity of regression slopes (tested by the treatment group × baseline interaction), normality of residuals, homoscedasticity, and the absence of influential outliers. In addition to the total CU-Q2oL score, exploratory domain-specific analyses were performed. For each CU-Q2oL domain, week-12 scores were compared between groups using ANCOVA, adjusting for the corresponding baseline domain score. These domain-level analyses were considered exploratory and were not corrected for multiple comparisons; therefore, they were interpreted cautiously. No formal adjustment for multiple comparisons was applied to the prespecified main outcomes. The primary analyses used a complete-case approach and included participants with both baseline and week-12 outcome measurements. No imputation was performed for missing outcome data. All statistical tests were two-sided, and P values <0.05 were considered statistically significant. In addition to P values, adjusted mean differences with 95% confidence intervals and partial eta-squared values were reported for ANCOVA models to show the magnitude and precision of between-group effects.

RESULTS

A total of 122 patients were screened for eligibility. Of these, 9 were excluded before randomization, including 5 who did not meet the eligibility criteria and 4 who declined to participate. The remaining 113 participants were randomized, with 60 allocated to the intervention group and 53 to the control group. In the intervention group, 6participants were lost to follow-up and 4 withdrew from the intervention before completing the week-12 assessment. In the control group, three participants were lost to follow-up before the week-12 assessment. Consequently, the complete-case analysis included 100 participants (50 in each group). The participant flow is presented in Figure 1.

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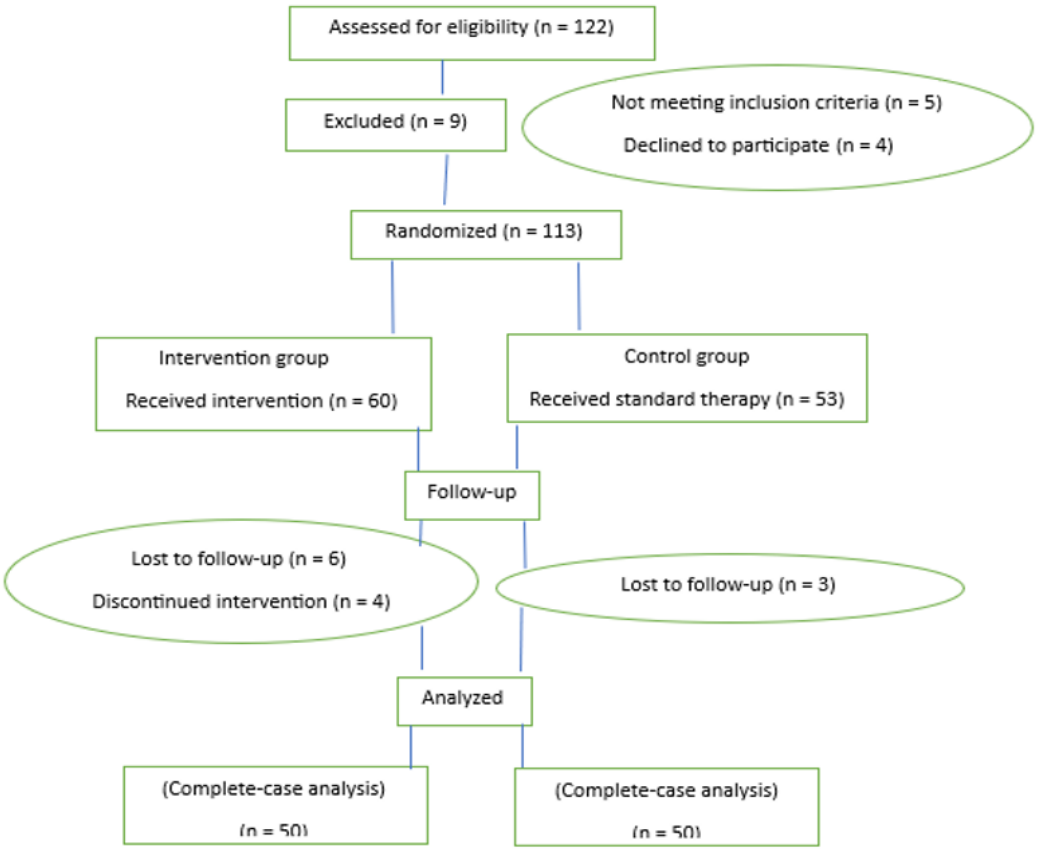

Figure 1. CONSORT flow diagram illustrating the flow of participants through a two-arm randomized controlled trial evaluating a 12-week structured psychological stress-management intervention as an adjunct to guideline-based pharmacologic therapy in adults with chronic spontaneous urticaria (CSU). The diagram shows the numbers of patients assessed for eligibility, excluded before randomization, randomized to the intervention or control group, those lost to follow-up or withdrawn, and included in the final complete-case analysis (n=50 per group).

However, the baseline total CU-Q2oL score was significantly higher in the intervention group (70.16±13.36 vs. 65.08±11.49; p=0.043), indicating greater quality-of-life impairment, and domain-level imbalances were also present in the itch (p=0.006), sleep disturbance (p=0.040), and life activities (p<0.001) domains. These imbalances were addressed in baseline-adjusted analyses. Mean BAI, CU-Q2oL, and UAS7 scores decreased from baseline to week 12 in both groups, and between-group comparisons at week 12, including adjusted mean differences, 95% confidence intervals, P values, and partial eta-squared values, are presented in Table 2. Anxiety scores decreased in both groups, with a greater reduction observed in the intervention group; the mean BAI score decreased from 23.08±9.76 at baseline to 13.20±6.14 at week 12 in the intervention group, compared with a decrease from 22.02±10.53 to 15.86±7.01 in the control group. After adjustment for baseline BAI scores using ANCOVA, the adjusted between-group difference at week 12 favored the intervention group (p=0.042). Disease-specific quality of life also improved in both groups, as reflected by reductions in CU-Q2oL scores, with a numerically greater reduction observed in the intervention group. The mean total CU-Q2oL score decreased from 70.16±13.36 to 46.18±11.48 in the intervention group and from 65.08±11.49 to 49.38±8.31 in the control group. After adjustment for baseline CU-Q2oL scores, the adjusted between-group difference at week 12 favored the intervention group (p=0.034). To further characterize the quality-of-life findings, exploratory domain-specific analyses of the CU-Q2oL were performed using ANCOVA adjusted for the corresponding baseline domain scores (Table 3). After

baseline adjustment, the intervention group showed significantly greater improvement than the control group in the itch domain (p=0.021), swelling domain (p=0.041), sleep disturbance domain (p=0.048), and life activities domain (p=0.031). No significant adjusted between-group differences were observed in the appearance domain (p=0.089) or limitations domain (p=0.271). These findings were consistent with the improvement observed in the total CU-Q2oL score**.** As these domain-level comparisons were exploratory and not corrected for multiple testing, these results should be interpreted with caution. UAS7 scores decreased significantly from baseline to week 12 in both groups. In the intervention group, mean UAS7 decreased from 29.00±10.91 to 8.06±7.18, corresponding to a mean reduction of 20.94 points. In the control group, mean UAS7 decreased from 30.30±10.22 to 9.02±6.16, corresponding to a mean reduction of 21.28 points. However, ANCOVA adjusted for baseline UAS7 showed no significant between-group difference at week 12 (p=0.665). These findings indicate that urticaria activity improved substantially in both groups, but the psychological stress management intervention did not result in a statistically significant additional improvement in UAS7 compared with standard pharmacologic therapy alone.

Table 1. Baseline Demographic and Clinical Characteristics of Participants Included in the Complete-Case Analysis

Characteristic	Intervention (n=50)	Control (n=50)	*p*
Age, Mean (SD)	41.3 (10.9)	40.1 (7.6)	0.526
Gender, n (%)			1.0
Male	13 (26%)	13 (26%)	
Female	37 (74%)	37 (74%)	
Marital Status, n (%)			0.61
Single	33 (66%)	36 (72%)	
Married	17 (34%)	14 (28%)	
Education, n (%)			0.202
High school	14 (28%)	13 (26%)	
Bachelor's degree	19 (38%)	11 (22%)	
Master's degree	13 (26%)	17 (34%)	
Doctorate degree	4 (8%)	9 (18%)	
Baseline pharmacologic treatment, n (%)			0.218
Standard-dose H1-antihistamine	23 (46%)	17 (34%)	
Up-dosed H1-antihistamine	24 (48%)	32 (64%)	
Omalizumab-based therapy	3 (6%)	1 (2%)	
Baseline BAI score, Mean (SD)	23.08 (9.76)	22.02 (10.53)	0.603
Baseline CU-Q2oL score, Mean (SD)	70.16 (13.36)	65.08 (11.49)	0.043
Baseline UAS7 score, mean (SD)	29.00 (10.91)	30.30 (10.22)	0.540

Values are presented as mean (SD) or number (%). Between-group comparisons at baseline were performed using independent-samples t-tests or Mann–Whitney U tests for continuous variables, as appropriate, and chi-square or Fisher's exact tests for categorical variables. BAI: Beck Anxiety Inventory; CU-Q2oL: Chronic Urticaria Quality of Life Questionnaire; UAS7: Urticaria Activity Score over 7 days; SD: standard deviation. H1-antihistamines refer to second-generation H1-antihistamines. Up-dosed H1-antihistamine therapy refers to dose escalation up to fourfold according to guideline-based practice

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Table 2. Changes in Clinical Outcomes from Baseline to Week 12 in the Intervention and Control Groups

Outcome	Group	Baseline Mean (SD)	Week 12 Mean (SD)	Within-Group *p**	Between-Group *p*†	Adjusted Mean Difference (95% CI)	Partial η²
BAI	Intervention	23.08 (9.76)	13.20 (6.14)	<0.001	0.042	−2.58 (−5.02 to −0.14)	0.041
	Control	22.02 (10.53)	15.86 (7.01)	<0.001			
CU-Q2oL	Intervention	70.16 (13.36)	46.18 (11.48)	<0.001	0.034	−3.85 (−7.40 to −0.30)	0.045
	Control	65.08 (11.49)	49.38 (8.31)	<0.001			
UAS7	Intervention	29.00 (10.91)	8.06 (7.18)	<0.001	0.665	−0.52 (−2.89 to 1.85)	0.002
	Control	30.30 (10.22)	9.02 (6.16)	<0.001			

Values are presented as unadjusted mean (SD), unless otherwise indicated. *Within-group changes from baseline to week 12 were assessed using paired-samples t-tests or Wilcoxon signed-rank tests, as appropriate. †Between-group comparisons at week 12 were performed using analysis of covariance (ANCOVA), with treatment group as the fixed factor and the corresponding baseline value as the covariate. The between-group P value, adjusted mean difference (95% CI), and partial η² are reported once for each outcome and apply to the comparison between the intervention and control groups. Adjusted mean difference represents the intervention group minus the control group after adjustment for the corresponding baseline value. Negative values indicate lower week-12 scores in the intervention group compared with the control group. Higher BAI scores indicate greater anxiety; higher CU-Q2oL scores indicate greater quality-of-life impairment; and higher UAS7 scores indicate greater urticaria activity. BAI: Beck Anxiety Inventory; CU-Q2oL: Chronic Urticaria Quality of Life Questionnaire; UAS7: Urticaria Activity Score over 7 days; CI: confidence interval.

Table 3. Domain-Specific CU-Q2oL Scores at Baseline and Week 12

CU-Q2oL Domain	Maximum Score	Intervention Baseline	Intervention Week 12	Control Baseline	Control Week 12	Baseline *p*	Adjusted Week 12 *p**
Itch	8	7.30 (1.20)	3.60 (1.20)	6.70 (1.10)	3.90 (0.90)	0.006	0.021
Swelling	8	6.60 (1.50)	3.80 (1.40)	6.10 (1.40)	4.20 (1.00)	0.080	0.041
Sleep disturbance	20	15.30 (3.20)	10.20 (3.10)	14.00 (3.00)	10.90 (2.30)	0.040	0.048
Life activities	24	19.20 (3.90)	12.30 (3.60)	16.00 (3.70)	13.20 (2.80)	<0.001	0.031
Appearance	20	13.10 (3.60)	9.10 (3.00)	13.30 (3.20)	9.70 (2.40)	0.770	0.089
Limitations	12	8.66 (2.30)	7.18 (2.40)	8.98 (2.30)	7.48 (1.90)	0.490	0.271
Total score	92	70.16 (13.36)	46.18 (11.48)	65.08 (11.49)	49.38 (8.31)	0.043	0.034

Values are presented as unadjusted mean (SD). Baseline *p* values were obtained using independent-samples t-tests or Mann–Whitney U tests, as appropriate. *Adjusted week-12 P values were obtained using analysis of covariance (ANCOVA), with treatment group as the fixed factor and the corresponding baseline domain score as the covariate. Domain-level analyses were exploratory and were not adjusted for multiple comparisons; therefore, these findings should be interpreted with caution. Higher scores indicate greater quality-of-life impairment. CU-Q2oL: Chronic Urticaria Quality of Life Questionnaire.

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DISCUSSION

A 12-week structured psychological stress management program, when added to guideline-based pharmacologic therapy, resulted in greater improvements in anxiety symptoms and disease-specific quality of life than pharmacologic therapy alone in patients with chronic spontaneous urticaria. These differences remained significant after adjustment for baseline values. In contrast, urticaria activity, assessed by UAS7, improved substantially in both groups without a significant between-group difference. Collectively, these findings suggest that the intervention primarily enhanced patient-reported psychological and quality of life outcomes rather than symptom-based urticaria activity during the 12-week study period.

The greater reduction in anxiety observed in the intervention group is consistent with previous evidence linking psychological distress, anxiety symptoms, and psychiatric comorbidity to increased disease burden and poorer quality of life in CSU.[5,16] Psychological interventions such as relaxation training, cognitive-behavioral approaches, and mindfulness-based techniques have been shown to improve anxiety and other patient-reported outcomes in stress-sensitive conditions.[8,17] The present findings suggest that a structured multicomponent stress-management program may offer additional psychological benefit when used alongside guideline-based pharmacologic therapy.

Several mechanisms may explain the observed benefits of the intervention. Psychological stress has been proposed to exacerbate CSU through neuroendocrine and immune pathways, including activation of the hypothalamic–pituitary–adrenal axis, autonomic dysregulation, and stress related mast-cell activation.[5,18] In addition, relaxation, mindfulness, and behavioral strategies may improve emotional regulation, sleep, coping, and itch perception, thereby reducing the patient-perceived burden of the disease.[19–23] However, these mechanisms remain speculative in the context of the present study because perceived stress, biological stress markers, and other mechanistic outcomes were not assessed. Consequently, the observed improvements in anxiety and quality of life cannot be attributed to specific neuroimmune pathways. Future studies incorporating validated stress measures and biological markers are needed to clarify the mechanisms through which psychological stress management interventions influence outcomes in CSU.

Although both groups showed substantial improvement in UAS7 scores over the 12-week study period, the adjusted between-group difference was not statistically significant. This finding is not unexpected because all participants received guideline-based pharmacologic treatment, including standard-dose or updosed second-generation H1-antihistamines and omalizumab when clinically indicated, therapies that are well established in reducing urticaria activity.[24] Consequently, any additional effect of the psychological intervention on symptom-based disease activity may have been difficult to detect beyond the benefits of guideline-based medical treatment. Moreover, psychological stress management interventions are more likely to influence patient-reported aspects of the disease, such as anxiety, coping, sleep, emotional distress, and perceived disease burden, than the underlying mast cell–mediated inflammatory processes reflected by UAS7. Therefore, the absence of an additional effect on UAS7 should not be interpreted as evidence that the intervention lacked benefit. Rather, it suggests that its principal contribution may be to complement pharmacologic therapy by improving patient-centered outcomes rather than further reducing symptom-based urticaria activity. In this trial, the purpose of adding the stress-management program was not to replace pharmacologic treatment but to determine whether it could provide additional benefits in quality of life and psychological well-being among patients receiving standard guideline-based care.

This interpretation is supported by the observed improvements in disease-specific quality of life. Chronic spontaneous urticaria affects patients far beyond its physical manifestations, with persistent anxiety, sleep disturbance, fear of symptom recurrence, social embarrassment, impaired daily functioning, and reduced productivity often continuing despite partial control of wheals and angioedema.[25,26] Similar reductions in quality of life have also been described in other chronic allergic diseases, including asthma.[27] Consistent with this broader psychosocial burden, participants receiving the stress-management intervention experienced significantly greater improvement in disease-specific quality of life than those receiving pharmacologic treatment alone. These findings suggest that the intervention may have enhanced patients' ability to cope with their disease, improved emotional well-being and sleep-related behaviors, and reduced the overall perceived burden of

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living with CSU, even in the absence of additional improvement in symptom-based disease activity.

Our findings support the importance of addressing psychological distress as part of a multidimensional management approach for chronic spontaneous urticaria, rather than focusing exclusively on pharmacologic symptom control. Although no well-established minimal clinically important difference (MCID) has been defined for the Beck Anxiety Inventory (BAI), a previous study proposed an MCID of approximately 15 points for the Chronic Urticaria Quality of Life Questionnaire (CU-Q2oL) (28). In the present study, the improvement in total CU-Q2oL score in the intervention group exceeded this proposed threshold, whereas the control group also demonstrated improvement close to or slightly above it. Because meaningful improvement occurred in both groups, the clinical value of the stress management intervention is more appropriately reflected by the adjusted between-group difference at week 12 rather than by within-group changes alone. From this perspective, the greater improvement observed in the intervention group is consistent with a potentially meaningful additional patient-reported benefit beyond standard pharmacologic care. These findings should, however, be interpreted with caution because the proposed CU-Q2oL MCID was derived from a single Thai validation study and has not yet been widely validated across diverse CSU populations. Future studies are needed to establish robust MCIDs for both disease-specific quality of life and anxiety outcomes, particularly those measured using the BAI, in patients with CSU.

Exploratory domain-specific analyses of the CU-Q2oL provided additional insight into the aspects of quality of life most responsive to the intervention. After adjustment for baseline domain scores, participants in the intervention group showed significantly greater improvements in the itch, swelling, sleep disturbance, and life activities domains, whereas no significant between-group differences were observed for the appearance or limitations domains. These findings are broadly consistent with the intervention content, which emphasized relaxation, mindfulness, sleep hygiene, lifestyle modification, and adaptive coping strategies that may particularly influence symptom perception, sleep-related impairment, and everyday functioning. However, because these analyses were exploratory and were not adjusted for multiple comparisons, they should be interpreted cautiously and confirmed in future studies.

From a clinical perspective, the findings suggest that structured psychological stress management may provide meaningful additional benefit for patient-reported outcomes when used alongside guideline-based pharmacologic therapy, particularly in patients with prominent anxiety, sleep disturbance, or quality-of-life impairment. However, the intervention should be viewed as an adjunct rather than a replacement for standard pharmacologic treatment, as no significant additional improvement was observed in UAS7-measured urticaria activity.

Several limitations should be considered when interpreting these findings. First, because of the behavioral nature of the intervention, blinding of participants and intervention providers was not feasible. Consequently, performance bias, expectancy effects, Hawthorne effects, and the influence of additional therapeutic attention cannot be excluded, particularly because the control group did not receive an attention-matched intervention.

Second, adherence to home-based stress management techniques and prescribed pharmacologic treatment was assessed by participant self-report rather than objective measures and may therefore have been influenced by recall or social desirability bias. Although intervention fidelity was supported by a predefined protocol, structured session checklists, and regular clinical supervision, it was not independently evaluated using observers, audio or video recordings, or formal fidelity ratings.

Third, perceived stress was not measured using a validated instrument, such as the Perceived Stress Scale, and no biological markers of stress or inflammation were assessed. Consequently, it was not possible to determine whether the observed improvements in anxiety and disease-specific quality of life were mediated by reductions in perceived stress or by changes in neuroimmune pathways. Future studies incorporating validated stress measures together with mechanistic biomarkers are needed to clarify the biological and psychological pathways underlying the effects of stress-management interventions in CSU.

Fourth, a baseline imbalance in disease-specific quality of life was observed, with higher baseline CU-Q2oL scores in the intervention group. Although this imbalance was addressed using baseline-adjusted analysis of covariance (ANCOVA), the possibility of residual confounding cannot be completely excluded. In addition, pharmacologic treatment was individualized

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according to routine clinical care rather than fixed by the study protocol. Although baseline medication categories were comparable between groups, treatment modifications during follow-up may have influenced clinical outcomes, particularly UAS7, thereby potentially reducing the ability to detect any additional effect of the psychological intervention on symptom-based urticaria activity.

Finally, the single-center design, modest sample size, complete-case analysis without imputation for missing outcome data, and relatively short 12-week follow-up limit the generalizability and long-term interpretation of the findings. In addition, most participants had moderate-to-severe CSU, limiting applicability to patients with milder disease. Psychotropic medication use and concurrent psychiatric treatment were not systematically recorded and may have influenced patient-reported outcomes. Larger multicenter randomized controlled trials with longer follow-up, intention-to-treat analyses, objective adherence assessment, validated stress measures, and mechanistic biomarkers are warranted to confirm these findings and identify the patients most likely to benefit from adjunctive psychological stress-management interventions.

Despite these limitations, the present study has several important strengths. To our knowledge, it is among the few randomized controlled trials evaluating a structured multicomponent psychological stress-management program as an adjunct to guideline-based pharmacologic therapy in patients with chronic spontaneous urticaria. Additional strengths include the randomized controlled design, a standardized intervention protocol supported by structured session checklists and regular clinical supervision, baseline-adjusted statistical analyses, and the use of validated disease-specific and psychological outcome measures to comprehensively evaluate patient-reported outcomes.

In this randomized controlled trial, adding a structured multicomponent psychological stress-management program to guideline-based pharmacologic therapy resulted in greater improvements in disease-specific quality of life and anxiety symptoms than pharmacologic therapy alone in patients with chronic spontaneous urticaria. No additional benefit was observed for UAS7-measured urticaria activity beyond that achieved with standard pharmacologic treatment. These findings support the use of structured psychological stress management as an adjunct to guideline-based CSU care, particularly for patients with substantial psychological burden or impaired quality of life, while recognizing that pharmacologic therapy remains the cornerstone of disease control. Larger multicenter randomized trials with longer follow-up, attention-matched control conditions, intention-to-treat analyses, objective adherence assessment, and mechanistic evaluations are needed to confirm these findings, assess their durability, and identify the patients most likely to benefit.

STATEMENT OF ETHICS

The study protocol was approved by the Ethics Committee of Islamic Azad University, Tehran North Branch, Tehran, Iran (approval code: IR.IAU.TNB.REC.1404.113; approved on July 2, 2025). The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. Written informed consent was obtained from all participants before enrollment. The trial was retrospectively registered in the Iranian Registry of Clinical Trials (IRCT20250912067222N1).

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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DATA AVAILABILITY

The data supporting the findings of this study are available from the corresponding author (a_pourvali@yahoo.com) upon reasonable request.

AI ASSISTANCE DISCLOSURE

No artificial intelligence (AI) tools were used in the preparation of this manuscript.

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