

CLINICAL STUDY

Comparison of clinical effectiveness of acupuncture and a Western drug on allergic rhinitis: study protocol for a randomized controlled trial

Yanping Wang, Sheng Chen, Peng Wang, Cheng Tan, Chang Zhang, Zhihong Shi, Jiping Zhao

Yanping Wang, School of Acupuncture-Moxibustion and Tuina, Beijing University of Chinese Medicine, Beijing 100029, China

Sheng Chen, Peng Wang, Cheng Tan, Zhihong Shi, Jiping Zhao, Department of Acupuncture and Moxibustion, Dongzhimen Hospital Affiliated to Beijing University of Chinese Medicine, Beijing 100700, China

Chang Zhang, Chinese Medicine Department, Central Hospital of China Aerospace Corporation of Peking University, Beijing 100049, China

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Correspondence to: Prof. Jiping Zhao, Department of Acupuncture and Moxibustion, Dongzhimen Hospital Affiliated to Beijing University of Chinese Medicine, China. zjp7883@sina.com; **Prof. Sheng Chen**, Department of Acupuncture and Moxibustion, Dongzhimen Hospital Affiliated to Beijing University of Chinese Medicine, China. qdchensheng@126.com

Telephone: +86-10-84013161

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be randomized to receive acupuncture or pharmacotherapy (1: 1) for 4 weeks with a 4-week follow-up. The primary outcome will be changes in 7-day average total nasal symptom score. Secondary outcome measures include rhinoconjunctivitis quality of life questionnaire score and total non-nasal symptom score.

RESULTS: The presence and seriousness of psychological and emotional impairments should be considered in therapeutic programs for allergic rhinitis. No clinical trial for treating allergic rhinitis via acupuncture regulation of psychological and emotional activities has been reported.

CONCLUSION: The findings of the trial will allow us to determine the effects of the mind (Shen)-regulation treatment approach. We will also be able to confirm if the effects of acupuncture are equivalent to those of the conventional drug cetirizine hydrochloride.

Abstract

OBJECTIVE: To compare the efficacy of an acupuncture regimen for persistent allergic rhinitis (PER), aimed at improving a patient's mind or Shen in Traditional Chinese Medicine, to that of a second-generation H₁-receptor antagonist, cetirizine hydrochloride.

METHODS: This multicenter, randomized, controlled clinical trial on PER will be conducted at three institutions in China. The total study period will be 9 weeks. After a 1-week preparatory screening period, 240 eligible participants with PER will

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Key words: Acupuncture; Rhinitis; Psychological and emotional impairment; Mind (Shen)-regulation; Randomized controlled trial

INTRODUCTION

Allergic rhinitis (AR) causes major illness and disability worldwide. Patients from all countries, all ethnic groups, and all ages suffer from AR.¹ The management of AR includes allergen avoidance, pharmacotherapy, immunotherapy, and surgery. Allergen avoidance and pharmacotherapy are first-line treatments for AR, but

recurrence of the disorder makes medication less effective over time. Although a new generation of medications with decreased side effects has been developed, side effects have not been completely eliminated.²

AR is called "Bi Qiu" (running nose) in Traditional Chinese Medicine (TCM) literature. Acupuncture has been used to treat AR since the first TCM classic, *Huang Di Nei Jing*.³ In recent years, clinical trials have been conducted to evaluate the efficacy of acupuncture for AR. Some trials showed that active acupuncture was more effective than sham acupuncture in decreasing the symptom scores for persistent allergic rhinitis (PER) and increasing the number of symptom-free days.^{4,5} In conjunction with routine care, acupuncture leads to clinically relevant and persistent benefits,⁶ is cost-effective according to international benchmarks,⁷ and has shown no serious adverse effects.⁴ However, because of experimental design weaknesses, such as lack of sham or placebo controls, lack of clear selection criteria, and inclusion of a mixture of different allergic rhinitis categories, the conclusions made by these trials are weak. Other problems in previous studies include insufficient details on acupuncture treatment procedures, particularly those related to rationales for acupoint selection and needling techniques.⁸ A systematic review of the clinical effectiveness of acupuncture for AR published in 2008 concluded that "there is currently insufficient evidence to support or refute the use of acupuncture in patients with AR. It is not possible to recommend acupuncture as a proven treatment for AR on the basis of published evidence."⁹ Consequently, 2010 Allergic Rhinitis and its Impact on Asthma (ARIA) guidelines suggest clinicians not administer and patients not use acupuncture.¹⁰

However, trial design weakness and a lack of detailed descriptions of acupuncture treatment procedures could keep the modality from being recommended for AR. Better designed clinical acupuncture trials should be conducted, and reports of study results should conform to the Standards for Reporting Interventions in Clinical Trials of Acupuncture.¹¹ Additionally, new treatment protocols should be developed to improve acupuncture treatment effects so that choices besides pharmacotherapy can be offered to AR patients.

Psychological and emotional dysfunction and allergic rhinitis

Research reveals an interaction between psychological factors and allergic diseases. Allergic diseases can influence the psychological status of individuals to produce imbalances or other disturbances.^{12,13} Marshall *et al.*¹⁴ found that seasonal allergic rhinitis patients reported higher levels of general and mental but not physical fatigue, reduced motivation, and significant mood changes during ragweed season. A similar study also conducted by Marshall *et al.*¹⁵ showed that AR patients experienced subtly slowed cognitive processing speeds and some had difficulty with working memory during rag-

weed season. Kremer *et al.*¹⁶ reported that psychological wellbeing was significantly impaired in patients with symptomatic allergic rhinitis, as shown by higher scores in feelings of insufficiency, complaints of somatization, sleep disturbances, and depressive feelings. Leger *et al.*¹⁷ found that patients with moderate to severe symptoms of intermittent allergic rhinitis or PER suffered from impaired sleep, and all dimensions of sleep were involved. Baybek *et al.*¹⁸ assessed the psychological status of AR patients and found statistically significant differences between patients and controls in all subscales of the Symptom Checklist-90 (SCL-90), particularly in somatization, depression, and general symptom index subscales. A study conducted in China also used SCL-90 to investigate the psychological status in AR patients and got a similar result.¹⁹ Sansone and Sansone²⁰ found that the majority of studies indicate associations between allergies and anxiety and mood syndromes in their review of PubMed and PsycINFO databases. For example, 97.1% of individuals in 10 of 12 studies on depressive syndromes expressed a positive relationship between allergy symptoms and some type of depressive syndrome. Moreover, 99.9% of individuals in nine of 11 studies on anxiety syndromes decisively expressed a positive relationship between allergy symptoms and anxiety syndromes.

On the other hand, allergic symptoms can be triggered and worsened by several psychological factors, including stress. Wright *et al.*²¹ suggested that psychological stress should be conceptualized as a social pollutant that can be "breathed" into the body to disrupt a number of physiological pathways, just as air pollutants and other physical toxicants can lead to increased risk of atopy. Stress might have independent effects in addition to its influence on atopy through its enhancement of neuroimmune responses to other environmental factors that operate through similar pathways. Nishioka *et al.*²² found that exposure to acute restraint stress inhibits antigen-specific antibody production in mice. This response suggests that acute stress has the potential to modulate the initiation of AR. A survey also showed that shy young adults had a higher frequency of hay fever than do extremely outgoing individuals.²³ Investigations into the personality traits of AR patients indicate a correlation between AR and poorer psychological functioning compared with control individuals.^{24,25} Kiecolt-Glaser *et al.*²⁶ observed the effects of stress and anxiety on immediate and late-phase skin test responses in AR and concluded that stress and anxiety can enhance and prolong AR symptoms.

Although the relationship between psychological factors and AR is recognized, few answers are available regarding whether regulating patient psychological and emotional state can improve the therapeutic effects of AR treatment.

Psychological factors and emotions are ascribed to mind, or Shen, in TCM. The aim of the current study is to assess the efficacy of an acupuncture regimen for AR that adds Shen-regulating points to the traditionally

used acupoint formula to improve psychological and emotional states in PER patients. The effect of this regimen will be compared with that of pharmacotherapy.

METHODS

Trial design

This will be a multicenter, randomized, controlled clinical trial comparing the effect of Shen-regulating acupuncture with that of pharmacotherapy in PER. It was registered in Chinese Clinical Trial Register ChiCTR-TRC-11001245. It will be conducted in three institutions in China: Dongzhimen Hospital Affiliated to Beijing University of Chinese Medicine, Beijing Tongren Hospital, and Beijing Hospital of Traditional Chinese Medicine. The total study period will be 9 weeks. After a 1-week preparatory screening, participants will be randomized to receive either acupuncture or pharmacotherapy for 4 weeks with a 4-week follow-up period (Figure 1).

Recruitment

Participants will be recruited through a notice posted in the research hospitals and nearby communities. After screening for eligibility, qualified patients will be informed of the trial design. They will then give their written informed consent and undergo a week-long

preparatory screening consisting of routine blood tests, creatinine (Cr), blood urea nitrogen (BUN), alanine aminotransferase (ALT), and aspartate aminotransferase (AST). These are required as safety indicators for the intervention. Eosinophil (EOS) count and immunoglobulin E (IgE) are also required as efficacy and mechanism indicators, and patients will be asked to keep a diary on nasal and non-nasal symptoms (TNSS and TNNSS) for 1 week. Participants who are qualified but have taken PER symptomatic relief medication in the 14 days before preparatory screening will be instructed to stop therapy for 14 days, after which they may undergo preparatory screening. All qualified patients will be provided with the usual care instructions for AR. After the 1-week preparatory screening period, eligible patients will be enrolled in the trial. Ineligible patients will be thanked and offered routine treatment. Recruitment will continue until recruitment targets are achieved.

Inclusion criteria

Included patients must be diagnosed with AR plus persistent PER and classified as moderate to severe depending on the severity of symptoms and quality of life outcomes.¹ Participants must be between 18 and 60 years old, be well informed about the study, and have signed the written informed consent form. Their 7-day mean Total Nasal Symptom Score (TNSS) must be ≥ 4 .²⁷

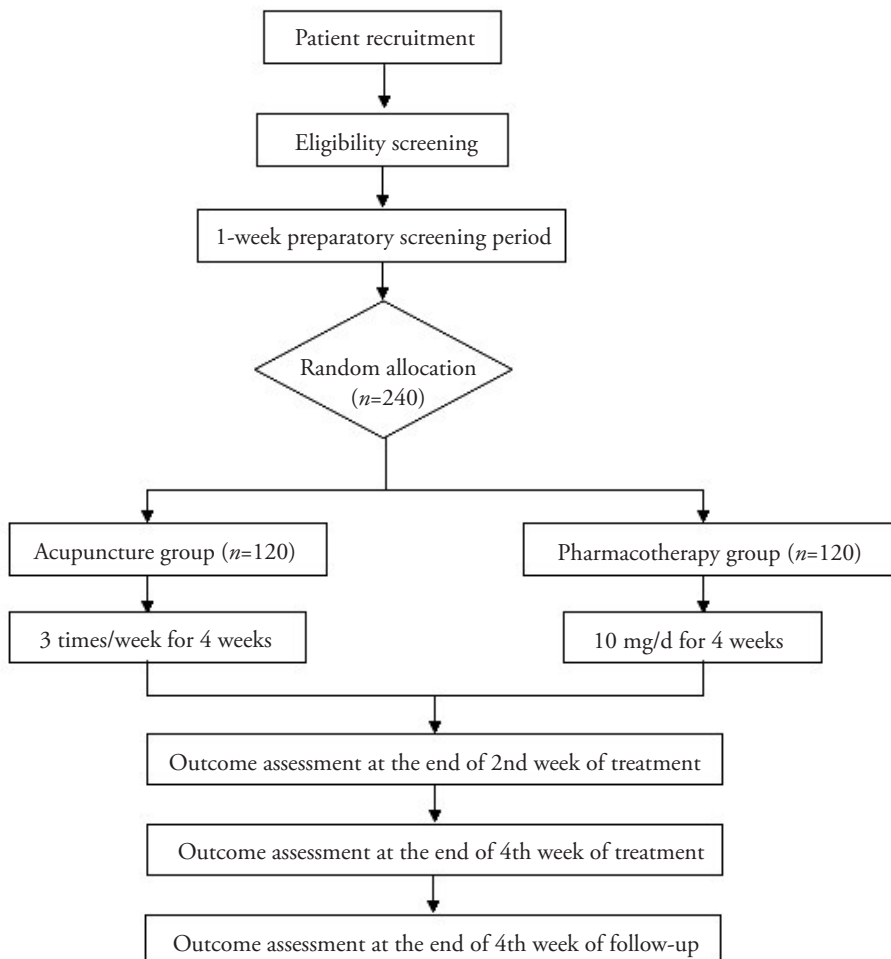


Figure 1 Study flow chart

Exclusion criteria

Individuals will be excluded from the study if any of the following are applicable. (a) Patients have suffered from diseases related to the nose, paranasal sinus, or upper respiratory tract such as acute paranasal sinusitis or an upper respiratory infection within the last 14 days; show signs of chest inflammation in an X-ray; have a history of chronic paranasal sinusitis as shown by accessory nasal cavity X-ray examination; or have had organic nasal cavity disease, have undergone nasal cavity surgery, or have paroxysmal respiratory diseases such as asthma. (b) Patients are receiving or have received treatment that might influence the assessment of results including H₁ antihistamines, steroids, antihistamines, decongestants (nasal, oral, or ophthalmic), corticosteroids, or antibiotics within 14 days of enrollment; have had specific immunotherapy or systematic hormone therapy in the last year; have had acupuncture, moxibustion, cupping, nasal inhalation of herbal medicine, or other physical alternative medicine therapy within the last 14 days; or have taken herbal preparations for AR within the last 14 days. (c) Patients that have suffered from mental disorders, tuberculosis, hepatitis, or have blood Cr or AST/ALT values twice the normal level. (d) patients that are pregnant, lactating, or planning to become pregnant. (e) Patients that have a history of smoking more than 10 cigarettes daily over 10 consecutive years. (f) Patients presenting with scars at the acupoint locations or suffering from a systemic disease and are therefore considered unsuitable for acupuncture. (g) Patients that are determined to be unable to cooperate in the trial.

Sample size

As we did not conduct a pilot study on acupuncture for PER, we searched the literature for the effective rate parameters of acupuncture in AR and used those to calculate the sample size. The literature shows that the effective rate of acupuncture in most AR/acupuncture studies is between 85% and 90%,^{28,29} and the effective rate of cetirizine hydrochloride for AR in China is also between 85% and 90%.^{30,31} Because our study is a noninferiority trial, we calculated the sample size based on a noninferiority clinical trials design. The formula used is: $N = ([P_0q_0 + P_1q_1] / \Delta^2) \times (Z_{\alpha} + Z_{\beta})^2$ (Bolton, Kim, 1997).

Type I error is controlled under 0.05, type II error is controlled under 0.20 (power of test is 80%), the alpha value is 5% (single-tailed), the beta value is 20%, (single-tailed), $P_0=0.85$, $q_0=0.15$, $P_1=0.85$, $q_1=0.15$, and $d=0.15$.

The results indicate that there should be 98 subjects in each group. A 1:1 ratio was applied to both groups. We plan to enroll 120 participants in each group to allow for a 20% dropout rate.

Randomization and blindness

A central stratified block randomization will be designed for this study by the central randomization sys-

tem. Stratified randomization will be performed by each center. After inclusion of an eligible patient, researchers can log into the web edition of the Central Randomization System for Clinical Research or use the telephone edition developed by the Clinical Research Centre of China Academy of Chinese Medical Sciences to get the randomized number for group assignment. The randomized numbers are produced by professional biostatisticians with SAS 9.3.1 software (SAS Institute Inc., Cary, NC, USA). A total of 240 participants will be randomized to receive acupuncture or pharmacotherapy at the three trial centers in a 1:1 ratio. The number of researchers at the three centers differs. Therefore, the number of patients enrolled at each center will be unequal: Dongzhimen Hospital Affiliated to Beijing University of Chinese Medicine will have 100; Beijing Tongren Hospital, 80; and Beijing Hospital of Traditional Chinese Medicine, 60. The researcher performing outcome assessments and the trial biostatistician analyzing the study data will be blinded to participant group allocation. However, patients and the acupuncturists who perform the treatment will not be blinded due to the nature of the trial in which the patient could easily tell whether they receive acupuncture treatment or medicine.

Intervention

Acupuncture intervention: participants in the acupuncture group will be treated by certified acupuncturists at the three centers. Acupuncture treatment will be given three times a week for 4 weeks in a total of 12 sessions. The treatment protocol is intended to eliminate AR symptoms and improve patients' psychological and mental states.

The acupuncture points used will be Yingxiang (LI 20), Yintang (GV 29), Hegu (LI 4), Dazhui (GV 14), Feishu (BL 13), Pishu (BL 20), Shenshu (BL 23), Ganshu (BL 18), Taichong (LR 3), and Baihui (GV 20). Acupoints are located according to the People's Republic of China, State Standard Name and Location of Acupoints (GB 12346-2006).³² Needles will be 0.25 mm (diameter) × 40 mm (length) disposables (Beijing Zhongyan Taihe Medicine Co., Ltd., Beijing, China). With the patient prone, the back points, Dazhui (GV 14), Feishu (BL 13), Pishu (BL 20), Shenshu (BL 23), and Ganshu (BL 18), will be needled. After de-*Qi* sensations are felt by the patient and acupuncturist, reinforcing manipulation will be performed for 30 s, then the needles will be withdrawn.

The other five points will be needled with the patient supine. After de-*Qi*, the practitioner will apply even reinforcing and reducing manipulation for 30 s. Then, Yintang (GV 29) and Baihui (GV 20), and bilateral Yingxiang (LI 20) will be connected to a Han's Electroacupuncture Apparatus (Nanjing Jisheng Medical Medical Technology Co., Ltd., Nanjing, China). The 2/100 Hz sparse-dense waves will be applied at an intensity within participants' tolerance. Needles will be re-

tained for 20 min. During retention, the practitioner will lift, thrust, and rotate the needles at Hegu (LI 4) and Taichong (LR 3) for 10 s to maintain or intensify the needle sensation.

The acupuncture treatment procedure (Table 1) will be standardized in the three centers by a training session conducted before the beginning of the study.

Pharmacotherapy

Participants in the pharmacotherapy group will take 10 mg of cetirizine hydrochloride (Lunan Pharmaceutical Group Corp., Linyi, China) orally once a day for 4 weeks. Patients will receive a 2-week supply of the drug twice during the study period, the first time during enrollment in the pharmacotherapy group and the second at the beginning of the third week of the study.

Outcome measures

Primary outcomes: nasal symptoms will be assessed with a 7-day average TNSS^{5,33} that will be reviewed by an assessor blinded to the participants' treatment groups at the end of the 1-week preparatory screening period, the second and fourth weeks of treatment, and the fourth week of the follow-up period. TNSS will be determined by four nasal symptoms, self-assessed daily, and recorded in a diary by participants throughout the study.

Secondary outcomes

Quality of life will be assessed with the Rhinoconjunctivitis quality of life questionnaire (RQLQ) score.³⁴ RQLQ consists of 28 items and seven domains: activity, sleep, nasal symptoms, ocular symptoms, non-nose/non-eye symptoms, practical problems, and emotions. Each item is rated from 0 (not troubled) to 6 (extremely troubled). RQLQ will be assessed by researchers at the end of the 1-week preparatory screening period, the second and fourth weeks of treatment, and the follow-up period.

Non-nasal symptoms will be assessed by the 7-day average total non-nasal symptom score (TNNSS).³³ TNNSS will be self-assessed daily and recorded in a di-

ary by participants through the study. Scores will be reviewed by an assessor blinded to the participants' treatment group at the end of the 1-week preparatory screening period, the second and fourth weeks of treatment, and the follow-up period.

The use of PER relief medication will be recorded on the medication quantification scale during the follow-up period.

Immunological state change will be assessed by EOS count and total serum total IgE in the preparatory period and after the treatment period as an efficacy and mechanism indicator.

Adverse events

Any unexpected events will be recorded on an adverse event report form during the trial.

Blood, liver function, and kidney function will be tested by a routine blood test, Cr, BUN, ALT, and AST during preparatory screening and after 4 weeks of treatment.

Data collection

Data will be collected throughout the trial. TNSS and TNNSS will be collected from participants' diaries during their visits.

Statistical analysis

Baseline and efficacy data will be respectively analyzed with the full analysis set and per-protocol set. Adverse effect data will be analyzed with the safety set.

Statistical analyses will be performed using the SPSS statistical package program (ver. 9.1.3, SAS Institute Inc., Cary, NC, USA), and the level of significance will be established at $\alpha=0.05$.

Baseline analyses

Demographic data (age, sex ratio, duration of PER, and family history of PER) and clinical characteristic data (TNNS, TNNSS, and RQLQ) of study participants will be collected before randomization. Acupuncture and pharmaceutical group data will be compared to identify potential imbalances not accounted for by

Table 1 Acupoints and needling procedure

Acupoint	Angle and direction	Depth (mm)
Yingxiang (LI 20)	Transversely, along the nasolabial sulcus towards the root of nose	13-26
Yintang (GV 29)	Transversely, downward toward the nose	13-21
Hegu (LI 4)	Perpendicular to the skin	13-26
Dazhui (GV 14)	Perpendicular to the skin	21-32
Feishu (BL 13)	Obliquely toward the spine	13-21
Pishu (BL 20)	Obliquely toward the spine	13-21
Shenshu (BL 23)	Perpendicular to the skin	13-26
Ganshu (BL 18)	Obliquely toward the spine	13-21
Taichong (LR 3)	Perpendicular to the skin	13-21
Baihui (GV 20)	Transversely, anterior to the forehead	13-21

randomization. The *Chi*-square test will be used for demographic enumeration data, while the student's *t*-test will be used for measurement data. Student's *t*-test or Wilcoxon rank-sum test will be used for clinical characteristic data.

Efficacy analysis of outcomes

All data will be analyzed descriptively. Changes in TNSS, TNNSS, RQLQ, EOS, and total serum IgE of the two groups will be compared with the student's *t*-test or Wilcoxon rank-sum test. If there are baseline differences between the two groups, ANOVA will be used.

Safety analysis

Frequency of adverse events in the two groups will be compared with the *Chi*-square test or Fisher's exact test.

Data management

Researchers performing outcome measurements will enter the collected data into case report forms. Data from all centers will be pooled and randomized according to demographic baseline characteristics, effectiveness, and safety observations. Regular data monitoring will be conducted for quality control.

DISCUSSION

AR includes more than the classical symptoms of sneezing, rhinorrhea, and nasal obstruction. AR is also associated with mental and psychological problems.¹ Patients may suffer from mental fatigue, mood changes,^{14,15} cognitive impairment, and sleep problems.^{16,17} AR is associated with higher rates of depression and anxiety disorder, and outpatient healthcare expenditures for patients are 207 USD higher on average annually when AR and anxiety disorder are comorbid and 363 USD when AR and depression are comorbid.^{18,20,35} Therefore, the presence and seriousness of these mental and psychological impairments should be taken into consideration in therapeutic programs for allergic rhinitis.³⁶ The routine acupuncture treatment for AR has traditionally focused on the nasal symptoms without consideration of possible mental and psychological impairments. In an authoritative TCM textbook, AR is attributed to Lung, Spleen, and Kidney deficiency. Exogenous pathological factors, Wind, and Cold invade the Lung and affect the nose, resulting in nasal symptoms such as rhinorrhea, sneezing, nasal congestion, and nasal itching.³⁷ Therefore, we selected Yingxiang (LI 20) and Yintang (GV 29), local points around the nose, to relieve nasal symptoms; Hegu (LI 4) and Dazhui (GV 14), to expel wind and cold; and Feishu (BL 13), Pishu (BL 20), and Shenshu (BL 23), the Back-Shu points of the Lung, Spleen, and Kidney, respectively, to regulate those organs. Based on our understanding of the reciprocal effects of mental and psychological factors and allergic symptoms, we will add points that regulate the mind and improve psychological wellbeing. In TCM

theory, emotions and psychological factors are ascribed to mind (Shen). Therefore, points that regulate Shen might help to regulate emotion and improve psychological activity. The Liver, in TCM, ensures the smooth flow of *Qi*, which has a deep influence on the emotional state,³⁸ and the Brain is where the primordial Shen resides. Therefore, these two organs actively regulate Shen. The Shen-regulating points we will use are Ganshu (BL 18), the Back-Shu points of Liver; Taichong (LR 3), the Yuan-source points of the Liver Channel; and Baihui (GV 20), a local point for the Brain and a crossing point of Governor Vessel and Liver Channel. These three points are related to Liver and Brain function and are believed to calm the mind and regulate the emotions in TCM theory. Consequently, we hypothesize that they will regulate psychological and emotional imbalance in AR patients.

Cetirizine hydrochloride, a second-generation H₁-receptor antagonist, works to treat allergy symptoms by decreasing histamine in the body. Though not recommended as the first choice therapy for moderate to severe persistent rhinitis in ARIA,¹ it is the first-line medicine for AR in China.

To our knowledge, no AR clinical trial evaluating acupuncture regulation of patients' psychological and emotional activities has been reported.

The findings of the trial will allow us to determine the effects of the mind (Shen)-regulation treatment approach, and we anticipate discovering whether acupuncture is equivalent to those of the conventional drug cetirizine hydrochloride.

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