

Clinical Efficacy of Acupuncture as Adjunctive Therapy for Cough Variant Asthma: Study Protocol for a Pilot Randomized Controlled Trial

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Background: Cough variant asthma (CVA) is a clinically significant asthma phenotype and a major cause of chronic cough, with a substantial risk of progressing to classic asthma. Acupuncture has shown potential in alleviating cough, modulating airway inflammation, and improving quality of life, though high-quality evidence in CVA remains limited. This multicenter pilot trial aims to evaluate the feasibility and preliminary efficacy of acupuncture as adjunctive therapy for CVA.

Methods and Analysis: This multicenter, randomized, sham-controlled pilot trial is designed to assess the feasibility, safety, and preliminary efficacy of acupuncture as adjunctive therapy for CVA. Eighty-eight participants will be randomized 1:1 to receive real acupuncture (RA) or sham acupuncture (SA), in addition to inhaled corticosteroid (ICS)-based standard care. The intervention comprises 16 sessions over 8 weeks, with an additional 8-week follow-up. The primary outcome is the effective response rate at week 8, defined as a $\geq 50\%$ reduction in cough severity on the visual analogue scale (VAS). Secondary outcomes include patient-reported measures such as the Cough Severity Diary (CSD), Cough Hypersensitivity Questionnaire (CHQ), Cough Evaluation Test (CET), and Leicester Cough Questionnaire (LCQ); psychological and sleep assessments using the Hamilton Anxiety Scale (HAMA), Hamilton Depression Scale (HAMD), and Pittsburgh Sleep Quality Index (PSQI); and objective biomarkers including fractional exhaled nitric oxide (FeNO) and peripheral blood eosinophil counts.

Ethics and Dissemination: Ethical approval was obtained from the Medical Ethics Committee of the Affiliated Hospital of Chengdu University of Traditional Chinese Medicine (No. 2024KL-208). The results of this study will be distributed through peer-reviewed journals.

Clinical Trial Registration: <https://itmcctr.ccebtcm.org.cn>, identifier ITMCTR2025000435. Registered on 27 February 2025.

Keywords: cough variant asthma, acupuncture, randomized controlled trial, study protocol

Introduction

Cough-variant asthma (CVA) is a distinct phenotype of asthma characterized by chronic cough as the predominant or sole symptom, without wheezing, chest tightness, or dyspnea.¹ The cough is often nocturnal or exercise-induced and may be productive in some patients. Routine spirometry is frequently normal, whereas airway hyperresponsiveness represents the principal physiological abnormality detected by bronchial provocation testing.² Unlike other chronic cough conditions, such as non-asthmatic eosinophilic bronchitis, CVA is characterized by variable airway obstruction and bronchial hyperresponsiveness, which contribute to persistent cough and increased risk of progression to classic asthma.³ CVA accounts for approximately 25–42% of chronic cough cases in China and Japan and represents one of the most common etiologies in Europe and the United States.⁴ Beyond respiratory symptoms, CVA substantially impairs physical health,

psychologic well-being, and social functioning.⁵ Risk factors for disease progression include heightened airway hyper-responsiveness, sputum eosinophilia, atopic status, and prolonged disease duration.⁶ Importantly, up to one-third of patients may progress to classic asthma if not adequately treated,^{7,8} underscoring the importance of prompt therapeutic intervention to prevent disease advancement and optimize outcomes.^{9,10}

Current guidelines recommend inhaled corticosteroids (ICS), alone or in combination with bronchodilators, as first-line therapy for CVA, with continued use for at least three months following symptom control.^{1,11,12} Although ICS effectively suppress airway inflammation and alleviates cough, several challenges remain in clinical practice.¹³ A proportion of patients exhibits suboptimal responses, and long-term adherence is often limited by concerns regarding prolonged use and potential adverse effects.^{14,15} Other pharmacological options, such as montelukast, demonstrate clinical benefits¹⁶ but are associated with neuropsychiatric side effects including nightmares, depression, and insomnia.¹⁷ These limitations highlight the need for complementary or adjunctive interventions that are both effective and well tolerated.

Acupuncture is a widely used complementary and alternative therapy with a long history in managing chronic respiratory diseases. Accumulating evidence suggests that acupuncture may alleviate chronic cough by modulating airway inflammation, regulating immune responses, and attenuating cough hypersensitivity. Previous studies have reported improvements in cough symptoms, quality of life, inflammatory cell profiles,^{18,19} peak expiratory flow variability,²⁰ and forced expiratory volume in one second following acupuncture interventions.²¹ Preliminary observations further indicate that acupuncture may enhance treatment response in CVA, reduce relapse after medication withdrawal, and improve pulmonary and immunological markers.²² However, existing studies are often limited by small sample sizes, methodological heterogeneity, and inadequate controls, leaving the clinical value of acupuncture for CVA insufficiently defined.²²

To address these gaps, we designed a multicenter, randomized, sham-controlled pilot trial to evaluate the feasibility, safety, and preliminary efficacy of acupuncture as an adjunctive therapy for patients with CVA. The findings of this study are expected to inform the design of future large-scale randomized controlled trials and provide methodological references for optimizing acupuncture-based interventions in CVA management.

Materials and Methods

Study Design

This study is a multicenter, two-arm, randomized clinical trial designed to evaluate the efficacy of acupuncture in patients with CVA. The trial will be conducted at four hospitals in China. Eligible participants will be randomly allocated in a 1:1 ratio to either real acupuncture (RA) group or the sham acupuncture (SA) group. The study will include three phases: screening period, an 8-week treatment phase, and an 8-week follow-up period, with a total duration of 16 weeks. Ethical approval has been obtained from the Medical Ethics Committee of the Hospital of Chengdu University of Traditional Chinese Medicine and the institutional review boards of all participating centers. All investigators and clinical staff have completed standardized training in accordance with the study protocol to ensure methodological consistency across sites. Recruitment commenced on March 1, 2025, and is anticipated to continue through January 2026. The trial protocol has been developed in compliance with the SPIRIT statement,²³ and the reporting of trial results will adhere to the Consolidated Standards of Reporting Trials (CONSORT) guidelines,²⁴ including an extension of the Revised Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA).²⁵ A flow diagram of the study design is provided in [Figure 1](#), and the schedule of enrollment, interventions, and assessments is summarized in [Table 1](#).

Participants

Inclusion Criteria

Participants who meet the diagnostic criteria for CVA according to the Global Initiative for Asthma (GINA) 2024 will be eligible for inclusion. Specifically, CVA is characterized by a chronic cough lasting longer than 8 weeks, positive bronchial provocation test, and symptom improvement with ICS or bronchodilators in the absence of wheezing or dyspnea. Eligible participants must also meet all of the following criteria: (1) Male or female participants aged 18–60

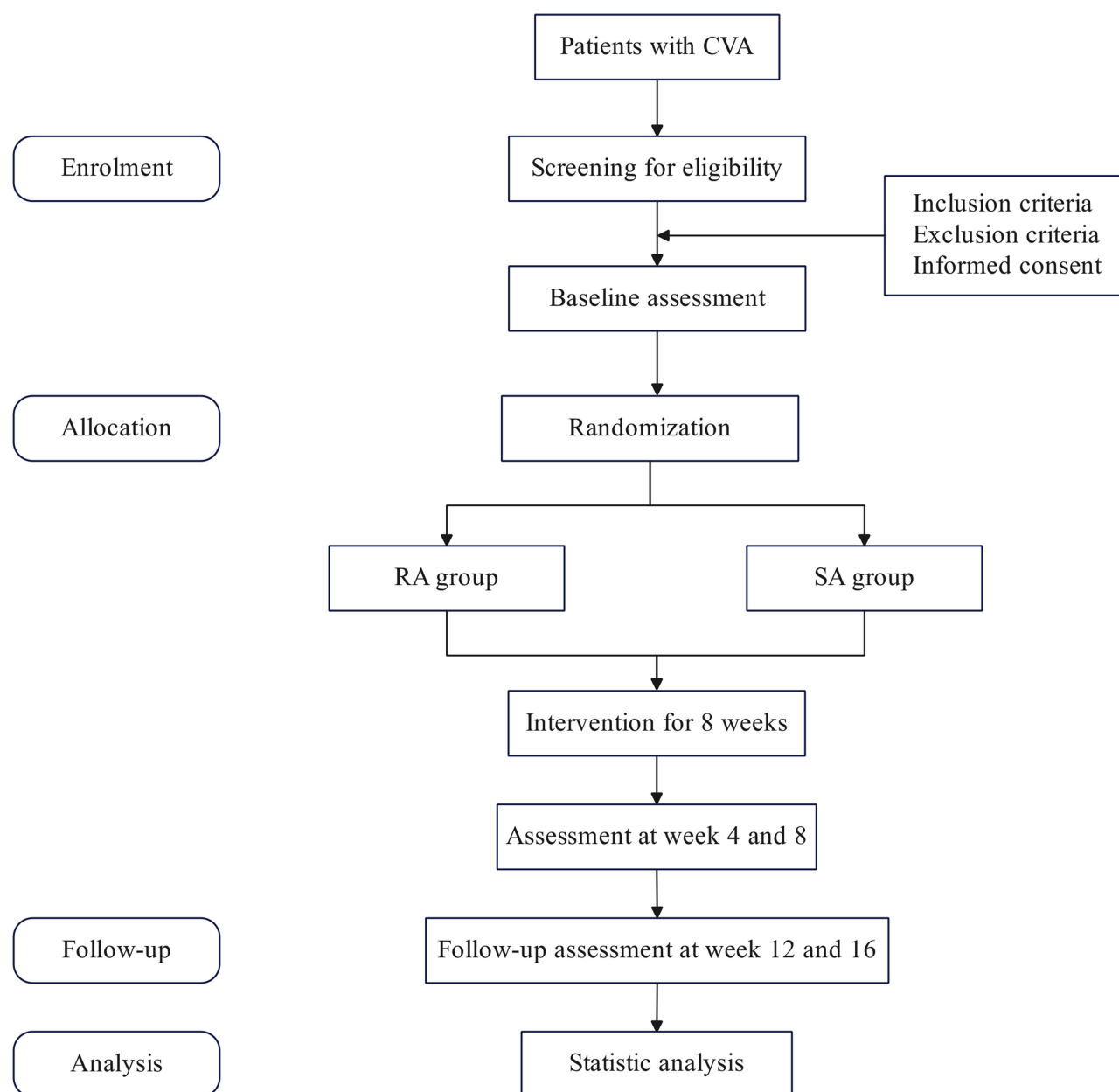


Figure 1 Flow chart.

years. (2) Received regular anti-asthmatic treatment (primarily bronchodilators and/or ICS) for at least 4 weeks, with incomplete symptom relief and a cough severity visual analogue scale (VAS) score >30 mm. (3) Willing and able to provide written informed consent and voluntarily participate in the study.

Exclusion Criteria

Participants will be excluded if they meet any of the following conditions: (1) History of acute respiratory infection within the past 2 weeks or presence of an active respiratory infection, such as common cold, pneumonia, or active pulmonary tuberculosis. (2) Presence of other chronic respiratory disease with symptoms beyond cough, such as typical asthma or chronic obstructive pulmonary disease (COPD), where dyspnea or wheezing predominates. (3) Diagnosis of cancer, psychiatric illness, cognitive impairment, or significant hearing impairment that may interfere with

Table 1 Schedule of Enrollment, Intervention, and Assessments

	Enrollment	Baseline	Intervention		Follow-Up	
Time Points	Week 4	Week 0	Week 4	Week 8	Week 12	Week 16
Enrollment						
Eligibility screen	×					
Informed consent		×				
Demographic characteristics		×				
Disease history		×				
Combined disease		×				
Medication history		×				
Allocation		×				
Interventions						
Real acupuncture			→			
Sham acupuncture			→			
Laboratory Tests						
Bronchial provocation test	×					
FeNO		×		×		
Blood detection		×		×		
Assessment						
CSD		×	→		×	×
CHQ		×	×	×	×	×
LCQ		×	×	×	×	×
CET		×	×	×	×	×
HAMA		×		×		×
HAMD		×		×		×
PSQI						
Blinding assessment				×		
Safety assessment			×	×		
Adherence evaluation				×		×

Notes: × indicates assessment performed; → indicates ongoing treatment or assessment during the period.

Abbreviations: FeNO, fractional exhaled nitric oxide; CSD, cough severity diary; CHQ, cough hypersensitivity questionnaire; LCQ, Leicester cough questionnaire; CET, cough evaluation test; HAMA, Hamilton anxiety scale; HAMD, Hamilton depression scale; PSQI, Pittsburgh sleep quality index.

communication or compliance. (4) Local skin lesions or contraindications at acupoint sites, such as burns, eczema, ulcers, frostbite with ulceration, or coagulation disorders. (5) Pregnancy, lactation, or intention to conceive during the study period. (6) Participation in another clinical trial within the past 6 months or current enrollment in another clinical study.

Written Informed Consent

Prior to randomization, all potential participants will be informed of the study purpose, procedures, potential benefits, and risks. Written informed consent will be obtained from those who agree to participate. Participation is entirely voluntary, and individuals may withdraw from the study at any time. The reason for withdrawal will be documented in the case report form (CRF), and no penalty or loss of entitled benefits will be incurred. To facilitate communication and ensure adherence, participants will be asked to provide a telephone number for regular contact by the research team.

Patient Adherence

To promote adherence, participants will first receive detailed explanations during the informed consent process. The study procedures, potential benefits and risks, and individual responsibilities will be clearly communicated. Patients will be informed that acupuncture is provided as an adjunct to conventional therapy and does not increase treatment risks. Standardized instructions regarding the procedure, safety, and possible efficacy will be delivered to reduce anxiety. During the trial, psychological support and encouragement will be provided, while communication with family members will be maintained to reinforce compliance. Each treatment session will be recorded on standardized forms, documenting dates, procedures, and responses, which allows for continuous monitoring. All trial-related tests and treatments will be offered free of charge. Participants completing the study will receive appropriate compensation. Withdrawals and their reasons will be systematically recorded during follow-up to ensure transparent reporting.

Randomization, Allocation, Concealment, and Blinding

Participants will be randomized in a 1:1 ratio to the RA or SA groups using a computer-generated sequence generated centrally by an independent statistician. Given the multicenter design, stratified block randomization by study center will be applied to ensure balanced allocation across sites. Allocation concealment will be maintained using sequentially numbered, opaque, sealed envelopes opened only after participant enrollment. Participants, outcome assessors, data managers, and statisticians will be blinded to group allocation. Because of the nature of acupuncture, practitioners cannot be blinded but will not be involved in outcome assessment or data analysis. To minimize unblinding, treatments will be conducted in individual cubicles with restricted communication between participants. The sham acupuncture procedure is designed to maintain participant blinding by using non-penetrating or superficial stimulation at non-therapeutic points, which has been shown to achieve acceptable blinding credibility in acupuncture trials. After completing all interventions, participants will be asked to identify whether they believed they received real or sham acupuncture, and blinding effectiveness will be assessed using the proportion of correct guesses and the Bang blinding index will be used where appropriate.

Interventions

The treatment protocol is developed based on acupuncture and traditional Chinese medicine (TCM) theory, supported by previous literature research and expert consensus. Two intervention arms will be established: RA and SA. All patients will continue to receive conventional pharmacological managements as recommended by GINA 2024 guidelines.¹ The intervention design follows the STRICTA recommendations.²⁵ Licensed acupuncturists with over three years of experience will perform the interventions. Acupoint locations will be determined in accordance with the National Standard of the People's Republic of China (GB/T 12346–2021).²⁶ All selected acupoints are located on the upper back, neck, and extremities. Patients will be treated in the prone position to facilitate blinding. To enhance credibility, both groups will use identical needling devices. For most acupoints, a rubber pad will be applied to prevent patients from distinguishing whether needle penetration has occurred, except at Lieque (LU7) (Figure 2). Sham control will be achieved through a combination of real acupoints with sham needling and sham acupoints with real needling. Participants will undergo 16 treatment sessions over 8 weeks, with two sessions per week (2–3-day intervals). Each session will last approximately 30 minutes.

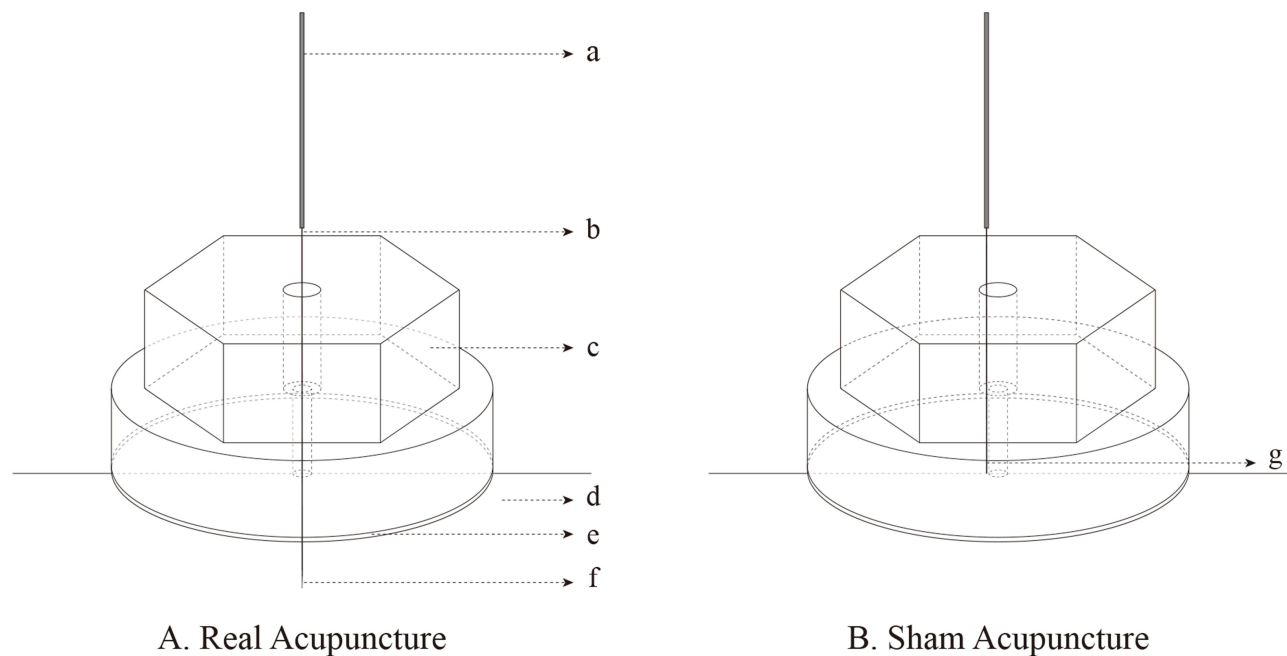


Figure 2 The diagram of acupuncture devices. **(A)** Real acupuncture device; **(B)** Sham acupuncture device; a. Needle handle; b. Needle body; c. Double-layer rubber cushion; d. skin; e. Paster; f. Needle tip; g. Blunt tip.

Real Acupuncture Group

The acupoints used in this group are composed of 6 fixed acupoints, including Fengchi (GB 20), Dazhui (DU 14), Feishu (BL 13), Pihu (BL 42), Lieque (LU 7), Zhaohai (KI 6). Detailed descriptions of those acupoints are provided in [Table 2](#) and [Figure 3](#). After skin sterilization, disposable stainless 1 cun needles (0.25mm×25mm; Huatuo Suzhou, China) will be inserted. Lieque (LU 7) will be obliquely punctured toward the proximal end at an angle of 60° to a depth of 0.3–0.5 cun. Other acupoints will be needled through rubber pads ([Figure 2A](#)): Fengchi (GB 20), Dazhui (DU 14), Feishu (BL 13), and Pihu (BL 42) will be punctured perpendicularly 0.5–0.8 cun, while Zhaohai (KI 6) will be punctured perpendicularly 0.3–0.5 cun. Mild, equal manual stimulation (twirling, lifting, and thrusting) will be applied to elicit *deqi*, typically described as soreness, numbness, distension, or heaviness. Needles will be retained for 30 minutes. Bilateral Feishu (BL

Table 2 Location of Acupoint

Acupoints	Locations
Dazhui (GV 14)	On the back of the neck, in the depression below the spinous process of the seventh cervical vertebra, on the posterior midline.
Fengchi (GB 20)	In the nape of the neck, below the occipital bone, in the depression between the upper end of the sternocleidomastoid muscle and the upper end of the trapezius muscle.
Feishu (BL 13)	On the back, 1.5 cun lateral to the depression below the spinous process of the 3rd thoracic vertebra.
Pihu (BL 42)	On the back, 3 cun lateral to the depression below the spinous process of the 3rd thoracic vertebra.
Lieque (LU 7)	On the lateral aspect of the forearm, 1.5 cun above the distal transverse crease on the palmar side of the wrist, in the depression between the tendon of the extensor pollicis brevis and the tendon groove of the abductor pollicis longus.
Zhaohai (KI 6)	On the medial aspect of the foot, 1 cun below the inner ankle bone, in the depression at the edge of the inner ankle bone.
Sham LU 7	On the lateral aspect of the forearm, 5 cun above the LU 7, at the midpoint between the Lung Meridian of Hand-Taiyin and the Large Intestine Meridian of Hand-Yangming.

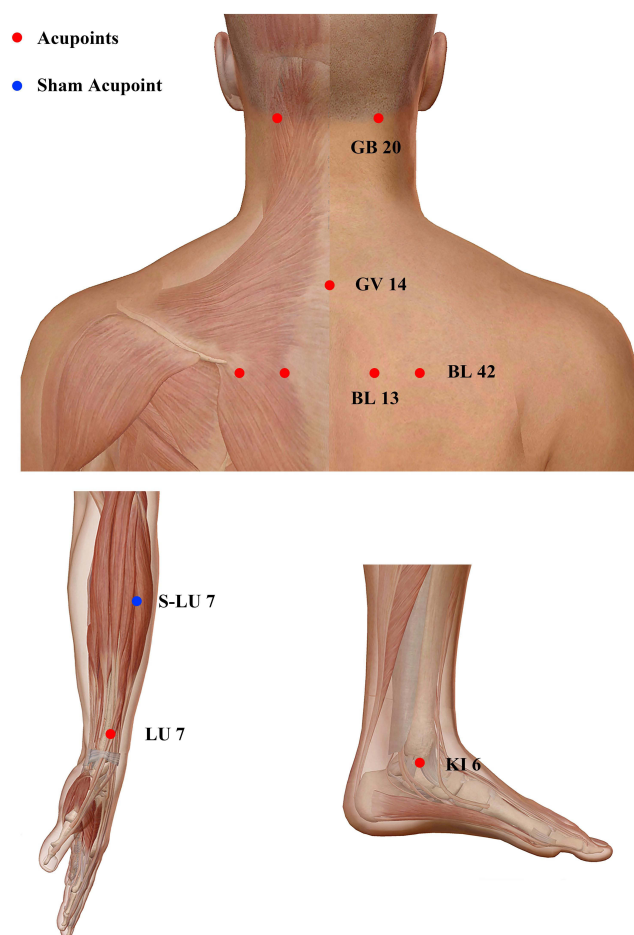


Figure 3 Locations of acupoints.

13) and Pohu (BL 42) will be connected to an electroacupuncture (EA) device delivering continuous waves at 80 Hz, with intensity gradually increased to the maximum level tolerated by participants (0.1–1 mA).

Sham Acupuncture Group

To ensure successful blinding, the acupoint set in the SA group will mirror that of the RA group, except that Lieque (LU 7) will be replaced by a non-acupoint, termed sham Lieque (S-LU 7). Its positioning follows two principles: (1) the site is located away from recognized meridians and acupoints; (2) its distribution area is similar to that of the acupuncture acupoints to avoid patients differentiating groups by the location of acupoints. This is common practice for sham controls in acupuncture research.^{27,28} Sham Lieque (S-LU 7) will be superficially punctured by disposable stainless needles (0.25mm×13mm; Huatuo Suzhou, China) for 0.1–0.2 cun. For all other points, specially designed sham stainless steel needles with blunt tip will be used, rendering it difficult to pierce the skin and enter the subcutaneous tissue (Figure 2B). No manual stimulation for *deqi* will be performed. Although bilateral Feishu (BL 13) and Pohu (BL 42) will be connected to an EA device identical to that used in the RA group, no electrical current will be delivered. To meet ethical requirements, participants in the SA group will be offered free acupuncture treatment after study completion.

Basic Treatment and Rescue Medication

According to the GINA 2024 guidelines,¹ CVA should be managed following the same principles as typical asthma, with ICS or ICS combined with long-acting β_2 -agonists (LABA) recommended as maintenance therapy. In this study, all patients will receive budesonide-formoterol dry powder inhaler (budesonide 160 μ g and formoterol fumarate 4.5 μ g per inhalation), administered as one inhalation twice daily (morning and evening).

Any changes in concomitant medications during the study will be recorded in the CRF, including drug name, dosage, frequency, route, and duration of administration.

Outcome Measurements

Primary Outcome

The primary outcome will be the effective response rate at week 8, defined as the proportion of patients with a $\geq 50\%$ reduction in cough severity VAS (as part of the Cough severity diary) from baseline, maintained for at least 3 consecutive days.

Secondary Outcome

Secondary outcomes will include validated patient-reported outcome measures, psychological assessments, sleep quality indices, and biomarkers of airway inflammation. These are summarized below:

- (1) Cough severity diary (CSD): The CSD ([Supplementary Table 1](#)) captures the patient's perception of cough frequency, intensity, and related disruption. It includes a series of seven items: three addressing frequency, two assessing intensity, and two evaluating disruptiveness. Each item is scored on an 11-point numeric rating scale ranging from 0 to 10 with anchors on each end, with higher scores indicating greater severity.^{29,30}
- (2) Cough hypersensitivity questionnaire (CHQ): The CHQ is designed to evaluate cough hypersensitivity, with a particular focus on laryngeal symptoms and common triggers such as temperature changes or speaking. It comprises 22 dichotomous items, including 6 on sensations and 16 on triggers. The total score, obtained by summing all affirmative responses after unidimensionality testing, represents the level of cough hypersensitivity.^{31,32}
- (3) Cough evaluation test (CET): The CET is a brief, five-item self-reported tool evaluating cough frequency during the day, nocturnal disturbance, intensity, interference with daily life, and associated emotional distress. Each item is rated on a 5-point Likert scale with total scores ranging from 5 to 25. Higher scores denote greater symptom burden. The CET has demonstrated good validity and responsiveness.³³
- (4) Leicester cough questionnaire (LCQ): The LCQ consists of 19 items scored on a 7-point Likert response scale, measuring cough-related impact across physical, psychological, and social domains. Domain scores (range 1–7) are averaged, and a total score (range 3–21) is calculated by summation. Higher scores indicate better health-related quality of life.^{34,35}
- (5) Hamilton anxiety scale (HAMA): The HAMA is a clinician-administered tool with 14 items, covering psychic anxiety (mental agitation and psychological distress) and somatic anxiety (physical complaints related to anxiety). Each item is rated on a 5-point scale (0–4), yielding a total score from 0 to 56, where higher scores indicate more severe anxiety.³⁶
- (6) Hamilton depression scale (HAMD): The HAMD (17-item version) evaluates depressive symptoms including mood, guilt, suicidality, insomnia, work impairment, psychomotor changes, and somatic symptoms. Items are scored on a 3- or 5-point scale, and total scores classify depression severity.³⁷
- (7) Pittsburgh sleep quality index (PSQI): The PSQI assesses sleep quality over the past month across seven domains: sleep latency, duration, efficiency, subjective quality, disturbances, medication use, and daytime dysfunction. Global score reflects overall sleep quality, with higher scores indicating poorer sleep.^{38,39}
- (8) Fractional concentration of exhaled nitric oxide (FeNO): FeNO is a non-invasive biomarker of airway inflammation, particularly type 2 (eosinophilic) inflammation. It will be measured using standardized breath analysis. FeNO assists in asthma diagnosis, monitoring, and treatment adjustment.⁴⁰
- (9) Peripheral blood eosinophil counts: Peripheral eosinophil levels provide a practical and reproducible surrogate marker of airway eosinophilic inflammation and are strongly correlated with induced sputum eosinophilia in asthma and CVA.⁴¹

Safety and Adverse Events

All adverse events (AEs) will be systematically monitored and documented by patients, outcome assessors, and acupuncturists using standardized forms. Information such as type, onset, duration, severity, and outcome will be collected. Within 24 hours, acupuncturists will classify each AE as treatment-related or not. Common acupuncture-related events may include dizziness, subcutaneous hematoma, local bleeding, pain, and itching. Appropriate management will be provided as needed. Serious AEs will be reported immediately to the principal investigators and ethics committees, and affected participants will be withdrawn from the study.

Sample Size

This pilot trial is designed to evaluate feasibility and generate preliminary data for a subsequent definitive RCT. Methodological guidance suggests that 20–40 participants per group are generally sufficient for pilot studies.⁴² After consultation with statisticians, methodologists, and acupuncturists, we determined a sample size of 35 per group. Allowing for a 20% dropout rate, the final recruitment target is 44 participants per group, totaling 88. This sample is considered adequate to account for attrition, assess feasibility, and provide effect size estimates for planning a larger-scale trial.

Data Management

A CRF will be developed before recruitment for systematic data collection. Outcome assessors will enter trial data, and the database will be locked after study completion. Patient identifiers will remain confidential. To reduce attrition, trained researchers will maintain communication with participants and address concerns promptly. For withdrawals, follow-up data may be obtained by telephone with consent. All records will be retained for at least five years, with original data available upon request. Independent quality controllers at each center will monitor trial progress and evaluate early termination if safety concerns arise.

Statistical Analysis

All statistical analyses will be performed using SPSS 27.0 (IBM, Somers, NY, USA) by statisticians blinded to treatment allocation. The primary analysis will follow the full analysis set (FAS), consistent with intention-to-treat (ITT) principle, including all randomized participants with at least one post-baseline assessment. A per-protocol set (PPS) analysis will be conducted as sensitivity analysis and will include participants who complete the planned intervention with acceptable adherence (attend ≥ 12 of 16 sessions), have no major protocol violations, and have complete primary outcome data at week 8.

The primary outcome will be compared between groups using logistic regression with treatment group as the main effect and baseline VAS as a covariate. Results will be reported as odds ratios with 95% confidence intervals. Secondary outcomes measured at multiple time points will be analyzed using mixed-effects models for repeated measures (MMRM) to evaluate changes over time and group-by-time interactions. Relevant baseline characteristics, including ICS use, will be considered as covariates in adjusted models when appropriate.

Missing data will be handled primarily using multiple imputation under the missing-at-random assumption, with sensitivity analyses conducted using last observation carried forward (LOCF). Continuous variables will be summarized as mean $\pm$ standard deviation or median (interquartile range), and compared using parametric or nonparametric tests as appropriate. Categorical variables will be presented as counts and percentages and compared using the chi-square test or Fisher's exact test. All statistical tests will be two-sided, and a p value < 0.05 will be considered statistically significant.

Quality Control

The study protocol was reviewed by experts in acupuncture, respiratory medicine, and statistics. All staff will undergo standardized training on trial procedures and SOPs prior to participation. Licensed acupuncturists with at least three years of clinical experience will perform treatments after additional protocol-specific training to ensure inter-center consistency. Outcome assessors will verify data accuracy, and a quality control board will review CRFs and treatment

procedures every two months, issuing formal quality reports. Principal investigators will convene regularly to resolve issues identified during monitoring.

Ethics and Dissemination

This study will adhere to the principles of the International Conference on Harmonization Good Clinical Practice (ICH-GCP) and the Declaration of Helsinki.⁴³ Ethical approval was granted by the Medical Ethics Committee of the Affiliated Hospital of Chengdu University of Traditional Chinese Medicine (No. 2024KL-208). The trial has been registered with the International Traditional Medicine Clinical Trial Registry (ITMCTR) platform <https://itmctr.ccebtcn.org.cn/> (ITMCTR2025000435). Results will be disseminated through peer-reviewed journals and presentations at scientific conferences.

Discussion

As a prevalent asthma phenotype, CVA imposes significant health and quality-of-life burdens while contributing to global public health and economic costs. According to the GINA guideline, the primary therapeutic goals are to relieve chronic cough and suppress airway inflammation through ICS-based therapy, thereby preventing progression to classic asthma.¹ However, limitations such as incomplete symptom control and medication adherence challenges highlight the need for effective adjunctive strategies like acupuncture, which may further improve cough remission and overall well-being.

Despite accumulating evidence, existing studies on acupuncture for CVA have several notable methodological limitations. Most were small, single-center trials with heterogeneous acupoint prescriptions, stimulation parameters, and treatment durations, leading to inconsistent results. Sham controls and blinding procedures were often inadequate, increasing the risk of placebo effects. Moreover, most studies emphasized short-term symptom relief without incorporating objective biomarkers such as FeNO or airway inflammatory indices, and rarely evaluated psychological or sleep-related outcomes that are relevant to disease burden.^{18–22} These limitations highlight the need for rigorously designed, multicenter randomized controlled trials to provide more reliable and generalizable evidence.

The present study is designed as a multicenter, randomized, sham-controlled trial to evaluate the efficacy and safety of acupuncture as an adjunctive therapy for patients with CVA. This trial addresses the role of acupuncture in CVA management, with a particular focus on its potential to enhance cough control, reduce relapse rates, and improve quality of life. The present study incorporates a multidimensional outcome assessment strategy that represents a major methodological strength. The primary outcome, effective response rate defined by a $\geq 50\%$ reduction in cough severity VAS, directly reflects clinically meaningful symptom relief from the patient's perspective. This endpoint is simple, sensitive to change, and widely used in chronic cough trials, thereby enhancing comparability across studies.⁴⁴ The effective response rate at 8 weeks is selected as the primary endpoint for both clinical relevance and methodological rigor. Cough remission is the most direct outcome for CVA, and this timing allows adequate evaluation of acupuncture while avoiding premature assessment. The study applies acupuncture intervention based on standard ICS treatment in accordance with GINA 2024 recommendations. Aligning with guideline standards enhances interpretability, minimizes confounding from early remission, and ensures robust evidence to guide clinical practice.

An important strength of this trial lies in the comprehensive selection of outcome measures, which combine both subjective and objective dimensions to capture the multidimensional burden of cough. Instruments such as the CSD, CET, LCQ, and CHQ provide complementary perspectives on cough burden, ranging from frequency and intensity to quality-of-life impact and hypersensitivity triggers. Although not all instruments were originally developed specifically for CVA, the selected outcome measures have been validated in chronic cough and asthma populations and exhibit good reliability and responsiveness, supporting their applicability for evaluating symptom burden and treatment response in patients with CVA and capturing its multidimensional nature.⁴⁵

Beyond cough-specific assessments, this study incorporates validated psychological and sleep measures including the HAMA, HAMD, and PSQI. These outcomes are crucial, as chronic cough often coexists with anxiety, depression, and sleep disturbances,^{5,46} which significantly affect patients' overall well-being and treatment adherence. Their inclusion ensures a more holistic evaluation of therapeutic benefit.

Importantly, FeNO is included as an objective biomarker reflecting airway eosinophilic inflammation.⁴⁷ Although induced sputum has important value in the diagnosis and efficacy evaluation of CVA,⁴⁸ most patients present with a dry

cough and often have poor tolerance during sputum induction, limiting its feasibility in large-scale trials. Therefore, FeNO is selected as a noninvasive and patient-friendly alternative. FeNO not only strengthens the biological plausibility of acupuncture's effects but also bridges patient-reported outcomes with underlying pathophysiological changes.

EA has been increasingly applied in clinical and experimental studies, as it combines traditional acupuncture with electrical stimulation to enhance and stabilize therapeutic effects. Previous evidence suggests that EA may modulate airway inflammation, regulate autonomic nervous system activity, and improve bronchial hyperresponsiveness.⁴⁹ In particular, stimulation with specific parameters has been shown to influence inflammatory mediators and neuropeptides involved in cough hypersensitivity.⁵⁰ Considering that airway eosinophilic inflammation and heightened cough reflex sensitivity are key pathological features of CVA, EA may provide additional benefits beyond manual acupuncture. Therefore, in this study, bilateral Feishu (BL 13) and Pihu (BL 42) are connected to an EA device, aiming to strengthen therapeutic efficacy in CVA management.

In this study, a composite sham acupuncture strategy was designed, consisting of non-penetrating blunt needles at 5 real acupoints and superficial skin-penetrating insertion at S-LU7. Although an ideal placebo acupuncture should produce no specific therapeutic effects, be located at non-therapeutic sites, and remain indistinguishable from real acupuncture, these requirements are difficult to achieve in practice. Moreover, sham acupuncture may still induce nonspecific physiological responses through cutaneous stimulation and expectancy, which is an inherent limitation of acupuncture trials. Our design aimed to balance minimal physiological activation with adequate blinding. Non-penetrating needles at real acupoints reduce meridian-specific and deep-tissue stimulation while preserving the ritual of acupuncture. In contrast, superficial insertion at S-LU7 was introduced to enhance the credibility of needling and reduce the risk of unblinding, particularly in participants familiar with acupuncture. The insertion at S-LU7 was shallow and performed without manual manipulation or eliciting *deqi*, thereby limiting specific therapeutic effects while maintaining masking quality.⁵¹ Nevertheless, even minimal stimulation may exert nonspecific effects on cough perception. Therefore, observed between-group differences should be interpreted as effects beyond these contextual components, and future studies should further refine sham procedures to better isolate acupuncture-specific effects.

This study applied rigorous eligibility criteria, with participants having other respiratory diseases that could affect pulmonary function testing being excluded. Any concomitant use of Western medicine will be recorded in detail to reduce confounding effects. To facilitate manipulation and optimize patient comfort, participants received acupuncture in the prone position. In addition, participants in the sham acupuncture group will be assured of compensatory real acupuncture treatment after study completion, thereby reducing the risk of disappointment and enhancing compliance.

Several potential limitations should be acknowledged in advance. First, the sham acupuncture design may not fully eliminate nonspecific physiological effects. Second, the follow-up period is limited to 8 weeks after treatment, and long-term efficacy will not be assessed. Third, the trial will be conducted in Chinese hospitals, where cultural familiarity with acupuncture may influence patient expectations and thus affect generalizability. Finally, despite including both subjective and objective outcomes, some measures remain susceptible to reporting bias.

In summary, this multicenter, randomized, sham-controlled pilot trial will preliminarily assess acupuncture as an adjunctive therapy for CVA. Using a credible sham control with multidimensional patient-reported outcomes and objective inflammatory biomarkers, it provides a rigorous yet conservative evaluation framework. As a pilot study, the findings will inform feasibility, effect size estimation, and trial design for future definitive randomized controlled studies in CVA.

Trial Status

The approval of the ethics committee was given on December 9, 2024. The trial commenced on March 01, 2025, and is currently in the participant recruitment and acupuncture treatment phase.

Ethics Statement

This study protocol has been approved by the Medical Ethics Committee of the Affiliated Hospital of Chengdu University of Traditional Chinese Medicine (No. 2024KL-208). This study was conducted in accordance with the local legislation and institutional requirements. Before enrollment, every participant in this trial will be required to sign an informed consent document.

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Disclosure

The authors report no conflicts of interest in this work.

References

1. Global Initiative for Asthma. Global strategy for asthma management and prevention (2024 update). 2024. Available from: www.ginasthma.org. Accessed November 5, 2024.
2. Rybka-Fraczek A, Dabrowska M, Grabczak EM, et al. Does bronchial hyperresponsiveness predict a diagnosis of cough variant asthma in adults with chronic cough: a cohort study. *Respir Res*. 2021;22(1):252. doi:10.1186/s12931-021-01845-2
3. Sonoda K, Nayak R. Chronic cough: evaluation and management. *Am Fam Physician*. 2024;110(2):167–173.
4. Cox JK, Lockey R, Cardet JC. Cough-Variant asthma: a review of clinical characteristics, diagnosis, and pathophysiology. *J Allergy Clin Immunol Pract*. 2025;13(3):490–498. doi:10.1016/j.jaip.2024.11.005
5. Saito N, Itoga M, Tamaki M, Yamamoto A, Kayaba H. Cough variant asthma patients are more depressed and anxious than classic asthma patients. *J Psychosom Res*. 2015;79(1):18–26. doi:10.1016/j.jpsychores.2015.03.011
6. Diab N, Patel M, O'Byrne P, Satia I. Narrative review of the mechanisms and treatment of cough in asthma, cough variant asthma, and non-asthmatic eosinophilic bronchitis. *Lung*. 2022;200(6):707–716. doi:10.1007/s00408-022-00575-6
7. Fujimura M. Comparison of atopic cough with cough variant asthma: is atopic cough a precursor of asthma? *Thorax*. 2003;58(1):14–18. doi:10.1136/thorax.58.1.14
8. Fujimura M, Nishizawa Y, Nishitsuji M, Nomura S, Abo M, Ogawa H. Predictors for typical asthma onset from cough variant asthma. *J Asthma*. 2005;42(2):107–111.
9. Sugawara H, Saito A, Yokoyama S, Tsunematsu K, Takahashi H. Comparison of therapeutic effects of inhaled corticosteroids on three subtypes of cough variant asthma as classified by the impulse oscillometry system. *Respir Res*. 2019;20(1):41. doi:10.1186/s12931-019-1005-2
10. Zhan W, Wu F, Zhang Y, et al. Identification of cough-variant asthma phenotypes based on clinical and pathophysiologic data. *J Allergy Clin Immunol*. 2023;152(3):622–632. doi:10.1016/j.jaci.2023.04.017
11. Morice AH, Millqvist E, Bieksiene K, et al. ERS guidelines on the diagnosis and treatment of chronic cough in adults and children. *Eur Respir J*. 2020;55(1):1901136. doi:10.1183/13993003.01136-2019
12. Côté A, Russell RJ, Boulet LP, et al. Managing chronic cough due to asthma and NAEB in adults and adolescents: CHEST guideline and expert panel report. *Chest*. 2020;158(1):68–96. doi:10.1016/j.chest.2019.12.021
13. Liu M, Liu K, Zhu N, Xia J, Chen X. Inflammatory mediators in induced sputum and airway hyperresponsiveness in cough variant asthma during long-term inhaled corticosteroid treatment. *Mediators Inflamm*. 2012;2012:403868. doi:10.1155/2012/403868
14. Cooper V, Metcalf L, Versnel J, Upton J, Walker S, Horne R. Patient-reported side effects, concerns and adherence to corticosteroid treatment for asthma, and comparison with physician estimates of side-effect prevalence: a UK-wide, cross-sectional study. *NPJ Prim Care Respir Med*. 2015;25:15026. doi:10.1038/nppcr.2015.26
15. Amin S, Soliman M, McIvor A, Cave A, Cabrera C. Understanding patient perspectives on medication adherence in asthma: a targeted review of qualitative studies. *Patient Prefer Adherence*. 2020;14:541–551. doi:10.2147/PPA.S234651
16. Kita T, Fujimura M, Ogawa H, et al. Antitussive effects of the leukotriene receptor antagonist montelukast in patients with cough variant asthma and atopic cough. *Allergol Int*. 2010;59(2):185–192. doi:10.2332/allergolint.09-OA-0112
17. Haarman MG, van Hunsel F, de Vries TW. Adverse drug reactions of montelukast in children and adults. *Pharmacol Res Perspect*. 2017;5(5):e00341. doi:10.1002/prp2.341
18. Lee B, Kwon CY, Jeong YK, et al. Acupuncture-related therapy for chronic cough: a systematic review and meta-analysis. *Integr Med Res*. 2025;14(1):101121. doi:10.1016/j.imr.2025.101121
19. Pai HJ, Azevedo RS, Braga ALF, et al. A randomized, controlled, crossover study in patients with mild and moderate asthma undergoing treatment with traditional Chinese acupuncture. *Clinics*. 2015;70(10):663–669. doi:10.6061/clinics/2015(10)01
20. Scheewe S, Vogt L, Minakawa S, et al. Acupuncture in children and adolescents with bronchial asthma: a randomised controlled study. *Complement Ther Med*. 2011;19(5):239–246. doi:10.1016/j.ctim.2011.07.002
21. Chu KA, Wu YC, Ting YM, Wang HC, Lu JY. Acupuncture therapy results in immediate bronchodilating effect in asthma patients. *J Chin Med Assoc*. 2007;70(7):265–268. doi:10.1016/S1726-4901(07)70002-3
22. Xiong J, Qi W, Yang H, et al. Acupuncture treatment for cough-variant asthma: a meta-analysis. *Evid Based Complement Alternat Med*. 2021;2021:6694936. doi:10.1155/2021/6694936
23. Chan AW, Boutron I, Hopewell S, et al. SPIRIT 2025 statement: updated guideline for protocols of randomised trials. *BMJ*. 2025;389(e081477). doi:10.1136/bmj-2024-081477
24. Hopewell S, Chan AW, Collins GS, et al. CONSORT 2025 statement: updated guideline for reporting randomised trials. *BMJ*. 2025;389(e081123). doi:10.1136/bmj-2024-081123
25. MacPherson H, Altman DG, Hammerschlag R, et al. Revised Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA): extending the CONSORT statement. *J Evid Based Med*. 2010;3(3):140–155. doi:10.1111/j.1756-5391.2010.01086.x
26. Wu XD, Huang LX, Zhao JS. Interpretation of China national standard nomenclature and location of meridian points (GB/T 12346-2021). *Zhongguo Zhen Jiu*. 2022;42(5):579–582. doi:10.13703/j.0255-2930.20220117-k0001

27. Yang JW, Qi LY, Yan SY, et al. Efficacy of acupuncture in irritable bOwel syNdrome (ACTION): a multicenter randomized controlled trial. *Gastroenterology*. **2025**;169(5):958–969.e5. doi:10.1053/j.gastro.2025.05.016
28. Yan M, Fan J, Liu X, et al. Acupuncture and sleep quality among patients with parkinson disease: a randomized clinical trial. *JAMA Network Open*. **2024**;7(6):e2417862. doi:10.1001/jamanetworkopen.2024.17862
29. Vernon M, Kline Leidy N, Nacson A, Nelsen L. Measuring cough severity: development and pilot testing of a new seven-item cough severity patient-reported outcome measure. *Ther Adv Respir Dis*. **2010**;4(4):199–208. doi:10.1177/1753465810372526
30. Martin Nguyen A, Bacci E, Dicipinigitis P, Vernon M. Quantitative measurement properties and score interpretation of the cough severity diary in patients with chronic cough. *Ther Adv Respir Dis*. **2020**;14:1753466620915155. doi:10.1177/1753466620915155
31. Hirons B, Cho PSP, Krägeloh C, et al. The development of the cough hypersensitivity questionnaire for chronic cough. *ERJ Open Res*. **2024**;10(6):00468–02024. doi:10.1183/23120541.00468-2024
32. Kim MY, Lee HY, Oh JY, et al. Longitudinal evaluation of the cough hypersensitivity questionnaire in a cohort of chronic cough. *J Allergy Clin Immunol Pract*. **2025**;13(6):1471–1473.e1. doi:10.1016/j.jaip.2025.02.025
33. Zhan W, Zhang L, Jiang M, et al. A new simple score of chronic cough: cough evaluation test. *BMC Pulm Med*. **2020**;20(1):68. doi:10.1186/s12890-020-1106-1
34. Birring SS, Prudon B, Carr AJ, Singh SJ, Morgan MDL, Pavord ID. Development of a symptom specific health status measure for patients with chronic cough: leicester Cough Questionnaire (LCQ). *Thorax*. **2003**;58(4):339–343. doi:10.1136/thorax.58.4.339
35. Nguyen AM, Schelfhout J, Muccino D, et al. Leicester cough questionnaire validation and clinically important thresholds for change in refractory or unexplained chronic cough. *Ther Adv Respir Dis*. **2022**;16:17534666221099737. doi:10.1177/17534666221099737
36. Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol*. **1959**;32(1):50–55. doi:10.1111/j.2044-8341.1959.tb00467.x
37. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. **1960**;23(1):56–62. doi:10.1136/jnnp.23.1.56
38. Buysse DJ, Ancoli-Israel S, Edinger JD, Lichstein KL, Morin CM. Recommendations for a standard research assessment of insomnia. *Sleep*. **2006**;29(9):1155–1173. doi:10.1093/sleep/29.9.1155
39. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The pittsburgh sleep quality index: a new instrument for psychiatric practice and research. *Psychiatry Res*. **1989**;28(2):193–213. doi:10.1016/0165-1781(89)90047-4
40. Busse WW, Wenzel SE, Casale TB, et al. Baseline FeNO as a prognostic biomarker for subsequent severe asthma exacerbations in patients with uncontrolled, moderate-to-severe asthma receiving placebo in the LIBERTY ASTHMA QUEST study: a post-hoc analysis. *Lancet Respir Med*. **2021**;9(10):1165–1173. doi:10.1016/S2213-2600(21)00124-7
41. Pham DD, Kim Y, Song WJ, Kwon HS, Cho YS, Kim TB. Predictors of asthma exacerbation between high and low blood eosinophil counts. *ERJ Open Res*. **2025**;11(4):01218–02024. doi:10.1183/23120541.01218-2024
42. Qi LY, Yang JW, Yan SY, et al. Acupuncture for the treatment of diarrhea-predominant irritable bowel syndrome: a pilot randomized clinical trial. *JAMA Network Open*. **2022**;5(12):e2248817. doi:10.1001/jamanetworkopen.2022.48817
43. World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. *JAMA*. **2013**;310(20):2191–2194. doi:10.1001/jama.2013.281053
44. Dong R, Xu X, Yu L, et al. Randomised clinical trial: gabapentin vs baclofen in the treatment of suspected refractory gastro-oesophageal reflux-induced chronic cough. *Aliment Pharmacol Ther*. **2019**;49(6):714–722. doi:10.1111/apt.15169
45. Smith JA, Kitt MM, Butera P, et al. Gefapixant in two randomised dose-escalation studies in chronic cough. *Eur Respir J*. **2020**;55(3):1901615. doi:10.1183/13993003.01615-2019
46. Shin S, Poliwoda J, Whitmore GA, et al. Cough in adults with undiagnosed respiratory symptoms. *Ann Am Thorac Soc*. **2025**. doi:10.1513/AnnalsATS.202412-1329OC
47. Song WJ, Kim HJ, Shim JS, et al. Diagnostic accuracy of fractional exhaled nitric oxide measurement in predicting cough-variant asthma and eosinophilic bronchitis in adults with chronic cough: a systematic review and meta-analysis. *J Allergy Clin Immunol*. **2017**;140(3):701–709. doi:10.1016/j.jaci.2016.11.037
48. Chen Z, Jin K, Huang K, et al. Sputum metabolomic signature and dynamic change of cough variant asthma. *Am J Respir Cell Mol Biol*. **2025**;72(3):285–296. doi:10.1165/rcmb.2024-0219OC
49. Ma H, Liu X, Cai H, Yan Y, Li W, Zhao J. Electroacupuncture reduced airway inflammation by activating somatosensory-sympathetic pathways in allergic asthmatic rats. *Chin Med J*. **2025**;138(6):702–712. doi:10.1097/CM9.00000000000003074
50. Gong R, Liu X, Zhao J. Electroacupuncture-induced activation of GABAergic system alleviates airway inflammation in asthma model by suppressing TLR4/MyD88/NF-κB signaling pathway. *Chin Med J*. **2023**;136(4):451–460. doi:10.1097/CM9.00000000000002314
51. Tu JF, Shi GX, Yan SY, et al. Acupuncture vs sham acupuncture for chronic sciatica from herniated disk: a randomized clinical trial. *JAMA Intern Med*. **2024**;184(12):1417–1424. doi:10.1001/jamainternmed.2024.5463