

INPLASY202650138

doi: 10.37766/inplasy2026.5.0138

Received: 26 May 2026

Published: 26 May 2026

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### ADMINISTRATIVE INFORMATION

**Support - No.**

**Review Stage at time of this submission - Completed but not published.**

**Conflicts of interest - None declared.**

**INPLASY registration number: INPLASY202650138**

**Amendments -** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 26 May 2026 and was last updated on 26 May 2026.

### INTRODUCTION

**Review question / Objective** This systematic review and meta-analysis aims to evaluate the efficacy and safety of acupuncture-related Traditional Chinese Medicine therapies for patients with chronic fatigue syndrome.

Using the PICOS framework: Participants are patients diagnosed with chronic fatigue syndrome; Interventions include acupuncture-related therapies such as acupuncture, electroacupuncture, moxibustion, warm needling, special needling techniques, or acupuncture combined with Chinese herbal medicine or conventional treatment; Comparators include conventional treatment, pharmacotherapy, lifestyle intervention, sham or non-acupoint acupuncture, non-time-specific acupuncture, Chinese herbal medicine alone, or other non-acupuncture controls; Outcomes include overall fatigue, physical fatigue, mental fatigue, clinical response

rate, and adverse events; and Study design is limited to randomized controlled trials.

The objective is to determine whether acupuncture-related therapies improve fatigue-related outcomes and are safe for patients with chronic fatigue syndrome.

**Condition being studied** Chronic fatigue syndrome (CFS), also referred to as myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS), is a complex chronic disorder characterized by persistent or recurrent disabling fatigue lasting for at least six months and not fully relieved by rest. Patients may also experience post-exertional malaise, non-restorative sleep, cognitive difficulties, pain, and autonomic symptoms. Because there are no universally accepted diagnostic biomarkers, diagnosis is mainly based on symptom-based criteria and exclusion of other medical conditions. CFS can substantially impair daily activities, work, study, social functioning, and quality of life.

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## METHODS

**Participant or population** This review will include patients diagnosed with chronic fatigue syndrome (CFS), also referred to as myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS). Participants of any age, sex, ethnicity, or geographic region will be eligible, provided they have a clear diagnosis of CFS according to recognized diagnostic criteria or the diagnostic criteria specified by the original study. Studies including mixed populations will be eligible only if data for patients with CFS can be extracted separately.

**Intervention** The review will evaluate acupuncture-related Traditional Chinese Medicine therapies for chronic fatigue syndrome. Eligible interventions include manual acupuncture, electroacupuncture, time-specific acupuncture, special needling techniques, warm needling, moxibustion, ginger-separated moxibustion, and acupuncture combined with Chinese herbal medicine or conventional treatment. Studies will be included when acupuncture-related therapy is the main therapeutic component of the experimental intervention.

**Comparator** Eligible comparators will include conventional treatment, pharmacotherapy, lifestyle intervention, usual care, waiting-list or no treatment controls, sham acupuncture, non-acupoint acupuncture, non-time-specific acupuncture, Chinese herbal medicine alone, or other non-acupuncture interventions. Studies comparing different acupuncture-related approaches may also be considered if they provide relevant data for evaluating the effects of acupuncture-related therapies in patients with chronic fatigue syndrome.

**Study designs to be included** Randomized controlled trials (RCTs) evaluating acupuncture-related therapies for chronic fatigue syndrome will be included. Non-randomized studies, observational studies, case reports, case series, reviews, conference abstracts, animal studies, and basic research will be excluded.

**Eligibility criteria** Studies will be included if they enrolled patients with a clear diagnosis of chronic fatigue syndrome, evaluated acupuncture-related Traditional Chinese Medicine therapies, used an eligible comparator, reported at least one relevant fatigue-related or safety outcome, and used a randomized controlled trial design. Studies will be excluded if they were non-randomized studies, observational studies, case reports, case series,

reviews, systematic reviews, meta-analyses, conference abstracts, basic research, or animal studies. Duplicate publications, studies without extractable CFS data, studies with ineligible interventions or comparators, and studies without usable outcome data will also be excluded.

**Information sources** A systematic literature search will be conducted in the following electronic databases: PubMed, Embase, Web of Science, and the Cochrane Library. The search will cover records from database inception to April 1, 2026. Reference lists of included studies and relevant reviews will also be screened to identify additional eligible studies. Trial registries, grey literature sources, and direct contact with authors will not be used unless necessary to clarify missing or unclear study data.

**Main outcome(s)** The main outcomes will include changes in fatigue-related symptoms and clinical effectiveness in patients with chronic fatigue syndrome. Fatigue outcomes will include overall fatigue, physical fatigue, and mental fatigue, measured using validated or study-reported scales such as the Fatigue Severity Scale, Fatigue Scale-14, Chalder Fatigue Scale, Bell CFS score, or similar instruments. Clinical effectiveness will be assessed using the total response rate as defined by the included studies. Where multiple time points are reported, outcomes measured at the end of treatment will be used for the primary analysis, and follow-up outcomes will be summarized where available. Continuous outcomes will be expressed as standardized mean differences with 95% confidence intervals, and dichotomous outcomes as risk ratios with 95% confidence intervals.

**Quality assessment / Risk of bias analysis** The methodological quality of included randomized controlled trials will be assessed using the Cochrane Risk of Bias 2 (RoB 2) tool. Two reviewers will independently evaluate each study across five domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in outcome measurement, and bias in selection of the reported result. Each domain will be judged as “low risk,” “some concerns,” or “high risk,” leading to an overall risk-of-bias judgment for each study. Disagreements will be resolved through discussion, or by consultation with a third reviewer when necessary.

**Strategy of data synthesis** Data will be analysed using R software. For continuous outcomes measured using different fatigue scales, standardized mean differences (SMDs) with 95%

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confidence intervals (CIs) will be calculated. For dichotomous outcomes, such as total response rate and adverse events, risk ratios (RRs) with 95% CIs will be used. Statistical heterogeneity will be assessed using the  $I^2$  statistic and chi-square test. A random-effects model will be used when clinical or statistical heterogeneity is expected; otherwise, a fixed-effect model may be considered. If substantial heterogeneity is detected, subgroup analyses will be conducted according to intervention type where sufficient data are available. Sensitivity analyses may be performed to examine the robustness of the findings. If meta-analysis is not appropriate, results will be summarized narratively.

**Subgroup analysis** If sufficient data are available, subgroup analyses will be conducted according to the type of acupuncture-related intervention, such as simple acupuncture, warm needling or moxibustion, and acupuncture combined with other therapies. Additional subgroup analyses may be considered according to comparator type, treatment duration, outcome measurement scale, or diagnostic criteria if enough studies provide relevant data. Subgroup findings will be interpreted cautiously because of the expected small number of studies and potential clinical heterogeneity.

**Sensitivity analysis** Sensitivity analyses will be performed where sufficient studies are available to assess the robustness of the pooled results. Analyses may include excluding studies judged to be at high risk of bias, excluding studies with incomplete or imputed data, and comparing results using different statistical models or heterogeneity estimators. For outcomes with substantial heterogeneity, sensitivity analyses may also be conducted by removing studies one at a time to assess whether any single study has a major influence on the overall effect estimate. The findings will be interpreted cautiously in view of the limited number of included studies.

**Country(ies) involved** China. The review is being carried out by authors affiliated with The Second Affiliated Hospital of Guangdong Medical University, Zhanjiang, China.

**Keywords** Chronic fatigue syndrome; Acupuncture; Moxibustion; Traditional Chinese Medicine; Systematic review; Meta-analysis.

#### **Contributions of each author**

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