

# INPLASY PROTOCOL

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**Support:** None.

**Review Stage at time of this submission:** The review has not yet started.

**Conflicts of interest:**  
None declared.

## INTRODUCTION

**Review question / Objective:** The purpose of this study is to systematically review and meta-analyze the effectiveness and scientific basis of Xiao-Yao-San and acupuncture in the treatment of post-stroke depression, hoping to provide a reference for future research in this field.

## Herbal medicine Xiao-Yao-San and acupuncture for the treatment of post-stroke depression: A protocol for systematic review and meta-analysis

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**Review question / Objective:** The purpose of this study is to systematically review and meta-analyze the effectiveness and scientific basis of Xiao-Yao-San and acupuncture in the treatment of post-stroke depression, hoping to provide a reference for future research in this field.

**Information sources:** The following electronic databases will be searched from inception to January 2022: PubMed, the Cochrane Library, Embase, Scopus, EBSCO, Web of Science, Medline, China National Knowledge Infrastructure (CNKI), WanFang Data, Weipu Electronics. In addition, reference lists of the included studies were manually searched to identify additional relevant studies.

**INPLASY registration number:** This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 17 January 2022 and was last updated on 17 January 2022 (registration number INPLASY202210085).

**Condition being studied:** Stroke and depression are two important factors causing social and economic burden, and their incidence is increasing year by year in the population, becoming serious social and public problems. A bi-directional association between depression and stroke has been established, with stroke increasing the risk of depression after stroke, but depression is an independent

risk factor for stroke. Depression is the most common mental disorder after ischemic stroke, affecting about one-third of patients. Post-stroke depression (PSD) is a multifactorial, common, and treatable disorder that is related to gender and history of mental illness, with a higher incidence in women than men. The main manifestations are guilt, lack of euphoria, depressed mood, or lack of sense of self-worth. Evidence from relevant randomized controlled trials and meta-analyses suggests that conventional antidepressant therapy may have an effect on PSD. However, many antidepressants have significant contraindications and anticholinergic side effects. Xiao-Yao-San is one of the classical prescriptions in ancient China. It was first seen in "Taiping Huimin Heji Jufang" in the Song Dynasty and has been used to treat emotional diseases for thousands of years. Animal experiments have verified the effectiveness of Xiao-Yao-San in treating depression. However, there are few studies on the effect of Xiao-Yao-San on post-stroke depression. As a non-drug therapy, acupuncture and moxibustion are increasingly becoming complementary or alternative therapy for emotional diseases. Animal studies have shown that similar to antidepressants, acupuncture can affect levels of the neurotransmitters serotonin and norepinephrine, as well as the adenosine cyclic adenosine monophosphoryl kinase A cascade in the central nervous system (AC-cAMPPKA) to improve the effect of depression. At the same time, acupuncture can induce a wide range of central nervous system responses, including the amygdala, hippocampus, hypothalamus, cerebellum, and other limbic structures, among which the anterior cingulate cortex, amygdala, and hippocampus are associated with depression. It can be seen that the treatment of depression by Traditional Chinese medicine and acupuncture is a research hotspot.

## METHODS

**Participant or population:** All patients clinically diagnosed with PSD will be

included, regardless of race, sex, age, disease duration, severity, and educational status. and should be older than 18 years of age. Participants with unstable vital signs or inability to cooperate with rehabilitation treatment should be excluded, such as patients with impaired hearing, visual and cognitive or severe infection, organ dysfunction, and so on.

**Intervention:** The treatment group using herbal medicine Xiao-Yao-San and acupuncture while the control group received treatment with oral medication, acupuncture, Chinese herbal medication, physical therapy, and so on, or even with no treatment, will be included.

**Comparator:** The control group's treatment is not limited, including no treatment, placebo, or any control considered for comparison in a single systematic review.

**Study designs to be included:** This study will include randomized controlled trials (RCTs) on herbal medicine Xiao-Yao-San and acupuncture for PSD published in Chinese and English. We will exclude non-RCTs, review studies, case reports, and animal studies.

**Eligibility criteria:** All randomized controlled trials (RCTs) reported will be included without regional restrictions. Animal studies, cohort studies, case-controlled studies, case reports, and expert experience will be excluded.

**Information sources:** The following electronic databases will be searched from inception to January 2022: PubMed, the Cochrane Library, Embase, Scopus, EBSCO, Web of Science, Medline, China National Knowledge Infrastructure (CNKI), WanFang Data, Weipu Electronics. In addition, reference lists of the included studies were manually searched to identify additional relevant studies.

**Main outcome(s):** We will include the Hamilton depression rating scale (HAMD) and the effective rate. As previously reported, a  $\geq 25\%$  reduction in the Hamilton

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depression rating scale score was indicative of effective treatment.

**Additional outcome(s):** The secondary outcomes will include the National Institutes of Health Stroke Scale (NIHSS), Degree of neurological impairment, Barthel Index (BI), and incidence of adverse events.

**Quality assessment / Risk of bias analysis:** Two reviewers will separately assess the risk of bias of the selected RCTs using the Cochrane risk of the bias assessment tool. This tool has the following 7 domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. A bias value of “low,” “unclear,” or “high” will be used to rank the risk of bias. These even domains will be separately appraised by 2 reviews, and discrepancies will be addressed by consulting a third reviewer

**Strategy of data synthesis:** We will use Review Manager Version 5.3 statistical software for data analysis and quantitative data synthesis. For continuous data, we will use the standard mean difference to measure the treatment effect with 95% confidence intervals. For dichotomous data, a risk ratio with 95% confidence intervals for analysis will be adopted. Besides, the subgroup or sensitivity analysis will be performed to distinguish the source of it. When it comes to the situation that the data are insufficient for quantitative analysis, we will only perform a descriptive analysis.

**Subgroup analysis:** If the heterogeneity of the included data is significant, we will conduct subgroup analyses according to the course of treatment, gender, age, differences in severity, intervention measures for the control group, etc.

**Sensitivity analysis:** We will perform sensitivity analysis based on sample size, research design, heterogeneity quality, methodological quality, and statistical model, excluding trials with low quality, and ensure the stability of analysis results.

**Country(ies) involved:** China.

**Keywords:** Xiao-Yao-San; Acupuncture; Post-stroke depression; Meta-analysis; Protocol.

**Contributions of each author:**

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