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# The effectiveness and safety of manual acupuncture therapy in patients with post-stroke depression: protocol for a systematic review and meta-analysis



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# The effectiveness and safety of manual acupuncture therapy in patients with post-stroke depression: protocol for a systematic review and meta-analysis

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## Abstract

**Introduction:** Acupuncture is widely used on the rehabilitation of stroke survivors, including hemiplegia, constipation, emotional disorders and so on. Although the effectiveness of manual acupuncture therapy on post-stroke depression (PSD) has been confirmed by multiple randomized controlled trials, there were few meta-analysis focused on the connection between different techniques, durations or other detailed operations of manual acupuncture and their effectiveness of improving the depression severity and quality of life for PSD patients.

**Methods and analysis:** A systematic search will be performed on English databases (PubMed, The Cochrane Library, Medline, Embase), Chinese databases (CNKI, WanFang Data, VIP and Chinese biomedical databases) and Japanese databases(J-STAGE, CiNii). The retrieval time limit will be from the establishment of the database to November 2020. Two researchers will independently screen the literatures, extract data, and evaluate the quality of the included studies. Meta-analysis will be conducted by using STATA V. 14.0 and Review Manager V.5.3.

**PROSPERO registration number:** CRD42020222825.


**Keywords:** acupuncture; meta-analysis; post-stroke depression

## Strengths and limitations of this study Introduction

1. To our knowledge, this study is the first meta-analysis especially focused on the effectiveness of manual acupuncture therapy for PSD patients.
2. Compared with previous studies, we have extracted more detailed information on the treatment schedule of acupuncture (acupoints selection, twist technique, retention time, frequency, etc) in order to study the effectiveness of manual acupuncture therapy from multiple angles.
3. The electronic search will only include randomized controlled trials published in English, Chinese and Japanese that could limit the inclusion of studies.

## Introduction

Stroke is currently the second leading cause of death worldwide, the burden of

which has increased substantially over the past few decades due to expanding population numbers and aging as well as the increased prevalence of modifiable stroke risk factors [1,2]. Depression is a common and recurrent psychiatric disorder that starts shortly after stroke and affects patients in the long term. A meta-analysis of the frequency of depression after stroke shows that approximately one-third of stroke survivors experience depression at any time-point in the first year[3]. Depression after stroke is independently associated with poor health outcomes, including increasing mortality, disability, anxiety and lowering quality of life (QoL)[4].In addition, there is a two-way relationship between depression and stroke: stroke could increase the risk of PSD, meanwhile, depression is an independent risk factor for stroke and stroke mortality[5,6].

This bidirectional relationship makes it more difficult to develop the treatment of PSD, currently, few guidelines mentioned the assessment, treatment or prevention for it[7]. For depressive disorder, Canadian network for mood and anxiety treatments(CANMAT), the American psychiatric association (APA) and the World federation of societies of biological psychiatry (WFSBP) guidelines supported that selective serotonin uptake inhibitors (SSRIs) could be used as first-line treatment[8,9,10]. But the pharmacotherapy of PSD needs to be more cautious, as some studies[11,12,13]**Error! Reference source not found.** showed that the use of SSRI may relate to the potential risk of hemorrhagic stroke.

Acupuncture, a historic complementary therapy from China, has potential beneficial effects on improving dependency, global neurological deficiency, and some specific neurological impairments for people with stroke in the convalescent stage[14]. In the treatment of depression, a recent meta-analysis[15] suggests that acupuncture combined with antidepressant medication is effective for the treatment of depression and has an early onset of action, safe and well-tolerated over the first 6-week treatment period. However, few systematic reviews or meta-analysis focused on the effectiveness of acupuncture in treating PSD, although the number of papers related to this area has an upward trend recently[16,17].

Besides, there are no meta-analysis focusing on the effectiveness of manual acupuncture on improving the depression severity and QoL of post stroke patients, so far. What's more, there is a general problem of high heterogeneity in existing meta-analysis. One recent meta-analysis[18]**Error! Reference source not found.** showed that the curative effect of acupuncture for post stroke cognitive impairment may be related to manipulation and retention time, however, most of the existing meta-analysis on PSD didn't conduct subgroup analysis for such content due to the lack of attention to the details of acupuncture treatment. Therefore, we considered that the higher heterogeneity may be relevant with the difference in the type of acupuncture (manual acupuncture, electroacupuncture, dry needle, etc) and the treatment schedule (acupoints selection, twist technique, retention time, frequency, etc). Hence, we would like to extract the detailed description of manual acupuncture treatment in the included articles and conduct subgroup analysis according to them.

**Objectives**

The primary purpose of this meta-analysis is to examine the efficacy of manual acupuncture in improving depression severity in individuals with post-stroke depression. Secondary aims are to evaluate its role in enhancing QoL and assess the safety of this treatment.

## Methods and analysis

This systematic review protocol has registered in Prospero (registration number: CRD42020222825). It will follow the new edition of the Cochrane handbook for systematic reviews of interventions[19] and be reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P)[20]**Error! Reference source not found.**.

**Criteria for considering studies for this review**

**Types of studies**

Randomized controlled trials (RCTs) in English, Chinese and Japanese will be included. Animal studies or studies with incomplete data will be excluded.

**Participants**

We will include patients who suffered post stroke depression. The diagnosis of stroke should base on computer tomography (CT), magnetic resonance imaging (MRI), or clinical criteria. Meanwhile, depression should be diagnosed according to the International Classification of Diseases Tenth Edition (ICD-10), the Diagnosis and Statistical Manual of Mental Disorders (DSM), Chinese Classification of Mental Disorders (CCMD) or Hamilton Rating Scale for Depression (HAMD)[21,22,23].

**Types of interventions:**

The relevant RCTs will be included if the following criteria were met: (1) using manual acupuncture alone, or in combination with another rehabilitation therapy, or in combination with pharmacotherapy in experiment group (EG) (2) using rehabilitation therapy other than manual acupuncture, pharmacotherapy, sham acupuncture or no treatment in control group (CG). In addition, other kinds of acupuncture therapies, such as electroacupuncture, dry needle, laser needle or acupoint-injection, couldn't be used as interventions in EG or CG.

**Types of outcomes measures:**

**Primary outcomes:**

**Depression severity:** evaluated mainly by Hamilton Depression Rating Scale (HAMD), Montgomery-Asberg Depression Rating Scale(MADRS), Beck Depression Inventory (BDI) and Zung Self-Rating Depression Scale(SDS).

**Secondary outcomes:**

i. **QoL:** evaluated mainly by the Medical Outcomes Study Short Form 36 (SF-36), the Stroke Specific Quality of Life Scale (SS-QOL) or the World Health Organization Quality of Life (WHOQOL).

ii. **Safety:** evaluated mainly by the total numbers and severity of adverse events.

**Search methods for identification of studies**

The following ten databases will be searched from establishment to November 2020: PubMed, The Cochrane Library, Medline, Embase, Japan science and technology agency (J-STAGE), CiNii(National Institute of Informatics),China National

Knowledge Infrastructure (CNKI), WanFang Data, VIP and Chinese Biomedical Databases. The combination of free words and medical subject headings, including "depression, depressive disorder, acupuncture therapy, acupuncture, needle, needling, stroke, etc", will be used as the retrieval mode. The search strategy for Cochrane Library is shown in Table 1.

**Study selection and data extraction**

EndNote X8.2 will be used to manage studies. First, duplicate literature will be excluded by electronic & manual based steps in EndNote. Second, two reviewers will independently screen the titles and abstracts and select the studies which meet the eligibility criteria. If there are disagreements, the third reviewer will be consulted. The evaluators will read the full text of the included literature, and then preliminarily extracted relevant data, mainly including the following information: (1)Inclusion and exclusion criteria; (2) The number of included samples (total number of cases, number of cases in the treatment group, number of cases in the control group); (3)Grouping method and process; (4) Basic data of the included research samples (mainly including gender, age and disease); (5)The intervention of the treatment group and the control group :① the treatment method, drug dose, treatment frequency, course of treatment, etc. ② a detailed description of manual acupuncture treatment including acupoints selection, twist technique, retention time, frequency, etc.(6) Evaluation of the final research results (including the treatment efficiency of different treatment measures, the scale score at the beginning and end point, etc).

**Quality assessment**

The quality of evidence for main outcomes will be assessed by The Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach. Two reviewers will do this independently through GRADEpro Guideline Development Tool (GDT). GRADE approach provides guidance for rating quality of evidence and grading strength of recommendations for health care. It has important implications for those summarizing evidence for systematic reviews[24].It assessed a body of evidence by referring to the concepts of the GRADE system , and

determined and recorded the quality of a body of evidence for each clinical question, there are four quality levels: high, moderate, low and very low[25].

**Assessment of heterogeneity, Sensitivity analysis and subgroup analysis**

We'll use the $I^2$ statistic to assess the heterogeneity. If the $I^2$ value is below 50%, the fixed effect model will be used. Otherwise, sensitivity analysis and subgroup analysis will be conducted to explore the main sources of heterogeneity, after which, the random effect model will be used if the $I^2$ is still equal or greater than 50%. Both types of effect sizes will be presented with 95% CIs, and values of $p<0.05$ will be regarded as statistically significant. Continuous outcomes will be calculated as mean differences (MDs) or standardized mean differences (SMDs), meanwhile, binary outcomes will be calculated as odds ratios (ORs).

**Assessment of the risk of bias in individual studies**

According to Cochrane Handbook for Systematic Reviews of Interventions version 6 (https://training.cochrane.org/handbook/current/chapter-08), the risk of bias 2.0 (ROB 2.0) tool will be used to mean the methodological quality and the risk of bias of the included studies. One researcher assessed the risk of bias of included studies by using ROB 2.0 and another researcher confirmed the judgment. If there are any differences, the third researcher will be asked to solve the problem.

**Publication bias**

STATA V.14.0 will be used to evaluate publication bias. Begg's test and Egger's test will be used to assess the publication bias of the included trials and form the publication bias plot.

**Discussion**

This meta-analysis will focus on the different techniques, durations or other detailed operations of manual acupuncture applied in PSD patients to explore their influence on depression severity and QoL. PSD are generally more disabled[26]. As an important part of traditional Chinese medicine, acupuncture plays an important role in clinical treatment [27]. In terms of clinical efficacy, acupuncture can assist in eliminating negative emotions by significantly improving the functional communication and

language function [28], cognitive [29] and limb movement function [30] of stroke patients. At the mechanism level, acupuncture can modulate glutamate receptor and excitatory Amino Acid Transporter(EAAT) expression [31], down-regulated the levels of unclear factor kappa light chain enhancer of activated B cells(NF-κB) protein, Inducible Nitric-Oxide Synthase(iNOS) and Nitric Oxide(NO) [32], so as to achieve the purpose of relieving PSD.

## Ethics and dissemination

Non -applicable.

## Authors' contributions:

Wei Liu and Chang Rao conceived, designed and wrote this protocol. Wei Liu provided a clinical perspective, especially to the manual acupuncture. Yuzheng Du is the guarantor of this review, and approved the final manuscript of it.Xi Nan, Zefang Li and Chunsheng Yin provided a preliminary data retrieval.

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## Competing interests statement

None declared.

## Patient and Public Involvement

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research

## Abbreviation

PSD: post-stroke depression

QOL: quality of life

CANMAT: Canadian network for mood and anxiety treatments

APA: the American psychiatric association

WFSBP: the World federation of societies of biological psychiatry

SSRIs: selective serotonin uptake inhibitors

PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols

RCTs: Randomized controlled trials

CT: computer tomography

MRI: magnetic resonance imaging

ICD-10: International Classification of Diseases Tenth Edition

DSM: the Diagnosis and Statistical Manual of Mental Disorders

CCMD: Chinese Classification of Mental Disorders

HAMD: Hamilton Rating Scale for Depression

EG: experiment group

CG: control group

HAMD:Hamilton Depression Rating Scale

MADRS: Montgomery-Asberg Depression Rating Scale

BDI: Beck Depression Inventory

SDS: Zung Self-Rating Depression Scale

SF-36: the Medical Outcomes Study Short Form 36

SS-QOL: Stroke Specific Quality of Life Scale

WHOQOL: the World Health Organization Quality of Life

J-STAGE: Japan science and technology agency

CiNii: National Institute of Informatics

CNKI: China National Knowledge Infrastructure

GRADE: Grades of Recommendation, Assessment, Development, and Evaluation

GDT: Guideline Development Tool

MDs: mean differences

SMDs: mean differences

ORs: odds ratios

ROB 2.0: the risk of bias 2.0

EAAT: excitatory Amino Acid Transporter

NF-κB: unclear factor kappa light chain enhancer of activated B cells

iNOS: Inducible Nitric-Oxide Synthase

NO: Nitric Oxide

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| ID | Search |
|---|---|
| #1 | MeSH descriptor: [Stroke] explode all trees |
| #2 | poststroke or post-stroke. ti,ab,kw |
| #3 | MeSH descriptor: [Cerebral Infarction] explode all trees |
| #4 | MeSH descriptor: [Cerebral Hemorrhage] explode all trees |
| #5 | #1 or #2 or #3 or #4 |
| #6 | MeSH descriptor: [Depression] explode all trees |
| #7 | depress* or affective disorder or affective symptoms. ti,ab,kw |
| #8 | #6 or #7 |
| #9 | MeSH descriptor: [Acupuncture] explode all trees |
| #10 | acupunctur* or acupoint* or needl*. ti,ab,kw |
| #11 | #9 or #10 |
| #12 | #5 and #8 and #11 |

Table 1 Search strategy for Cochrane Library

**PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol***

| Section and topic | Item No | Checklist item | Reported on Page # |
|---|---|---|---|
| **ADMINISTRATIVE INFORMATION** | | | |
| Title: | | | |
| Identification | 1a | Identify the report as a protocol of a systematic review | P1 |
| Update | 1b | If the protocol is for an update of a previous systematic review, identify as such | NA |
| Registration | 2 | If registered, provide the name of the registry (such as PROSPERO) and registration number | P2 |
| Authors: | | | |
| Contact | 3a | Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author | P1 |
| Contributions | 3b | Describe contributions of protocol authors and identify the guarantor of the review | P8 |
| Amendments | 4 | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments | NA |
| Support: | | | |
| Sources | 5a | Indicate sources of financial or other support for the review | P8 |
| Sponsor | 5b | Provide name for the review funder and/or sponsor | P8 |
| Role of sponsor or funder | 5c | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol | P8 |
| **INTRODUCTION** | | | |
| Rationale | 6 | Describe the rationale for the review in the context of what is already known | P2-P4 |
| Objectives | 7 | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) | P4-P5 |
| **METHODS** | | | |
| Eligibility criteria | 8 | Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review | P4-P6 |
| Information sources | 9 | Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage | P5-P6 |
| Search strategy | 10 | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated | P5-P6 and Table1 |

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| Study records: | | | |
| Data management | 11a | Describe the mechanism(s) that will be used to manage records and data throughout the review | P6 |
| Selection process | 11b | State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) | P5-P6 |
| Data collection process | 11c | Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators | P6 |
| Data items | 12 | List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications | P7 |
| Outcomes and prioritization | 13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale | P5 and P7 |
| Risk of bias in individual studies | 14 | Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis | P7 |
| Data synthesis | 15a | Describe criteria under which study data will be quantitatively synthesised | P7 |
| | 15b | If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as $I^2$, Kendall's $\tau$) | P7 |
| | 15c | Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) | P7 |
| | 15d | If quantitative synthesis is not appropriate, describe the type of summary planned | NA |
| Meta-bias(es) | 16 | Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) | P7 |
| Confidence in cumulative evidence | 17 | Describe how the strength of the body of evidence will be assessed (such as GRADE) | P6 |

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

*From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.*

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| Primary Subject Heading: | Complementary medicine |
| Secondary Subject Heading: | Mental health |
| Keywords: | Neurology < INTERNAL MEDICINE, Depression & mood disorders < PSYCHIATRY, Stroke medicine < INTERNAL MEDICINE, COMPLEMENTARY MEDICINE |
| | |

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# The effectiveness and safety of manual acupuncture therapy in patients with post-stroke depression: protocol for a systematic review and meta-analysis

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## Abstract

**Introduction:** Acupuncture is widely used on the rehabilitation of stroke survivors, including hemiplegia, constipation, emotional disorders and so on. Although the effectiveness of manual acupuncture therapy on post-stroke depression (PSD) has been confirmed by multiple randomized controlled trials, there were few meta-analysis focused on the connection between different techniques, durations or other detailed operations of manual acupuncture and their effectiveness of improving the depression severity and quality of life for PSD patients.

**Methods and analysis:** A systematic search will be performed on English databases (PubMed, The Cochrane Library, Medline, Embase), Chinese databases (CNKI, WanFang Data, VIP and Chinese biomedical databases) and Japanese databases(J-STAGE, CiNii). The retrieval time limit will be from the establishment of the database to November 2020. Two researchers will independently screen the literatures, extract data, and evaluate the quality of the included studies. Meta-analysis will be conducted by using STATA V. 14.0 and Review Manager V.5.3.

**Ethics and dissemination:** The results of this meta-analysis will be disseminated through publication in peer-reviewed journals or conference presentations. The data used in this meta-analysis will not contain individual patient data, therefore, ethical approval is not required.

**PROSPERO registration number:** CRD42020222825.


**Keywords:** acupuncture; meta-analysis; post-stroke depression

## Strengths and limitations of this study

1. To our knowledge, this study is the first meta-analysis especially focused on the effectiveness of manual acupuncture therapy for PSD patients.

2. Compared with previous studies, we will extract more detailed information on the treatment schedule of acupuncture (acupoints selection, twist technique, retention time, frequency, etc) in order to provides more analytical basis for subgroup analysis and sensitivity analysis.

3. The electronic search will only include randomized controlled trials published in English, Chinese and Japanese that could limit the inclusion of studies.

## Introduction

Stroke is currently the second leading cause of death worldwide, the burden of which has increased substantially over the past few decades due to expanding population numbers and aging as well as the increased prevalence of modifiable stroke risk factors [1,2]. Depression is a common and recurrent psychiatric disorder that starts shortly after stroke and affects patients in the long term. A meta-analysis of the frequency of depression after stroke shows that approximately one-third of stroke survivors experience depression at any time-point in the first year[3]. Depression after stroke is independently associated with poor health outcomes, including increasing mortality, disability, anxiety and lowering quality of life (QoL)[4].In addition, there is a two-way relationship between depression and stroke: stroke could increase the risk of PSD, meanwhile, depression is an independent risk factor for stroke and stroke mortality[5,6].

This bidirectional relationship makes it more difficult to develop the treatment of PSD, currently, few guidelines mentioned the assessment, treatment or prevention for it[7]. For depressive disorder, Canadian network for mood and anxiety treatments(CANMAT), the American psychiatric association (APA) and the World federation of societies of biological psychiatry (WFSBP) guidelines supported that selective serotonin uptake inhibitors (SSRIs) could be used as first-line treatment[8,9,10]. But the pharmacotherapy of PSD needs to be more cautious, as some studies [11,12,13] showed that the use of SSRI may relate to the potential risk of hemorrhagic stroke.

Acupuncture, a historic complementary therapy from China, has potential beneficial effects on improving dependency, global neurological deficiency, and some specific neurological impairments for people with stroke in the convalescent stage[14]. In the treatment of depression, a recent meta-analysis[15] suggests that acupuncture combined with antidepressant medication is effective for the treatment of depression and has an early onset of action, safe and well-tolerated over the first 6-week treatment

period. However, few systematic reviews or meta-analysis focused on the effectiveness of acupuncture in treating PSD, although the number of papers related to this area has an upward trend recently [16,17].

Besides, there are no meta-analysis focusing on the effectiveness of manual acupuncture on improving the depression severity and QoL of post stroke patients, so far. What's more, there is a general problem of high heterogeneity in existing meta-analysis. One recent meta-analysis [18] showed that the curative effect of acupuncture for post stroke cognitive impairment may be related to manipulation and retention time, however, most of the existing meta-analysis on PSD didn't conduct subgroup analysis for such content due to the lack of attention to the details of acupuncture treatment. Therefore, we considered that the higher heterogeneity may be relevant with the difference in the type of acupuncture (manual acupuncture, electroacupuncture, dry needle, etc) and the treatment schedule (acupoints selection, twist technique, retention time, frequency, etc). Hence, we would like to extract the detailed description of manual acupuncture treatment in the included articles and conduct subgroup analysis according to them.

**Objectives**

The primary purpose of this meta-analysis is to examine the efficacy of manual acupuncture in improving depression severity in individuals with post-stroke depression. Secondary aims are to evaluate its role in enhancing QoL and assess the safety of this treatment.

## Methods and analysis

This systematic review protocol has registered in Prospero (registration number: CRD42020222825). It will follow the new edition of the Cochrane handbook for systematic reviews of interventions[19] and be reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) [20].

**Criteria for considering studies for this review**

**Types of studies**

Randomized controlled trials (RCTs) in English, Chinese and Japanese will be

included. Animal studies or studies with incomplete data will be excluded.

**Participants**

We will include patients who suffered post stroke depression. The diagnosis of stroke should base on computer tomography (CT), magnetic resonance imaging (MRI), or clinical criteria. Meanwhile, depression should be diagnosed according to the International Classification of Diseases Tenth Edition (ICD-10), the Diagnosis and Statistical Manual of Mental Disorders (DSM), Chinese Classification of Mental Disorders (CCMD) or Hamilton Rating Scale for Depression (HAMD)[21,22,23].

**Types of interventions:**

The relevant RCTs will be included if the following criteria were met: (1) using manual acupuncture alone, or in combination with another rehabilitation therapy, or in combination with pharmacotherapy in experiment group (EG) (2) using rehabilitation therapy other than manual acupuncture, pharmacotherapy, sham acupuncture or no treatment in control group (CG). In addition, other kinds of acupuncture therapies, such as electroacupuncture, dry needle, laser needle or acupoint-injection, couldn't be used as interventions in EG or CG.

**Types of outcomes measures:**

**Primary outcomes:**

**Depression severity:** evaluated mainly by Hamilton Depression Rating Scale (HAMD), Montgomery-Asberg Depression Rating Scale(MADRS), Beck Depression Inventory (BDI) , Zung Self-Rating Depression Scale(SDS), etc.

If the included studies used two or more of above scales, we will give preference to clinician-rated scales. Following hierarchy will be applied: (1) HAMD; (2) MADRS; (3) BDI; (4) SDS and (5) all other depression scales.

**Secondary outcomes:**

i. **QoL:** evaluated mainly by the Medical Outcomes Study Short Form 36 (SF-36), the Stroke Specific Quality of Life Scale (SS-QOL) or the World Health Organization Quality of Life (WHOQOL).

ii. **Safety:** evaluated mainly by the total numbers and severity of adverse events.

**Search methods for identification of studies**

The following ten databases will be searched from establishment to November 2020: PubMed, The Cochrane Library, Medline, Embase, Japan science and technology agency (J-STAGE), CiNii(National Institute of Informatics),China National Knowledge Infrastructure (CNKI), WanFang Data, VIP and Chinese Biomedical Databases. The combination of free words and medical subject headings, including "depression, depressive disorder, acupuncture therapy, acupuncture, needle, needling, stroke, etc", will be used as the retrieval mode. The search strategy for Cochrane Library is shown in Table 1.

| ID | Search |
|---|---|
| #1 | MeSH descriptor: [Stroke] explode all trees |
| #2 | poststroke or post-stroke. ti,ab,kw |
| #3 | MeSH descriptor: [Cerebral Infarction] explode all trees |
| #4 | MeSH descriptor: [Cerebral Hemorrhage] explode all trees |
| #5 | #1 or #2 or #3 or #4 |
| #6 | MeSH descriptor: [Depression] explode all trees |
| #7 | depress* or affective disorder or affective symptoms. ti,ab,kw |
| #8 | #6 or #7 |
| #9 | MeSH descriptor: [Acupuncture] explode all trees |
| #10 | acupunctur* or acupoint* or needl*. ti,ab,kw |
| #11 | #9 or #10 |
| #12 | #5 and #8 and #11 |

Table 1 Search strategy for Cochrane Library

**Study selection and data extraction**

EndNote X8.2 will be used to manage studies. First, duplicate literature will be excluded by electronic & manual based steps in EndNote. Second, two reviewers will independently screen the titles and abstracts and select the studies which meet the eligibility criteria. If there are disagreements, the third reviewer will be consulted. The evaluators will read the full text of the included literature, and then preliminarily extracted relevant data, mainly including the following information: (1)Inclusion and exclusion criteria; (2) The number of included samples (total number of cases, number

of cases in the treatment group, number of cases in the control group); (3)Grouping method and process; (4) Basic data of the included research samples (mainly including gender, age and disease); (5)The intervention of the treatment group and the control group :① the treatment method, drug dose, treatment frequency, course of treatment, etc. ② a detailed description of manual acupuncture treatment including acupoints selection, twist technique, retention time, frequency, etc.(6) Evaluation of the final research results (including the treatment efficiency of different treatment measures, the scale score at the beginning and end point, etc).

**Quality assessment**

The quality of evidence for main outcomes will be assessed by The Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach. Two reviewers will do this independently through GRADEpro Guideline Development Tool (GDT). GRADE approach provides guidance for rating quality of evidence and grading strength of recommendations for health care. It has important implications for those summarizing evidence for systematic reviews[24].It assessed a body of evidence by referring to the concepts of the GRADE system , and determined and recorded the quality of a body of evidence for each clinical question, there are four quality levels: high, moderate, low and very low[25].

**Assessment of heterogeneity, Sensitivity analysis and subgroup analysis**

We'll use the $I^2$ statistic to assess the heterogeneity. If the $I^2$ value is below 50%, the fixed effect model will be used. Otherwise, sensitivity analysis will be conducted to explore the main sources of heterogeneity, after which, the random effect model will be used if the $I^2$ is still equal or greater than 50%. Both types of effect sizes will be presented with 95% CIs, and values of $p<0.05$ will be regarded as statistically significant.

Meanwhile, subgroup analysis will also be conducted to explore the main sources of heterogeneity. Compared with previous studies, we will extract more detailed information on the treatment schedule of acupuncture which could provide us more analytical basis for subgroup analysis. If the necessary information is available,

subgroup analyses will be carried out according to certain factors (acupoints selection, twist technique, retention time, frequency, period of treatment and different types of control group). After grouping, two or more groups of studies will be analyzed and compared in order to explore the causes of high heterogeneity.

**Data synthesis**

Continuous outcomes will be calculated as mean differences (MDs) or standardized mean differences (SMDs). If different scales are used to measure continuous outcomes, like depression severity and QOL, SMD will be used as a measure of effect size in efficacy outcome. It's calculated as the difference in mean outcome between groups divided by the standard deviation of outcome among participants. If the same scale is used in the included literature, mean difference (MD) will be used. In addition, safety outcome will be the number of participants who dropped out due to adverse effects and the number of participants who reported at least one adverse event or effect. For these dichotomous outcomes, the odds ratio (OR) will be calculated as the effect estimate.

**Assessment of the risk of bias in individual studies**

According to Cochrane Handbook for Systematic Reviews of Interventions version 6 (https://training.cochrane.org/handbook/current/chapter-08), the risk of bias 2.0 (ROB 2.0) tool will be used to mean the methodological quality and the risk of bias of the included studies. One researcher assessed the risk of bias of included studies by using ROB 2.0 and another researcher confirmed the judgment. If there are any differences, the third researcher will be asked to solve the problem.

**Publication bias**

STATA V.14.0 will be used to evaluate publication bias. Begg's test and Egger's test will be used to assess the publication bias of the included trials and form the publication bias plot.

**Patient and Public Involvement**

It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

## Discussion

This meta-analysis will focus on the different techniques, durations or other detailed operations of manual acupuncture applied in PSD patients to explore their influence on depression severity and QoL. PSD are generally more disabled[26]. As an important part of traditional Chinese medicine, acupuncture plays an important role in clinical treatment [27]. In terms of clinical efficacy, acupuncture can assist in eliminating negative emotions by significantly improving the functional communication and language function [28], cognitive [29] and limb movement function [30] of stroke patients. At the mechanism level, acupuncture can modulate glutamate receptor and excitatory Amino Acid Transporter(EAAT) expression [31], down-regulated the levels of unclear factor kappa light chain enhancer of activated B cells(NF-κB) protein, Inducible Nitric-Oxide Synthase(iNOS) and Nitric Oxide(NO) [32], so as to achieve the purpose of relieving PSD.

## Ethics and dissemination

The results of this meta-analysis will be disseminated through publication in peer-reviewed journals or conference presentations. The data used in this meta-analysis will not contain individual patient data, therefore, ethical approval is not required.

# Authors' contributions

Wei Liu and Chang Rao conceived, designed and wrote this protocol. Wei Liu provided a clinical perspective, especially to the manual acupuncture. Qi zhao provided the writing and modification of part of the article. Yuzheng Du is the guarantor of this review, and approved the final manuscript of it. Xi Nan, Zefang Li and Chunsheng Yin provided a preliminary data retrieval.

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# Competing interests statement

None declared.

## Abbreviation

PSD: post-stroke depression

QOL: quality of life

CANMAT: Canadian network for mood and anxiety treatments

APA: the American psychiatric association

WFSBP: the World federation of societies of biological psychiatry

SSRIs: selective serotonin uptake inhibitors

PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols

RCTs: Randomized controlled trials

CT: computer tomography

MRI: magnetic resonance imaging

ICD-10: International Classification of Diseases Tenth Edition

DSM: the Diagnosis and Statistical Manual of Mental Disorders

CCMD: Chinese Classification of Mental Disorders

HAMD: Hamilton Rating Scale for Depression

EG: experiment group

CG: control group

HAMD: Hamilton Depression Rating Scale

MADRS: Montgomery-Asberg Depression Rating Scale

BDI: Beck Depression Inventory

SDS: Zung Self-Rating Depression Scale

SF-36: the Medical Outcomes Study Short Form 36

SS-QOL: Stroke Specific Quality of Life Scale

WHOQOL: the World Health Organization Quality of Life

J-STAGE: Japan science and technology agency

CiNii: National Institute of Informatics

CNKI: China National Knowledge Infrastructure

GRADE: Grades of Recommendation, Assessment, Development, and Evaluation

GDT: Guideline Development Tool

MDs: mean differences

SMDs: mean differences

ORs: odds ratios

ROB 2.0: the risk of bias 2.0

EAAT: excitatory Amino Acid Transporter

NF-κB: unclear factor kappa light chain enhancer of activated B cells

iNOS: Inducible Nitric-Oxide Synthase

NO: Nitric Oxide

**Word Count:** 1,967 words excludes the title page, abstract, tables, acknowledgements, contributions and references.

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**PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol***

| Section and topic | Item No | Checklist item | Reported on Page # |
|---|---|---|---|
| **ADMINISTRATIVE INFORMATION** | | | |
| Title: | | | |
| Identification | 1a | Identify the report as a protocol of a systematic review | P1 |
| Update | 1b | If the protocol is for an update of a previous systematic review, identify as such | NA |
| Registration | 2 | If registered, provide the name of the registry (such as PROSPERO) and registration number | P2 |
| Authors: | | | |
| Contact | 3a | Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author | P1 |
| Contributions | 3b | Describe contributions of protocol authors and identify the guarantor of the review | P9 |
| Amendments | 4 | If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments | NA |
| Support: | | | |
| Sources | 5a | Indicate sources of financial or other support for the review | P9 |
| Sponsor | 5b | Provide name for the review funder and/or sponsor | P9 |
| Role of sponsor or funder | 5c | Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol | P9 |
| **INTRODUCTION** | | | |
| Rationale | 6 | Describe the rationale for the review in the context of what is already known | P3-P4 |
| Objectives | 7 | Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO) | P4 |
| **METHODS** | | | |
| Eligibility criteria | 8 | Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review | P4-P6 |
| Information sources | 9 | Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage | P6 |
| Search strategy | 10 | Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated | P6 |

| | | | |
|---|---|---|---|
| Study records: | | | |
| Data management | 11a | Describe the mechanism(s) that will be used to manage records and data throughout the review | P6 |
| Selection process | 11b | State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis) | P6-P7 |
| Data collection process | 11c | Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators | P6-P7 |
| Data items | 12 | List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications | P6-P7 |
| Outcomes and prioritization | 13 | List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale | P5 and P7 |
| Risk of bias in individual studies | 14 | Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis | P8 |
| Data synthesis | 15a | Describe criteria under which study data will be quantitatively synthesised | P7-P8 |
| | 15b | If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as $I^2$, Kendall's $\tau$) | P7-P8 |
| | 15c | Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression) | P7-P8 |
| | 15d | If quantitative synthesis is not appropriate, describe the type of summary planned | NA |
| Meta-bias(es) | 16 | Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies) | P8 |
| Confidence in cumulative evidence | 17 | Describe how the strength of the body of evidence will be assessed (such as GRADE) | P7 |

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